

# Distinct implications of different BRCA mutations: efficacy of cytotoxic chemotherapy, PARP inhibition and clinical outcome in ovarian cancer

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**Abstract:** Approximately a fifth of ovarian carcinoma (OC) is associated with inherited germline mutations, most commonly in the DNA repair genes *BRCA1* or *BRCA2* (*BRCA*). *BRCA1*- and *BRCA2*-associated OCs have historically been described as a single subgroup of OC that displays a distinct set of characteristics termed the “BRCAness” phenotype. The hallmarks of this phenotype are superior clinical outcome and hypersensitivity to platinum-based chemotherapy and poly-(ADP-ribose) polymerase (PARP) inhibitors. However, growing evidence suggests that *BRCA1*- and *BRCA2*-associated OCs display distinct characteristics, most notably in long-term patient survival. Furthermore, recent data indicate that the site of *BRCA1* mutation is important with regard to platinum and PARP inhibitor sensitivity. Here, we summarize the body of research describing the BRCAness phenotype and highlight the differential implications of different *BRCA* mutations with regard to clinicopathologic features, therapy sensitivity and clinical outcome in OC.

**Keywords:** ovarian cancer, *BRCA1*, *BRCA2*, BRCAness

## Introduction

Ovarian cancer accounts for ~21% of malignancies diagnosed in the female genital tract and is responsible for >14,000 deaths per annum in the US alone.<sup>1</sup> More than 90% of cases are epithelial in origin. Ovarian carcinoma (OC) is now recognized to comprise a heterogeneous group of discrete disease entities, each displaying distinct clinical behavior and molecular landscapes.<sup>2,3</sup> The current standard of care for the first-line treatment of OC comprises maximal surgical resection of the tumor mass and platinum-based chemotherapy, usually in combination with paclitaxel.<sup>4</sup> While some therapy stratification based on our understanding of disease biology is beginning to emerge in OC – most notably in the advent of poly-(ADP-ribose) polymerase (PARP) inhibitor therapy – personalization of OC treatment based on histological subtype and molecular characterization remains in its infancy.<sup>4,5</sup>

Hereditary OC accounts for a significant proportion of cases, with around a fifth of patients harboring germline pathogenic sequence variants.<sup>6</sup> A large proportion of these mutations occur within genes encoding components of the homologous recombination DNA repair (HRR) pathway, most notably in *BRCA1* or *BRCA2* (*BRCA*), which together account for ~10% of OC cases.<sup>7</sup> Other inherited mutations in HRR pathway-related genes include *BARD1*, *BRIP1*, *CHEK2*, *PALB2* and *RAD51C*, which together account for a minority (≤5%) of cases.<sup>6</sup>

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Historically, *BRCA*-associated OC has been described as a single subtype of OC that displays a distinct set of characteristics – frequently referred to as the “BRCAness” phenotype.<sup>8</sup> However, the differential impact of *BRCA1* versus *BRCA2* inactivation has become increasingly apparent in recent years.<sup>9</sup> Here, we summarize the growing body of evidence describing the BRCAness phenotype and highlight the emerging evidence of the distinct implications of different *BRCA* mutations on the treatment and clinical outcome of OC patients.

## Structure and function of *BRCA* genes

### *BRCA1*

Since its identification in 1994, *BRCA1* has become one of the most extensively studied tumor suppressor genes to date.<sup>10</sup> *BRCA1* comprises 24 exons coding for 1863 amino acids, more than half of which are encoded by exon 11.<sup>11</sup> Its 208 kDa protein product, BRCA1, contains an N-terminal RING domain with E3 ligase activity and a phosphoprotein-binding C-terminal BRCT domain, encoded by exons 2–7 and 16–24, respectively (Figure 1).<sup>12–16</sup> Exons 11–13 are known to encode a region with two nuclear localization sequences (NLSs) and protein-binding domains for a multitude of proteins involved in various signaling pathways, including multiple tumor suppressors, oncogenes and DNA repair-associated proteins.<sup>17,18</sup> These include portions of a coiled-coil domain, which are known to mediate interactions with PALB2, and a serine cluster domain (SCD) whose phosphorylation sites are targeted by ATM and ATR kinases in response to DNA

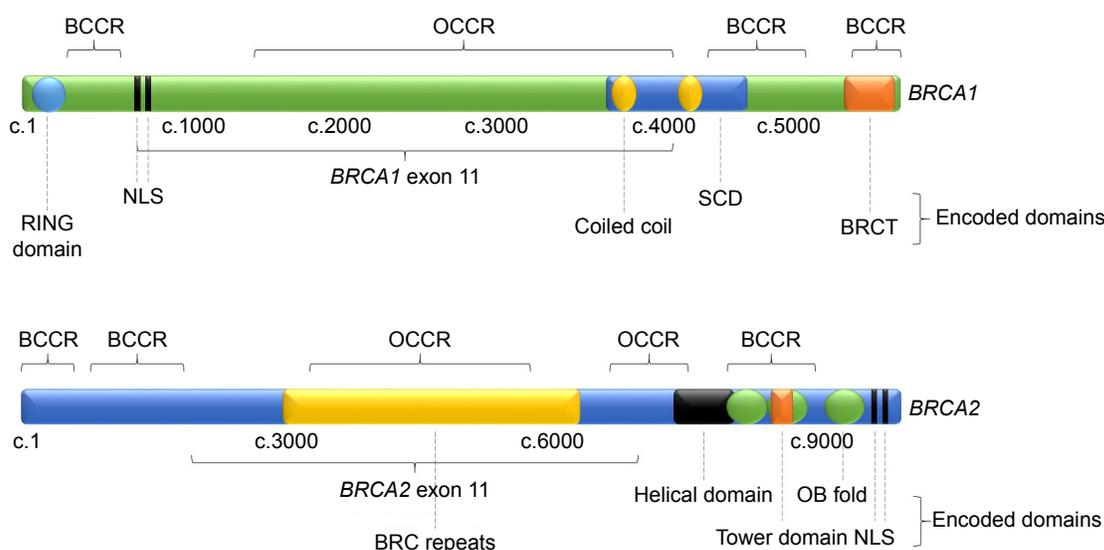
damage.<sup>11,19</sup> Cancer-predisposing *BRCA1* mutations are known to occur across these three regions, indicating important tumor suppressive function in each region.<sup>11</sup>

*BRCA1* is multifunctional, with roles in the DNA damage response, cell cycle checkpoint maintenance and DNA repair.<sup>20–24</sup> *BRCA1* is known to play a role in maintaining the G1/S, S-phase and G2/M cell cycle checkpoints; however, its principally associated role is in repair of double-stranded DNA breaks (DSB), primarily through HRR.<sup>20–24</sup> Briefly, *BRCA1* associates with ubiquitinated histones at DSBs and facilitates break resection and subsequent recruitment of RAD51 through interaction with PALB2 and *BRCA2*.<sup>25,26</sup> Accordingly, loss of *BRCA1* expression renders cells hypersensitive to ionizing radiation and interstrand DNA crosslinking agents, consistent with loss of high fidelity DSB repair.<sup>20,21</sup>

### *BRCA2*

*BRCA2* comprises 27 exons encoding 3418 amino acids, which form its 384 kDa protein product, *BRCA2*, also involved in repair of DSBs through HRR.<sup>27,28</sup> *BRCA2* exon 11 contains eight highly conserved BRC repeats that are known to interact with RAD51, an essential HRR protein whose family members RAD51C and RAD51D have been identified as OC susceptibility genes (Figure 1).<sup>6,29–33</sup> The C-terminal region of *BRCA2* also interacts with RAD51 and is known to contain two NLS.<sup>34</sup>

*BRCA2* contains a DNA-binding domain comprising an  $\alpha$ -helical domain, a tower domain and three



**Figure 1** Structure of *BRCA1* and *BRCA2* genes, showing regions encoding identified protein domains, BCCRs and OCCRs.

**Abbreviations:** BCCR, breast cancer cluster region; OCCR, ovarian cancer cluster region; NLS, nuclear localization sequence; SCD, serine cluster domain; BRCT, *BRCA1* C-terminal domain; OB, oligonucleotide binding.

oligonucleotide-binding (OB) motifs for binding single- and double-stranded DNA (ssDNA and dsDNA).<sup>26,35</sup> Pathogenic mutations have been detected across the length of *BRCA2*, including in its BRC repeats and DNA-binding domain.<sup>9</sup>

While *BRCA1* is multifunctional, *BRCA2* appears to function almost exclusively in HRR: it recruits RAD51 to DSB sites, a crucial step in repair.<sup>28</sup> *BRCA2*-mutant cells are hypersensitive to DNA damage, accumulate gross DNA damage with passage in culture and fail to recruit RAD51 to DSB sites, but do not appear to demonstrate substantial cell cycle checkpoint impairment.<sup>36–39</sup>

## Clinicopathologic features of *BRCA*-associated OC

### Cancer predisposition in *BRCA1* and *BRCA2* carriers

*BRCA* mutation carriers are predisposed to a number of malignancies, most notably OC and breast cancer (BC). However, the level of risk for the development of OC and BC appears dependent upon the affected gene.<sup>40,41</sup> The average cumulative risk of *BRCA1* carriers developing BC and OC by the age of 70 is ~50%–60% and 40%–50%, respectively, while the equivalent risk in *BRCA2* carriers is substantially lower at ~40%–50% and 10%–20%, respectively.<sup>40–42</sup>

Growing evidence has begun to elucidate the discrete impact of the type and location of *BRCA1* and *BRCA2* mutations with regard to cancer predisposition.<sup>43–46</sup> These studies were founded on the early observation that carriers of mutations in the central portion of *BRCA1* exon 11 displayed an augmented risk of OC versus BC relative to those with mutations in other areas of the gene.<sup>43,44</sup> Similarly, early observations identified increased risk of OC versus BC in those harboring mutations in exon 11 of *BRCA2* versus mutations in other regions.<sup>45</sup>

A recent study sought to more thoroughly investigate the relationship between *BRCA* mutation position and differential OC versus BC predisposition in an extensive cohort of *BRCA* carriers.<sup>46</sup> Analysis of *BRCA1* mutation positions revealed three regions associated with increased BC versus OC risk relative to mutations in other areas of the gene. These conferred a relative hazard ratio (HR) of BC versus OC (BC-RHR) ranging from 1.34 to 1.46. A cluster region within *BRCA1* exon 11 conferring increased risk of OC versus BC development, relative to other areas of the gene, was also identified (BC-RHR = 0.62, 95% CI, 0.56–0.70).<sup>46</sup> This is consistent with previous reports of *BRCA1* exon 11 mutations with augmented OC risk.<sup>43,44</sup> Such BC cluster

regions (BCCRs) and OC cluster regions (OCCRs) were also identified in *BRCA2*: multiple *BRCA2* BCCRs and OCCRs were identified with BC-RHRs ranging from 1.63 to 2.31 and 0.51 to 0.57, respectively.<sup>46</sup>

### Age at disease onset

As with many cancer predisposition syndromes, *BRCA*-linked OC is associated with earlier age at diagnosis.<sup>47–49</sup> Interestingly, *BRCA1* carriers appear to develop OC at an average of ~7 years earlier versus nonhereditary OC patients, while *BRCA2* carriers do not display a strong trend for earlier diagnosis (Table 1).<sup>47,50–53</sup> *BRCA1* mutations account for over 80% of *BRCA*-associated OC diagnosed below the age of 50, while *BRCA2* carriers account for ~60% of *BRCA*-associated OC diagnosed at >60 years old, despite the higher prevalence of *BRCA1* versus *BRCA2* mutations in OC.<sup>54</sup>

### Histological subtype of OC

OC is largely grouped into five core histologically defined subtypes (histotypes): high-grade serous (HGS), endometrioid, clear cell (CC), low-grade serous (LGS) and mucinous OC, which together represent over 95% of presenting cases.<sup>55</sup> HGS OC represents the bulk (~70%) of cases, while the endometrioid, CC, LGS and mucinous histotypes are reported to account for ~10%, 10%, <5% and 3% of OC, respectively.<sup>2,55,56</sup> These histotypes represent inherently different tumors, displaying differential chemosensitivity and survival, and are now acknowledged to have discrete developmental origins.<sup>57–62</sup> Indeed, a wealth of evidence now illustrates that these represent separate disease entities at both the genomic and transcriptomic levels.<sup>3,62–65</sup>

While a minority of *BRCA*-mutant CC and endometrioid OC have also been identified, *BRCA* mutations are associated predominantly with HGS OC.<sup>8,47,66</sup> Germline *BRCA* mutations account for ~15% of HGS OC, with an additional 5%–10% displaying somatic *BRCA* mutations.<sup>3,63,67</sup>

### Metastasis to the viscera

Although the vast majority of OC are diagnosed at advanced stage, disease is frequently confined to the peritoneal cavity, even at recurrence.<sup>68</sup> Even when distant metastases are present, the majority involve nonvisceral sites.

*BRCA*-linked OC has been associated with an increased frequency of visceral metastasis, most notably to the liver: approximately three in four patients with germline *BRCA* mutations who develop OC display visceral metastasis, while the rate in nonhereditary OC patients is estimated at less than 20%.<sup>69</sup> *BRCA1* mutation carriers appear to have a

**Table 1** Characteristics of *BRCA1*-associated, *BRCA2*-associated, and *BRCA* wild-type OC

	<i>BRCA1</i> -associated OC	<i>BRCA2</i> -associated OC	<i>BRCA</i> wild-type OC	References
<b>Clinicopathological features</b>				
Age at diagnosis	Younger versus WT	Similar to WT	Older versus <i>BRCA1</i> -mutant	47–52, 54
Histology	Predominantly HGS OC		All OC histotypes	8, 47, 66
Visceral metastasis	Highly likely	Likely	Unlikely	69, 70
<b>Chemosensitivity</b>				
Platinum	Highly sensitive Exon 11 and RING domain mutants may be more resistant	Highly sensitive May be more sensitive versus <i>BRCA1</i> -mutant	Sensitive Less sensitive versus <i>BRCA</i> -mutant	8, 49, 53, 71, 72, 74, 75
PLD	More sensitive versus WT		Less sensitive versus <i>BRCA</i> -mutant	96, 97
Taxanes	May be more resistant versus WT	Undetermined	May be more sensitive versus <i>BRCA1</i> -mutant	82, 84–87, 92, 93
PARP inhibitors	Sensitive Exon 11 and RING domain mutants may be more resistant	Sensitive	Resistant versus <i>BRCA</i> -mutant	72, 74, 75, 121–130
<b>Clinical outcome</b>				
PFS	Superior May be inferior to <i>BRCA2</i> -mutant	Superior May be superior to <i>BRCA1</i> -mutant	Inferior versus <i>BRCA</i> -mutant	53, 71, 144–149
Short-term OS	Superior versus WT Inferior versus <i>BRCA2</i> -mutant	Superior versus WT Superior versus <i>BRCA1</i> -mutant	Inferior versus <i>BRCA</i> -mutant	53, 66, 143, 147, 149, 155, 156
Long-term OS	Inferior versus <i>BRCA2</i> -mutant	Superior versus WT Superior versus <i>BRCA1</i> -mutant	Inferior versus <i>BRCA2</i> -mutant	8, 47, 66, 143, 147, 149, 155, 156

**Abbreviations:** *BRCA*, *BRCA1* or *BRCA2*; OC, ovarian carcinoma; WT, wild-type; HGS, high grade serous; PLD, pegylated liposomal doxorubicin; PFS, progression-free survival; OS, overall survival; PARP, poly-(ADP-ribose) polymerase.

particular propensity to develop visceral metastases: while investigations to date have been limited, current data suggest that almost all *BRCA1* carriers develop disease at visceral sites, compared to only around half of *BRCA2* carriers.<sup>69,70</sup> Furthermore, *BRCA1*-associated OC has also been shown to display an increased rate of brain metastasis specifically.<sup>70</sup>

## Chemosensitivity

### Platinum-based chemotherapy

A predominant characteristic of the BRCAness phenotype is their sensitivity to platinum-based DNA-damaging agents, even upon repeated exposure at disease recurrence.<sup>8,49,71</sup> Tan et al<sup>8</sup> demonstrated that the majority of *BRCA*-associated OC patients experience partial or complete response to platinum-based agents in the second- and third-line settings, compared to less than half and less than one-tenth of matched controls, respectively. However, they did not compare rates in a *BRCA1*- and *BRCA2*-mutant gene-specific manner. The superior sensitivity of *BRCA*-associated OC to platinum agents was confirmed in later studies of *BRCA*-associated versus nonhereditary OC.<sup>49,71</sup>

Yang et al<sup>53</sup> compared the frequency of primary platinum sensitivity of *BRCA1* versus *BRCA2*-associated HGS OC. They observed a significantly superior primary platinum

sensitivity in the *BRCA2*- versus *BRCA1*-mutant population: 100% of *BRCA2*-associated OC (25 of 25 in their cohort) displayed primary platinum sensitivity versus 80% (24 of 30 in their cohort) of *BRCA1*-associated OC.<sup>53</sup> They also observed a 5.5-month superior platinum-free interval in *BRCA2* versus *BRCA1* carriers and a “mutator phenotype” indicative of high genome instability in *BRCA2*-associated OC.<sup>53</sup> Similarly, Vencken et al<sup>71</sup> reported prolonged treatment-free intervals in *BRCA2*- versus *BRCA1*-associated OCs, although no significantly superior primary response rate was detected.

While investigations are beginning to dissect the differential implications of *BRCA1* versus *BRCA2* mutations with regard to chemosensitivity, less is known about the implications of the exact mutation site within each of the two genes. Recent work has begun to elucidate the distinct implication of frameshift-inducing mutations that occur in exon 11 of *BRCA1*.<sup>72</sup>

In vitro, cells harboring *BRCA1* exon 11 frameshifting mutations (E11mut) were found to express a *BRCA1* isoform missing the majority of exon 11 (*BRCA1*Δ11q). While wild-type cells and cells harboring mutations outside of exon 11 (OE11mut) displayed resistance and sensitivity to cisplatin, respectively, E11mut cells displayed partial platinum resistance.<sup>72</sup> E11mut cells were able to form RAD51 and

BRCA1 foci in response to ionizing radiation, indicating at least partial HRR proficiency. Interestingly, a recent investigation of OC patients harboring *BRCA1* exon 11 mutations revealed no significantly superior platinum response rate versus the wild-type population.<sup>73</sup>

While the functional characterization of *BRCA1* exon 11 remains poor, shrouding the mechanisms that underpin the partial HRR proficiency of E11mut cells, mutations in better characterized portions of the gene have also been correlated with chemosensitivity.<sup>74,75</sup> Recent investigations suggest that while BRCA1 RING domain function appears important for tumor suppression, hypomorphic BRCA1 isoforms lacking RING domain function display platinum resistance.<sup>74,75</sup> Introduction of the missense *brca1*<sup>C61G</sup> mutation into murine models demonstrated the poor efficacy of platinum agents against *brca1*<sup>C61G</sup> breast carcinomas in a study by Drost et al.<sup>74</sup> They later compared the effects of two *BRCA1* truncating mutations, reflecting two known founder mutations in the Ashkenazi Jewish population, on chemosensitivity.<sup>75–77</sup> This study demonstrated that introduction of *brca1*<sup>185stop</sup>, reflective of the *BRCA1*<sup>185delAG</sup> founder mutation, led to production of a RING-less BRCA1, which mediated resistance to cisplatin.<sup>75</sup>

Together, these data demonstrate a clear differential impact for different *BRCA* mutations. While both *BRCA1* and *BRCA2* mutations confer superior sensitivity to platinum-based chemotherapy, this phenotype may be exaggerated in *BRCA2*-associated OC. This is perhaps because *BRCA2*-associated OC is rendered HRR defective to a greater extent than *BRCA1*-associated tumors, manifesting as extensive genomic instability and exquisite sensitivity to DNA damage.<sup>53</sup> Furthermore, evidence that not all *BRCA1* mutations are equal is beginning to emerge. Specifically, mutations in exon 11 and mutations that abrogate RING domain function appear to result in the production of hypomorphic BRCA1 isoforms that mediate resistance to platinum agents but still predispose carriers to OC development.<sup>72–74</sup> This is consistent with the multifunctional role of BRCA1 in tumor suppression and suggests that multiple aspects of BRCA1 functionality, particularly RING domain function, appear dispensable for HRR function.

## Taxanes

Taxanes are typically used in combination with platinum agents in the treatment of OC but can also be used as single agents, usually in the context of platinum resistance.<sup>4,78–80</sup> They are distinct from DNA-damaging agents in their mechanism of action, primarily functioning via induction

of cell cycle arrest at the spindle assembly checkpoint through disruption of microtubule disassembly.<sup>81</sup> Paclitaxel sensitivity may therefore be dependent on intact cell cycle checkpoint regulation. Indeed, paclitaxel treatment has been shown to induce acute G2/M arrest in the context of BRCA1 expression.<sup>82</sup> Given both the known function of BRCA1 in cell cycle checkpoint regulation and the suggestion that there may be an inverse relationship between paclitaxel and cisplatin sensitivity in a range of malignancies, cells may be expected to demonstrate paclitaxel resistance in the absence of BRCA1 function.<sup>23,24,83</sup>

A number of in vitro studies have provided evidence that BRCA1 may play a role in modulating paclitaxel sensitivity.<sup>82,84–89</sup> BRCA1-defective BC and head and neck squamous cell carcinoma (HNSCC) cells are more resistant to paclitaxel treatment versus BRCA1-proficient cells, suggesting *BRCA1*-associated OC may display paclitaxel resistance.<sup>82,84–87</sup> Additionally, BRCA1 loss appears to modulate microtubule dynamics rendering them less susceptible to the action of paclitaxel.<sup>88</sup> However, some in vitro studies have reported conflicting results on the role of BRCA1 in modulating taxane sensitivity.<sup>90</sup>

In line with the notion that BRCA1 deficiency may mediate taxane resistance, expression of BRCA1 was associated with longer time to progression in a taxane-treated cohort of BC.<sup>91</sup> However, clinical data regarding the sensitivity of *BRCA*-linked OC to taxane monotherapy are severely limited, with most data described in the context of combination with platinum agents. There has been a suggestion that OC expressing high *BRCA1* mRNA levels may benefit from addition of taxanes to platinum, while those with low levels do not, though these data are yet to be confirmed in a comprehensive cohort of OC.<sup>92</sup> It has been shown that *BRCA*-linked OC can benefit from paclitaxel monotherapy in both the platinum-sensitive and platinum-resistant relapsed disease settings (response rate 60%, 9 of 15 patients and 33%, 3 of 9 patients, respectively); however, meaningful comparison of taxane monotherapy efficacy between *BRCA*-linked and *BRCA* wild-type OC has not been conducted.<sup>93</sup> Critically, the existing data have examined *BRCA*-associated OC as a single entity.

While the current data suggest that *BRCA1*-associated OC may be more resistant to paclitaxel, further studies are required to investigate this relationship in the clinical setting.<sup>71</sup> Given the preclinical evidence suggesting that *BRCA1* mutation specifically may mediate taxane resistance, a comprehensive comparison of *BRCA*-mutant versus *BRCA* wild-type OC in a gene-specific manner, is now needed to

elucidate the implication of *BRCA* status with regard to taxane monotherapy. Because *BRCA2* appears to function almost exclusively in HRR, and the mechanism of action of taxanes does not seem to involve induction of DNA damage, there is no clear rationale for differential paclitaxel sensitivity between *BRCA2*-associated and *BRCA* wild-type OC. This represents a potential pitfall for therapeutic stratification of taxanes while all *BRCA*-associated OCs continue to be considered as a single clinical entity. Future stratification within this population specifically will require a wider appreciation of the distinction between “BRCA1ness” and “BRCA2ness” in clinical practice.

## Nonplatinum DNA-damaging agents

Nonplatinum nontaxane chemotherapies are also used in the treatment of OC, primarily in the platinum-resistant relapsed disease setting.<sup>94,95</sup> Pegylated liposomal doxorubicin (PLD) represents one such drug whose mechanism of action involves DNA damage.

Retrospective studies examining differential response rate to PLD have reported superior response and superior clinical outcome after PLD treatment in *BRCA*-associated OC versus nonhereditary disease.<sup>96,97</sup> Differential sensitivity to nonplatinum DNA-damaging agents between *BRCA1*- and *BRCA2*-mutated OC may be expected to reflect those observed for platinum agents; however, these comparisons are yet to be made in the context of PLD monotherapy. Similarly, mutations in *BRCA1* exon 11 or mutations that affect RING domain function may be expected to confer differential sensitivity phenotypes versus other *BRCA1* mutations.

## Intraperitoneal chemotherapy administration

While the majority of OC treatment is given intravenously (IV), chemotherapy may also be administered intraperitoneally (IP).<sup>4,98,99</sup> IP chemotherapy achieves higher concentrations of drug within the peritoneum compared to IV administration, delivering dose intense chemotherapy to the tumor.<sup>99–101</sup>

Multiple randomized trials have shown a survival benefit for IP administration in advanced-stage OC, particularly in the context of optimal surgical debulking.<sup>102–106</sup> Although uptake of IP administration has increased, IV therapy remains the predominant treatment protocol in many centers.<sup>107</sup> Cost and resource implications for IP administration, as well as increased therapy-associated gastrointestinal toxicity, pain, and infection among IP-treated patients, have undoubtedly contributed to variable uptake of treatment regimens.<sup>108</sup> Thus,

identification of OC subgroups who are likely to benefit most from IP administration is an area of keen research interest.

Because *BRCA*-mutant OC is hypersensitive to platinum agents, it is plausible that *BRCA* status modulates the efficacy of this dose intense administration route. This hypothesis has in part been explored in the GOG 172 study: this phase III trial comparing IP versus IV cisplatin and paclitaxel reported greater clinical benefit for OC in the IP arm whose patients expressed low levels of *BRCA1* protein.<sup>109</sup>

These data suggest an interaction between *BRCA* status and administration route: the higher concentrations of chemotherapy achieved locally during IP treatment may well be particularly effective in treating HRR-defective tumors. Importantly, these data were limited to immunohistochemistry of *BRCA1* protein, and we therefore await translational analysis of IP-treated OC with matched sequencing data for both *BRCA1* and *BRCA2* in order to fully overlap these genomic features with IP chemotherapy outcome. Analysis of IP chemotherapy efficacy in *BRCA* wild-type OC will undoubtedly shed light on whether the clinical benefit, if any, experienced in this patient group is outweighed by excessive toxicity.

## Neoadjuvant chemotherapy

Historically, standard OC treatment begins with primary debulking surgery (PDS) of the tumor mass followed by adjuvant platinum-based or platinum-taxane combination chemotherapy.<sup>4</sup> However, neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) is increasingly used in OC management and is thought to reduce postsurgical mortality and morbidities.<sup>110,111</sup> Two large trials have demonstrated NAC as noninferior to PDS in the treatment of advanced stage OC.<sup>110,112</sup> However, a recent multi-institutional study reported inferior OS in NAC-treated OC with stage IIIC disease who achieved optimal primary surgical debulking, and there is a clear need to dissect exactly which OC patients will benefit most from NAC versus PDS.<sup>113</sup>

Although there has been no prospective comparison of NAC versus PDS in *BRCA*-associated OC specifically, early data are suggesting that *BRCA*-mutant OC may be associated with improved response to NAC.<sup>114</sup> These findings are consistent with the association between *BRCA* mutation and hypersensitivity with platinum.<sup>8,49,71</sup>

Alarming, and in keeping with the concern that NAC may promote platinum resistance, the limited data available suggest that NAC may provide a selection pressure toward *BRCA*-proficient cells.<sup>114</sup> NAC may therefore compromise the exquisite platinum sensitivity of *BRCA*-associated OC

by exposing a clonally diverse mass to the selection pressure of DNA-damaging agents.<sup>115,116</sup> Thus, *BRCA* carriers may benefit most from PDS followed by adjuvant chemotherapy directed at residual disease, in the hope that HRR-proficient subclones representing a route of chemoresistance may have been surgically removed prior to application of a selection pressure.

## Sensitivity to PARP inhibition

Cells harboring *BRCA1* or *BRCA2* mutation are heavily reliant upon PARP-mediated DNA repair of ssDNA breaks.<sup>117</sup> PARP-inhibited cells are thought to accumulate ssDNA damage, which is converted to DSBs during subsequent cellular replication, whether through defective ssDNA damage repair or PARP trapping at DNA damage sites.<sup>117–120</sup> In the context of HRR deficiency, accumulation of unrepaired DSBs results in cytotoxicity and cell death, and *BRCA* mutations therefore exhibit synthetic lethality with PARP inhibition.<sup>121</sup> Indeed, the PARP inhibitors olaparib, rucaparib and niraparib have shown marked antitumor activity in monotherapy or maintenance phase II and phase III trials of OC patients with particularly marked efficacy demonstrated in patients with germline *BRCA* defects.<sup>122–130</sup> Olaparib and rucaparib are now licensed by the FDA as a monotherapy for recurrent OC in this patient population and olaparib is licensed by the European Medicines Agency as a maintenance therapy following a response to chemotherapy in patients with germline or somatic *BRCA* mutations.

While both *BRCA1* and *BRCA2* mutations sensitize cells to PARP inhibition, the affected gene appears to have a modulating effect on sensitivity: *BRCA1*-defective cells demonstrate ~60-fold increase in sensitivity to olaparib versus *BRCA* wild-type cells, while the corresponding increase in sensitivity in *BRCA2*-defective cells is ~130-fold.<sup>121</sup> However, data regarding differential response rates of *BRCA1* versus *BRCA2* carriers to PARP inhibition in the clinical setting are currently limited. Some data suggest a trend for slightly superior response rate in *BRCA2*-associated OC treated with PARP inhibitors, while others report no difference in sensitivity or PFS, and the consensus remains that *BRCA*-associated OC is considered as a single clinical entity with regard to PARP inhibitor sensitivity.<sup>122–130</sup>

While the distinction in sensitivity between *BRCA1*- and *BRCA2*-associated OCs remains unclear in the clinical setting, emerging in vitro data suggest that the location of *BRCA1* mutation may influence the efficacy of PARP inhibitors.<sup>72,74,75</sup> Consistent with the notion that the hypomorphic *BRCA1* isoform *BRCA1Δ11q* can mediate partial

HRR function and consequentially platinum resistance, cells harboring *BRCA1* E11mut cells also appear to display an intermediate partially PARP inhibitor-resistance phenotype.<sup>72</sup> Similarly, loss of *BRCA1* RING domain function appears insufficient to fully sensitize cells to PARP inhibition, while still predisposing to cancer development.<sup>74,75</sup>

Given the financial implications of targeted therapy use in routine clinical practice, identifying patients most likely to benefit from these drugs is of great importance. Comparison of PARP inhibitor sensitivity in patients harboring *BRCA1* exon 11 and RING domain mutations with *BRCA* wild-type patients is warranted to determine whether these patients represent a truly HRR-deficient population that benefit from PARP inhibition.

## BRCA mutations in acquired therapy resistance

In recent years, secondary *BRCA* mutations have been implicated in platinum and PARP inhibitor resistance.<sup>131</sup> These mutations restore *BRCA* function and HRR proficiency by restoring open-reading frames, reverting mutant alleles back to wild type or removing premature stop codons.<sup>132–138</sup> Such mutations are a known mechanism of cisplatin and PARP inhibitor resistance when deriving drug-resistant clones in vitro.<sup>133–135</sup> In keeping with the notion that these secondary events are associated with acquired therapy resistance, secondary *BRCA2* mutations have been detected in cell lines derived from patients subsequent to chemotherapy, and these cells are reported to display platinum resistance.<sup>133,134,139,140</sup>

Mutational analysis of clinical specimens has also revealed the presence of secondary *BRCA* sequence events.<sup>132–138</sup> Secondary mutations have been detected in both *BRCA1* and *BRCA2* and correlated with resistance to platinum-based chemotherapy.<sup>132–135,138</sup> Analysis of BC and OC with acquired PARP inhibitor resistance has also uncovered secondary *BRCA* reversion events and demonstrated their potential to predict platinum and PARP inhibitor resistance at recurrence in *BRCA*-associated OC.<sup>136,137</sup>

## Clinical outcome

### Progression-free survival

Multiple studies have investigated the prognostic significance of *BRCA* mutations on PFS and OS within OC.<sup>8,47,53,66,71,141–146</sup> It has become clear that, together, *BRCA*-associated disease represents a subgroup of OC that experiences superior PFS, with studies reporting *BRCA*-mutant patients experience PFS around twice that of their *BRCA* wild-type counterparts.<sup>71,144–146</sup> Although many studies have failed to

analyze PFS in a gene-specific manner, others have suggested that *BRCA1*-associated OC may experience inferior PFS versus *BRCA2*-associated OC.<sup>53,71,147</sup> Indeed, some investigators have suggested that *BRCA1*-associated OC may not experience a PFS benefit compared to *BRCA* wild-type OC.<sup>53,148</sup>

A recent meta-analysis of over 18,000 OC patients reported superior PFS in both *BRCA1*- and *BRCA2*-associated OCs.<sup>149</sup> They reported HRs for PFS in *BRCA1*- and *BRCA2*-associated versus *BRCA* wild-type OC of 0.68 (95% CI, 0.52–0.89) and 0.48 (95% CI, 0.30–0.75), respectively. Interestingly, a recent study of *BRCA1* exon 11 mutation-associated OC revealed no PFS benefit versus the wild-type population, suggesting an interaction between mutation site and PFS.<sup>73</sup>

## Overall survival

A fundamental characteristic of the BRCAness phenotype is superior OS.<sup>8,47,53,141,146,150–154</sup> Recent work has begun to elucidate the distinction between *BRCA1* and *BRCA2* mutations with regard to survival.<sup>53,66,143,155</sup> The current consensus is that both *BRCA1*- and *BRCA2*-mutated OCs experience superior short-term OS; however, this survival advantage seems exaggerated in *BRCA2*- versus *BRCA1*-mutant disease.<sup>66,143,147,155,156</sup> Five-year survival in *BRCA1*- and *BRCA2*-mutant OC is estimated at ~44% and 52%–61%, respectively, versus ~25%–42% in *BRCA* wild-type OC.<sup>53,66,143</sup>

While *BRCA2* carriers continue to experience superior long-term OS, the survival of *BRCA1*-mutant OC patients appears limited to ~5 years, with investigators reporting no 10-year OS advantage in this group.<sup>143,155</sup> Hyman et al<sup>155</sup> reported long-term survival benefit in *BRCA2*-associated serous OC versus the *BRCA* wild-type population, with no such benefit in the *BRCA1*-mutant population. Later, Candido-dos-Reis et al<sup>143</sup> reported 10-year OS in *BRCA1*-associated, *BRCA2*-associated and *BRCA* wild-type OC of 25%, 35% and 30%, respectively, in a large cohort of OC. Their study showed an increasingly detrimental effect for *BRCA1* mutation after ~5 years compared to both *BRCA2*-mutated and *BRCA* wild-type populations.

The recent meta-analysis by Xu et al<sup>149</sup> reported HRs for OS in *BRCA1*- and *BRCA2*-associated versus *BRCA* wild-type OC of 0.73 (95% CI, 0.63–0.86) and 0.57 (95% CI, 0.45–0.73), respectively. The study by Dimitrova et al<sup>73</sup> of *BRCA1* exon 11-associated OC revealed no 5-year OS benefit in this population versus the wild-type population, suggesting that all *BRCA1* mutations are not equal in conveying survival advantage.

## Key future research avenues

### Dissecting BRCA1ness from BRCA2ness

A key aim of future research is to continue to dissect the distinct phenotypes of *BRCA1*- and *BRCA2*-associated OCs, both from one another and from *BRCA* wild-type OC. Critically, this will rely on investigators conducting gene-specific analyses. It is becoming clear that patients with *BRCA2*-associated OC experience an exaggerated BRCAness phenotype, displaying superior long-term OS in comparison to *BRCA1*-associated OC, and emerging data suggest that superior PFS and platinum sensitivity may also be exaggerated in this patient group.<sup>53,66,71,143,147,148,155,156</sup>

Future studies should aim to elucidate the differential sensitivity, if any, of *BRCA1*- and *BRCA2*-associated OCs to nonplatinum agents, including nonplatinum DNA-damaging agents, taxanes and PARP inhibitors. It has been suggested that *BRCA1*-associated OC may be more resistant to paclitaxel, and we await data from independent cohorts investigating the potential impact of *BRCA1* and *BRCA2* mutations with regard to taxane monotherapy sensitivity.<sup>71,82,84–89,91,92</sup> While in vitro data suggest that *BRCA2*-mutant cells are more sensitive to PARP inhibition compared to *BRCA1*-mutant cells, this comparison is yet to be made in the clinical setting.<sup>122–130</sup> Similarly, characterization of how *BRCA1* and *BRCA2* mutations may modulate clinical outcome in the context of NAC and IP chemotherapy administration is now warranted. An appreciation of the distinction between BRCA1ness and BRCA2ness by both researchers and clinicians will be paramount in the translation of findings from these studies into clinical practice.

### Correlating mutation site and type to chemosensitivity and clinical outcome

While some studies have investigated the impact of *BRCA1* and *BRCA2* mutation site on chemosensitivity and OC versus BC predisposition, the differential impact of distinct *BRCA* mutation sites remains largely understudied.<sup>40–46</sup>

Growing data suggest that *BRCA1* E11mut cells display a distinct partially platinum- and PARP inhibitor-resistant phenotype, and OC patients harboring *BRCA1* mutations in exon 11 may not experience a BRCAness survival benefit.<sup>72,73</sup> Similarly, *BRCA1* mutations affecting RING domain function may also not display hypersensitivity to platinum or PARP inhibition.<sup>74,75</sup> Further investigation of these findings in well clinically annotated OC datasets is now warranted to elucidate whether these groups of patients represent a non-BRCAness, partially HRR proficient subgroup of OC. It may transpire that after removal of these patient groups,

the characteristics of the remaining “true” *BRCA1*-mutant HRR-deficient population may be more *BRCA2* like.

While some progress has been made investigating site-specific implications of *BRCA1* mutation, correlation of *BRCA2* mutation site with platinum sensitivity, PARP inhibitor efficacy and survival is yet to be drawn. These investigations are likely to be hindered by the relative rarity of *BRCA2* versus *BRCA1* mutation and will require large multinational retrospective cohorts of OC. Furthermore, while *BRCA1* is multifunctional – providing a rationale for differential modulation of HRR activity with varying mutation site – *BRCA2* appears to function almost exclusively in HRR, and phenotypic differences between mutation sites may therefore be subtle. Indeed, *BRCA2* mutation site may not influence chemosensitivity or survival.

## Characterizing secondary *BRCA* mutations and their implications for treatment failure

Increasingly, research efforts have turned to characterizing mechanisms of acquired chemoresistance in *BRCA*-associated OC. Emergence of disease displaying secondary *BRCA* sequence changes that restore protein function has now been demonstrated in both the preclinical and clinical settings and has been correlated with therapy resistance.<sup>132–138</sup> Whether these changes arise de novo or through selection of preexisting subclones already present at diagnosis remains an area of keen interest and could influence the selection of NAC versus PDS. Furthermore, investigation into whether different mutation types display differential propensity for reversion – and indeed whether these correlate with prolonged sensitivity to platinum and PARP inhibitors – is yet to be undertaken. Collection of temporally and spatially separated biopsies throughout the disease journey in *BRCA*-associated OC will be invaluable in correlating acquisition of reversion events with clinical outcome, particularly with regard to platinum and PARP inhibitor sensitivity. Studies should aim to identify the frequency at which clinically relevant secondary *BRCA* mutations arise, the potential therapeutic options to rescue resistance in *BRCA*-reverted patients and whether these mutations arise de novo or are present in subclonal populations at diagnosis.

## Conclusion

Clearly, substantial advances in defining the characteristics of *BRCA*-associated OC have been made in the past decade. Emerging data are beginning to illuminate the distinction

between *BRCA1*- and *BRCA2*-associated OCs, highlighting distinctions between *BRCA1*ness and *BRCA2*ness, consistent with the discrete functions of the *BRCA1* and *BRCA2* gene products. However, dissecting the characteristics of these two distinct OC patient populations from one another is an area of ongoing research.

Perhaps most intriguingly, it is becoming clear that not all *BRCA1* mutations are equal and that mutations at particular sites – most notably within exon 11 and those affecting *BRCA1* RING domain function – may not confer a *BRCA*-ness phenotype. Instead, their role may be confined to compromising the tumor suppressive function of *BRCA1*, rather than inducing HRR deficiency, and thus chemosensitivity. We await further clinical data on the implications of mutations at these sites, particularly with regard to sensitivity to platinum-based agents and the efficacy of PARP inhibitors. Investigation of the impact, if any, of other *BRCA1* mutation sites and of different *BRCA2* mutations is eagerly anticipated.

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