Pathogenesis and heterogeneity of ovarian cancer

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Purpose of review
The most common type of ovarian cancer, high-grade serous ovarian carcinoma (HGSOC), was originally thought to develop from the ovarian surface epithelium. However, recent data suggest that the cells that undergo neoplastic transformation and give rise to the majority of HGSOC are from the fallopian tube. This development has impacted both translational research and clinical practice, revealing new opportunities for early detection, prevention, and treatment of ovarian cancer.

Recent findings
Genomic studies indicate that approximately 50% of HGSOC are characterized by mutations in genes involved in the homologous recombination pathway of DNA repair, especially *BRCA1* and *BRCA2*. Clinical trials have demonstrated successful treatment of homologous recombination-defective cancers with poly-ribose polymerase inhibitors through synthetic lethality. Recently, amplification of *CCNE1* was found to be another major factor in HGSOC tumorigenesis, accounting for approximately 20% of all cases. Interestingly, amplification of *CCNE1* and mutation of homologous recombination repair genes are mutually exclusive in HGSOC.

Summary
The fallopian tube secretory cell is the cell of origin for the majority of ovarian cancers. Although it remains unclear what triggers neoplastic transformation of these cells, certain tumors exhibit loss of *BRCA* function or amplification of *CCNE1*. These alterations represent unique therapeutic opportunities in ovarian cancer.

Keywords
BRCA1, BRCA2, Cyclin E (CCNE1), fallopian tube epithelium, high-grade serous ovarian carcinoma

INTRODUCTION

Worldwide, approximately 240 000 women are diagnosed with ovarian cancer each year, and 140 200 are expected to succumb to the disease in 2016 [1,2]. This case-to-fatality ratio is nearly three times that of breast cancer, and makes ovarian cancer the most deadly gynecologic malignancy in developed countries. Patients with stage III or IV disease have a dismal 25% 5-year survival rate [2]. However, despite its aggressive clinical course, the American Cancer Society expects the number of ovarian cancer survivors to increase by 45 000 over the next decade [3].

Ovarian cancer is a nonspecific term for a variety of tumors that involve the ovary. Ovarian cancers can be classified into three large groups: epithelial, germ cell, and specialized stromal cell tumors. The vast majority of ovarian cancers are epithelial ovarian cancers (EOCs). EOC can be further subdivided into various histological subtypes that fall into two main groups: Type I and Type II tumors. Type I tumors include low-grade serous, mucinous, endometrioid, clear cell carcinomas and tend to grow more slowly, often from an identifiable precursor.

In contrast, Type II tumors are characterized by high-grade and rapidly progressive disease. High-grade serous ovarian carcinoma (HGSOC) is the most common Type II tumor, accounting for almost 75% of all EOCs. Unfortunately, it is also one of the most aggressive. There are currently no robust methods for early detection of HGSOC. As a result, the majority of women are diagnosed when the cancer has already metastasized to other tissues, usually within the peritoneal cavity. The lack of

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KEY POINTS

- High-grade serous ovarian carcinoma is usually derived from fallopian tube secretory epithelial cells.

- Mutations in the *BRCA* genes, along with other homologous recombination repair genes, account for 50% of HGSOC.

- PARP inhibition is a personalized therapy that can be implemented in homologous recombination-deficient ovarian cancer.

- Tumors with amplified *CCNE1* upregulate replication fork protection and homologous recombination repair genes to tolerate genomic stress generated by unscheduled S-phase entry.

- *CCNE1* amplification and *BRCA* mutations are mutually exclusive in high-grade serous ovarian cancer because they are synthetic lethal.

specific symptoms, even when the disease has spread to the peritoneum, contributes to delayed diagnosis and poor survival rates.

The post-TCGA (The Cancer Genome Atlas) landscape for HGSOC is marked by surprisingly few recurrent somatic mutations [4]. Instead, this disease exhibits a complex genomic terrain, marked by copy number alterations that are so widespread that few other cancer types mirror its complexity. Intertumoral and intratumoral heterogeneity in HGSOC further decrease the likelihood of finding a single therapy that will prove beneficial for the majority of patients. Thus, HGSOC will require individualized therapy in which we unbraid a tumor's genomic profile to identify altered genes or pathways that offer an opportunity for therapeutic intervention.

## Pathogenesis of epithelial ovarian cancer

Originally, the ovary was thought to be the primary site of HGSOC tumorigenesis and the ovarian surface epithelium (OSE) represented the cell of origin. The 'incessant ovulation' hypothesis suggested that HGSOC developed because of repetitive injury to the OSE with each ovulatory cycle [5]. It was thought that this repetitive injury causes increased inflammation and changes in hormone levels, leading to DNA damage produced by oxidative stress [5]. Incessant ovulation, through a rupture and repair mechanism, along with the normal proliferation of the OSE, was thought to drive metaplastic changes toward a more Müllerian-type epithelium. If this Müllerian-type epithelium harbored unresolved DNA damage, it would represent a prime target

for neoplastic transformation [6]. Although the OSE model could account for a number of important features associated with ovarian cancer, particularly Type I tumors, it fails to present a path toward understanding of Type II tumors. Perhaps most importantly, attempts to reproducibly identify precursor lesions for HGSOC in the OSE have been largely unsuccessful.

The cloning of the *BRCA1* and *BRCA2* genes quickly led to the practice of risk-reducing bilateral salpingo-oophorectomies in mutation carriers to reduce the risk of developing ovarian cancer [7■]. These specimens afforded pathologists the opportunity to examine these tissues for occult cancers. Some of the earliest studies suggesting that the fallopian tube epithelium plays a much larger role in the development of ovarian cancer were reported by Piek *et al.* [8,9]. Subsequent studies confirmed the paradoxical observation that in the search for early ovarian cancers, most lesions were identified in the fallopian tube [10–15]. The development of a pathology protocol, called the SEE-FIM (Sectioning and Extensively Examining the FIMbriated end) protocol, to systematically evaluate the fallopian tubes of *BRCA* mutation carriers led to the reproducible identification of early serous carcinomas in the distal end of the fallopian tube. The vast majority of cases was localized to the fimbria and included serous tubal intraepithelial carcinoma (STIC) [16–18]. No intraepithelial or invasive serous carcinomas were identified in the ovaries of these samples [18,19]. Like the foci of invasive HGSOC, the STIC lesions were proliferative, as measured by Ki67 immunohistochemistry (IHC) and stained strongly for p53. More importantly, DNA sequencing revealed that the majority of STIC lesions harbor the same *TP53* mutation as the concurrent HGSOC [20,21], indicative of their clonal nature.

Further examination of the fallopian tubes identified short stretches of benign-appearing secretory cells that stained strongly for p53 and γ-H2AX, a marker of DNA damage. These foci of p53-positive cells harbored *TP53* mutations but were not proliferative [17]. These patches were called 'p53 signatures' based on the requisite p53 IHC necessary to identify the otherwise benign looking cells. Importantly, the 'p53 signature', the STIC lesion, and HGSOC from the same patient harbor the same *TP53* mutation [17], implying a clonal relationship between the nonproliferative 'p53 signature', the intraepithelial lesion, and the invasive cancer (Fig. 1).

What percentage of HGSOCs arises from the fallopian tube? Studies that implement the SEE-FIM protocol report that approximately 50–60% of HGSOCs are associated with a STIC lesion in the fallopian tube (Table 1). A number of explanations
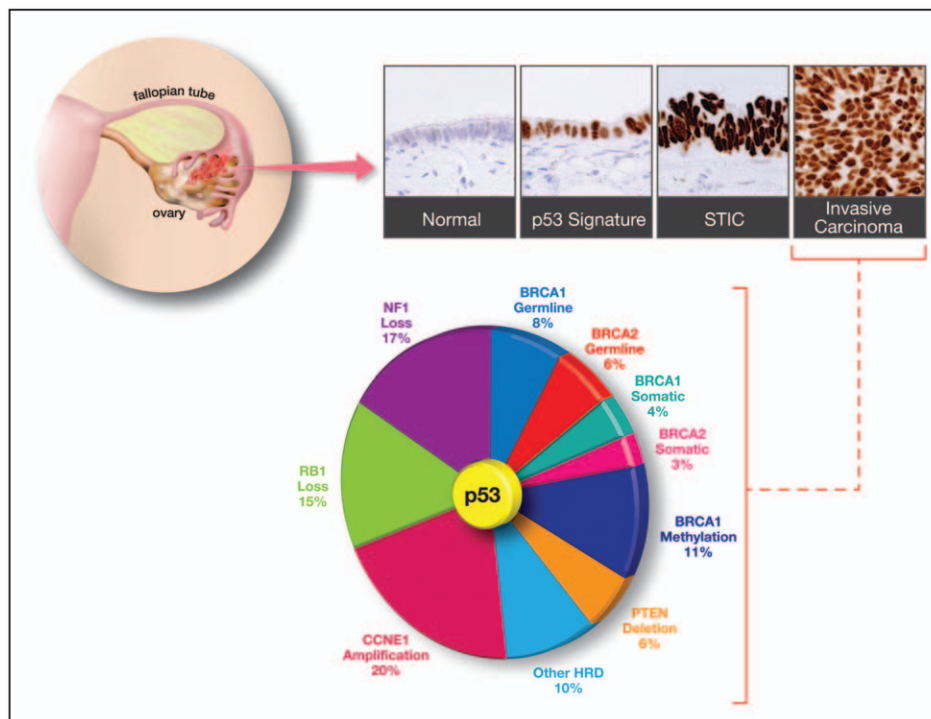
FIGURE 1. Pathological and genomic features of high-grade serous ovarian carcinomas (HGSOCs). The majority of HGSOCs emerge from the fallopian tube epithelium through a series of precursor lesions that target the secretory cell. Normal fallopian tube epithelium contains both secretory and ciliated cells and is typically immunonegative for p53. The benign 'p53 signature' is composed entirely of secretory cells that exhibit strong p53 expression and evidence of DNA damage but are not proliferative. With progression to a serous tubal intraepithelial carcinoma or 'STIC', there is acquisition of nuclear pleomorphism, mitoses, and loss of polarity. Invasive HGSOC shares all these properties and clinical symptoms typically emerge with advanced disease [22].

have been offered to explain why the association between HGSOC and STIC is not higher. These include insufficient sampling of tissue blocks [50,51], interobserver variability [52–54], consumption of precursors by the invasive carcinoma, and the high frequency of p53-negative STIC lesions [55]. It is also possible that extrauterine Müllerian epithelium [56] or derivatives of the OSE harbor precursor lesions. However, until reproducible precursors are identified at these sites, their contributions remain unclear. Resolving whether all HGSOCs arise from the fallopian tube or other sites remains to be determined and will likely require additional shared common resources and specimen banks [57■].

The fallopian tube paradigm for HGSOC pathogenesis has motivated the development of new, robust, and tractable experimental model systems that focus on the fallopian tube as the site of origin. In particular, several mouse models were created by genetically manipulating murine oviductal cells [58–62]. Some of these models have recapitulated the development of tubal precursor lesions [58,60] and demonstrated that salpingectomy blocks tumor development [58,61]. More recently, Cho and

colleagues developed a mouse in which the *Ovgp1* promoter controls expression of a tamoxifen-regulated Cre recombinase in oviductal epithelium – the murine equivalent of human fallopian tube epithelium [59]. Deletion of *Apc* and *Pten* in this model was compared with a model in which an adenovirus expressing Cre was injected into the ovarian bursa to target the OSE. Tumors that emerged from the fallopian tube more closely resembled human endometrioid ovarian cancers than those from the OSE. The slow progression and late metastasis of oviductal tumors resemble the relatively indolent behavior characteristic of so-called Type I ovarian carcinomas in humans, for which endometrioid carcinoma is a prototype. This model emphasizes that importance of cellular context and the need to further understand the cell of origin for ovarian cancer [63].

Genomic landscape of high-grade serous ovarian carcinoma: the role of TP53

One of the hallmarks of HGSOC is the universal presence of mutations in the *TP53* tumor suppressor

gene [4,64,65"",66""]. The most common site of mutation of *TP53* is the DNA-binding domain, but mutations in other regions have been identified [64]. Mutation of *TP53* is the first known molecular event in the transformation of fallopian tube secretory cells, and can be identified in early tumor precursors [17]. Recent studies indicate that stabilizing *TP53* missense mutations, but not loss of endogenous wildtype *TP53*, promote secretory cell survival and cell–cell aggregation under anchorage independent growth conditions. This mutant-mediated autocrine matrix deposition leads to the formation of cell clusters with mesothelial-intercalation capacity which is likely necessary for peritoneal dissemination [67"]. Interestingly, it appears that the most common *TP53* missense mutations, including R273H, R175H, and R248Q, express a large number and high amounts of shorter p53 protein isoforms that are translated from the mutated full-length p53 mRNA. These shorter isoforms, like Δ160p53, exhibit all the gain-of-function properties attributed to the mutant protein, including enhanced cell survival, proliferation, adhesion, and invasion [68"]. These data suggest that early mutation of *TP53* is necessary for HGSOC initiation. For these reasons, mutant p53 has re-emerged as an appealing therapeutic target in HGSOC. Small molecules that sculpt the mutant protein into a more wildtype confirmation are being evaluated in preclinical and clinical trials [69]. In addition, perturbation of pathways, like the mevalonate pathway, that lead to degradation of mutant p53 are being exploited for therapeutic gains [70].

Drugging BRCA in high-grade serous ovarian carcinoma

Despite the high frequency of *TP53* mutations observed in the development of HGSOC, TCGA data suggest that recurrent mutations in other genes are relatively uncommon, with the exception of *BRCA1* and *BRCA2* [4]. BRCA1 and BRCA2 are proteins that play a critical role in maintaining the integrity of the genome by orchestrating DNA repair through homologous recombination. Homologous recombination is a high-fidelity process and is considered to be an error-free mechanism of repairing double-stranded breaks (DSBs) because it uses the sister chromatid as a template for repairs. This mechanism is in contrast to the other major pathway, known as nonhomologous DNA end joining (NHEJ), which simply ligates DSB ends without a template and is more error-prone. Double-stranded DNA breaks occur most frequently during DNA replication, especially when the replication machinery encounters a single-stranded break (SSB), ultimately leading to genomic instability and cell death if unrepaired. Mutations in *BRCA1* and *BRCA2* cause homologous recombination deficiency (HRD), making cells rely much more heavily on the NHEJ pathway to repair DSB. Although germline and somatic mutations in the *BRCA* genes account for approximately 15–20% of all HGSOCs, dysfunction in the BRCA network and homologous recombination appears to be more widespread, with approximately 50% of HGSOC harboring alterations in genes involved in homologous recombination [4,65"",71–73]. For instance, the promoter of *BRCA1* can be highly methylated, resulting in loss of gene expression and mimicking the *BRCA1* mutant phenotype [4]. In addition to the *BRCA* genes, there are several inherited DNA repair genes that likely contribute to HRD when mutated. These include genes in the Fanconi anemia complex, the *RAD51* paralogs (*RAD51B*, *RAD51C*, and *RAD51D*), *BRIP1*, *BARD1*, *PALB2*, as well as *RAD50*, *CHEK2*, *ATR*, and *ATM* [74–76]. These alterations collectively display HRD and are often described as having a 'BRCAness' phenotype [77,78] because of the genomic instability associated with BRCA dysfunction [65"",79–81].

Traditionally, ovarian cancers have been treated with cytotoxic agents, typically platinum-based chemotherapy, regardless of histological subtype. In fact, there are only two FDA approved targeted agents for use in ovarian cancer. The first is bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). This antiangiogenic therapy was approved for use in recurrent, platinum-resistant ovarian cancer [82–84]. The second is olaparib, a poly-ribose polymerase (PARP) inhibitor. Olaparib was approved in 2014 for use in patients with *BRCA* mutations and recurrent disease [85,86]. The success of PARP inhibition is grounded in the idea that loss of PARP1 function in the setting of HRD (i.e., *BRCA1/2* mutation) causes an increase in DNA aberrations, not all of which could be repaired due to HRD, resulting in cell death via synthetic lethality [86–89]. Synthetic lethality occurs when there is an inactivation of two genes or pathways, neither of which produces lethal effects on its own, but when combined cause cell death. There are a number of mechanisms that may underlie PARP–BRCA synthetic lethality. First, PARP-1 is involved in the repair of single strand breaks (SSBs), which, in the presence of a PARP inhibitor, may persist and cause collapse of replication forks leading to DSBs. Because BRCA defective cancer cells lack homologous recombination, the resulting DSBs would be selectively toxic to the cancer cells. Another mechanism involves PARP trapping. PARP inhibitors trap PARP-1 onto SSBs that form spontaneously or during base excision repair. Trapped PARP-1 can pose an obstacle

Table 1. Incidents of tubal precursors in HGSOC

Author	% STIC in HGSOC[a]	# STIC	# HGSOC	SEE-FIM	Notes
Leeper et al. [12]	60	3	5	No	
Powell et al. [13]	57	4	7	No	
Carcangiu et al. [23]	50	3	6	No	
Finch et al. [14]	86	6	7	No	
Medeiros et al. [18]	100	5	5	Yes	
Callahan et al. [24]	100	7	7	No	
Kindelberger et al. [20]	48	20	42	Yes	
Carlson et al. [25]	40	18	45	Some	47% with SEE-FIM, 35% without SEE-FIM
Hirst et al. [26]	80	4	5	Yes	
Jarboe et al. [27]	23	5	22	Yes	
Roh et al. [28]	35	30	87	Yes	
Maeda et al. [29]	47	7	15	Yes	
Przybycin et al. [30]	59	24	41	Yes	
Leonhardt et al. [31]	33	3	9	Yes	
Manchanda et al. [32]	71	10	14	No	
Diniz et al. [33]	71	24	34	Some	
Powell et al. [34]	50	5	10	No	
Seidman et al. [35]	56	5	9	Some	
Tang et al. [36]	19	6	32	Yes	
Gao et al. [37]	92	107	116	Yes	
Lee et al. [38]	32	6	19	No	
Reitsma et al. [39]	75	3	4	Some	Cases after 2006 are SEE-FIM
Conner et al. [40]	74	14	19	Yes	
Koc et al. [41]	36	9	25	Yes	
Mingels et al. [42]	43	23	54	Yes	
Sherman et al. [43]	16	4	25	No	
Gilks et al. [44]	95	20	21	Yes	
Munakata and Yamamoto [45]	22	5	23	Some	Only 10% SEE-FIM
Seidman [46]	40	81	202	Some	1991–2007 no SEE-FIM, 2007–2011 half SEE-FIM
Malmberg et al. [47]	61	8	13	No	
Mittal et al. [48]	22	7	32	Yes	
Zakhour et al. [49■]	64	9	14	Some	

HGSOC, high-grade serous ovarian carcinoma; SEE-FIM, Sectioning and Extensively Examining the FIMbriated end; STIC, serous tubal intraepithelial carcinoma.
[a]Values are in %.

to replication that would require homologous recombination to resolve [90]. Interestingly, despite the selective activity of PARP inhibitors in *BRCA* mutant tumors, more patients responded to PARP inhibitor therapy than those individuals with confirmed *BRCA* mutations [91]. In fact, a recently published phase III clinical trial using the PARP inhibitor niraparib as maintenance therapy for patients with platinum-sensitive, recurrent ovarian cancer, demonstrated significantly prolonged progression free survival of patients regardless of their BRCA or HRD status [92■■].

These observations suggest that PARP inhibitors may have a broader role in ovarian cancer therapy. To date in the United States, only olaparib is FDA approved, although rucaparib was recently given breakthrough status by the FDA and others are expected to follow in the near future [93,94]. Currently, several clinical trials are progressing using different PARP inhibitors alone, or in combination with other drugs [95,96]. Studies like these show that PARP inhibitors have the potential to change the course of therapy for many individuals with ovarian cancer.
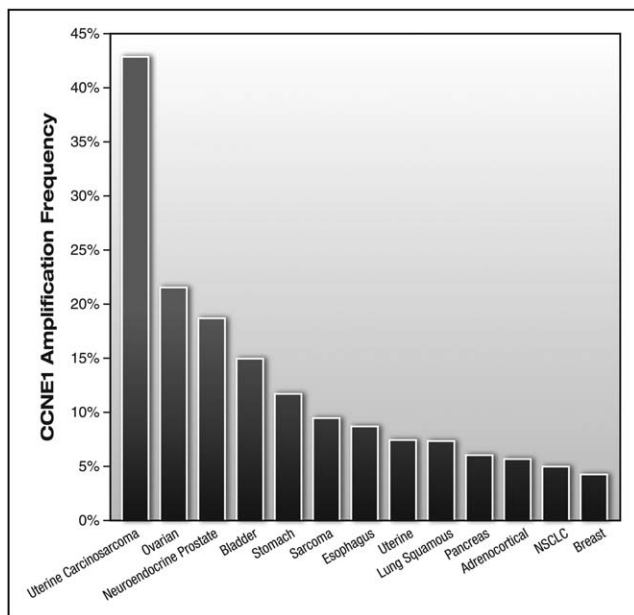
FIGURE 2. Amplification of CCNE1 across human cancers. The cbioportal (http://www.cbioportal.org) was queried for 'CCNE1: AMP' and the resulting bar graph was limited to tumors with at least 4% amplification.

CCNE1: a unique opportunity in high-grade serous ovarian carcinoma

HGSOC is characterized by obligatory mutation of the *TP53* gene, mutations in the homologous recombination DNA repair pathway, and widespread copy number alterations [4]. One of the most common copy number alterations in ovarian cancer is the amplification of the 19q12 locus. The Bowtell laboratory used a systematic knockdown of genes within the 19q12 amplicon to map *CCNE1* as a key driver of the 19q12 amplicon [97]. *CCNE1* encodes Cyclin E1, and it is amplified in a number of solid tumors (Fig. 2) and in approximately 20% of HGSOC cases (Fig. 1) [4,65▪▪]. Cyclin E1 protein levels vary during the cell cycle and play a major role in the G1-S phase transition by binding and activating the cyclin-dependent kinase 2 (CDK2) [98]. Aberrant Cyclin E1 expression is known to trigger unscheduled DNA replication, centrosome amplification, and chromosomal instability [99,100,101▪,102]. Importantly, *CCNE1* amplification is associated with primary or refractory chemoresistant ovarian cancer [103] and poor overall survival [104,105]. Interestingly, amplification of *CCNE1* and increased Cyclin E1 protein can be detected in STIC lesions, indicating that dysregulation of *CCNE1* is an early event in the development of HGSOC [100,101▪,106].

Protein abundance of Cyclin E1 is controlled at several levels, including by ubiquitin-mediated proteolysis by E3 ligases FBXW7 and PARK2, both of which are frequently deleted in human tumors [107], and by PP2A-B55β, a phosphatase that also controls Cyclin E1 turnover [108]. Proteolytic cleavage of Cyclin E1 to low-molecular weight (LMW) isoforms by the elastase family of serine proteases enhances transformation [109,110] and increased expression of LMW isoforms is associated with poor outcome in breast cancer [111]. We recently showed that induced expression of *CCNE1* in fallopian tube secretory epithelial cells harboring a *TP53* missense mutation leads to increase proliferation, colony formation, loss of contact inhibition, centrosome amplification, and modest anchorage independent growth [100,101▪]. As expected, we detected increased DNA damage in these cells as measured by phosphorylation of histone H2AX and increased comet tails [100]. Expression analysis of these *CCNE1*-overexpressing cells revealed that they upregulate key factors involved in homologous recombination and replication fork protection. Most notable was the upregulation of *BRCA1*, *FANCD2*, *CDC25C*, *BLM*, and *XRCC2* (a RAD51 paralog). Amazingly, a synthetic lethal screen identified many of the same proteins as essential in *CCNE1*-amplified HGSOC cell lines [112]. These findings strongly suggest that the chromosomal instability generated by defects in the homologous recombination pathway and amplification of *CCNE1* cannot coexist within the same cell and at least one of these pathways must be functional for survival of the cell. It also suggests that inhibition of DNA repair and replication fork protection pathways may be a viable therapeutics strategy in *CCNE1*-amplified tumors.

Although *CCNE1*-amplified tumors represent a subset of HGSOC that deserve clinical attention, there are currently no targeted therapies for these tumors. The most obvious target is CDK2, the kinase partner of Cyclin E [113,114,115▪▪]. In fact, the development of small molecule inhibitors of CDKs has been an intense area of research [116] given their central role as regulators of cell division. Unfortunately, most compounds are not CDK2-specific and target multiple CDKs, eliciting dose-limiting toxicities that have slowed further clinical development [112,115▪▪,117]. However, the recent impressive findings with the CDK4/6 inhibitor palbociclib, targeted to Cyclin D1 and estrogen receptor-positive breast cancer [118], have renewed interest in the field [119–123]. In particular, a recent high-throughput compound screen in *CCNE1*-amplified ovarian cancer cell lines was performed to identify selective synergistic drug combinations with dinaciclib, a CDK1/2 inhibitor in clinical development. A synergistic therapeutic

effect was elicited when dinaciclib was combined with an AKT2 inhibitor [115▪▪]. *AKT2* and *CCNE1* both reside on chromosome 19 and analysis of genomic data from TCGA demonstrated coamplification of *CCNE1* and *AKT2* in HGSOC. This finding suggests a specific dependency of *CCNE1*-amplified tumors for AKT activity, and points to a novel combination of dinaciclib and AKT inhibitors that may selectively target patients with *CCNE1*-amplified HGSOC, and possibly other solid tumors.

CONCLUSION

There is now significant clinical and experimental evidence pointing to the fallopian tube as the site of origin for a majority of HGSOCs. Next generation sequencing efforts have provided us with a panoramic view of HGSOCs and have revealed significant genomic heterogeneity. Alterations in the BRCA and CCNE1 pathways represent two distinct genotypes that exhibit unique vulnerabilities in DNA repair. The emergence of PARP inhibitors will change the clinical management of patients with BRCA mutant tumors as well as patients with tumors that are not HRD. Therapeutic approaches for *CCNE1*-amplified tumors are evolving and will likely exploit their dependency on homologous recombination and replication fork protection pathways.

Conflicts of interest

R.D. serves on the Scientific Advisory Board of Siamab Therapeutics, Inc.

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