The addition of new drugs to standard therapy in the first-line treatment of ovarian cancer

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Advanced-stage epithelial ovarian cancer is generally managed with cytoreductive surgery and chemotherapy consisting of carboplatin and paclitaxel, achieving clinical complete remission in the majority of patients. However, most tumors recur, and are associated with progressive chemotherapy resistance. Techniques to optimize chemotherapy have included intraperitoneal administration and weekly scheduling of paclitaxel. Efforts to improve on the long-term results of primary therapy through addition of a third cytotoxic agent have not been successful, including extended maintenance, as well as strategies to overcome chemotherapy resistance. Limited data emerging from phase III trials using bevacizumab suggest some advantage in progression-free survival, particularly in the maintenance setting, and further data are awaited. At present, primary therapy with carboplatin and paclitaxel remains a well-tolerated standard regimen, including the option of weekly paclitaxel dosing, intraperitoneal delivery and neoadjuvant therapy in selected patients. Emerging biological paradigms will hopefully contribute to individualized treatment options in the future.

Key words: angiogenesis, carboplatin, chemotherapy, chemotherapy resistance, dose-density, ovarian carcinoma

optimized primary treatment

Current optimal management of advanced-stage ovarian cancer includes maximal cytoreductive surgery and a program of chemotherapy with a platinum agent (carboplatin or cisplatin) and paclitaxel. While this is a validated, well-tolerated and effective approach, there are areas of controversy, as well as emerging data that will guide future standards. In addition, there are acceptable variations in clinical practice as applied to individual patients, including intraperitoneal drug administration and neoadjuvant chemotherapy. A number of strategies have been evaluated with the goal of overcoming drug resistance and improving long-term treatment outcomes, including dose intensity, maintenance–consolidation, schedule variations, regional hyperthermia and incorporation of additional cytotoxic or molecular targeted agents.

Platinum compounds remain dominant as the most active category of cytotoxic agents. Improvements in the therapeutic ratio of platinum-based primary chemotherapy have been achieved through the development of better tolerated analogs (carboplatin), together with evolving data on dosing, sequence and duration of treatment [1–4]. In general, the administration of higher doses of chemotherapy with hematopoietic support, or extended administration of multiple cycles of chemotherapy (beyond six cycles), has not improved long-term outcomes, and these strategies carry an increased risk of serious cumulative toxicity [5–7].

In view of the importance of paclitaxel, a number of studies have evaluated the dose, schedule, sequence and route of administration [8–12]. Longer infusions (>24 h) increase mucosal and bone marrow toxicity, but without improved efficacy. Shorter infusions (<3 h) are generally better tolerated from a hematological perspective, although higher individual doses can increase the risk of arthralgia–myalgia and neuropathy. Weekly scheduling permits higher cumulative dose delivery, while avoiding hematological toxicity and alopecia, and has demonstrated consistent activity in patients who have recurred within 6 months of primary therapy with conventional carboplatin and paclitaxel [13, 14]. The Japanese Gynecologic Oncology Group (JGOG) conducted a phase III trial in women with newly diagnosed advanced-stage ovarian cancer, demonstrating superiority of weekly dose-dense paclitaxel in combination with standard doses of carboplatin compared with standard scheduling of the same drugs [15]. This is an important finding, illustrating the need to examine carefully how we use established agents, in addition to strategies to incorporate new agents. Ongoing phase III trials through the GOG and other groups aim to extend the JGOG findings, including integration with intraperitoneal chemotherapy and molecular targeted agents. Of note, the GOG0172 phase III trial of intraperitoneal chemotherapy incorporated a second dose of paclitaxel (intraperitoneal) on day 8, which may have contributed to the superiority of the experimental arm [16].

There had been considerable interest in the incorporation of a third cytotoxic agent, balanced by expectations of increased host toxicity. However, based on multiple international phase III trials involving >10 000 women to evaluate topotecan,
gemcitabine, pegylated liposomal doxorubicin and epirubicin, the addition of a third cytotoxic agent has not been shown to improve long-term clinical outcomes [17–21]. Some agents, such as topotecan and gemcitabine, exhibit schedule- and sequence-dependent hematological toxicity, particularly when combined with carboplatin. These agents can interfere with repair of platinum–DNA adducts, but often at the expense of increased hematological toxicity. In contrast, combinations of paclitaxel with carboplatin are well tolerated, with the capability of administering full doses of both drugs. This has been attributed to a ‘platelet-sparing’ effect of paclitaxel on carboplatin-mediated thrombocytopenia, raising questions about possible drug–drug antagonism [22]. Indeed, one potential advantage of weekly paclitaxel could be the temporal separation from carboplatin, optimizing the cytotoxicity of both agents.

In reviewing the cumulative results of these phase III trials, one is struck by the consistent lack of benefit, including subpopulations with more favorable prognostic features, such as microscopic optimal cytoreductive surgery. At some level, this is perplexing, in view of previously documented single-agent activity for these agents and a demonstrated benefit in combination with carboplatin in the setting of platinum-sensitive recurrent disease for gemcitabine [23] and pegylated liposomal doxorubicin [24].

There are several potential explanations for these observations:

• First, perhaps the dose or schedule of chemotherapy was not optimal to reveal a benefit. This would appear unlikely, as there are several trials with similar agents using different doses, sequences or schedules. In view of the large number of patients, one might hypothesize a trend for improvement, even if the dosing was suboptimal.

• Secondly, perhaps only a subset of patients is sensitive to each new agent, but this effect is lost in the setting of a trial with randomized allocation of drugs among the entire population. In theory, this could be evaluated by tumor profiling of chemotherapy response. However, in order to define a true predictive marker of response, it would still require randomized assignment of treatments to patients with tumor profiles. While potentially important, this explanation also seems unlikely, as there should still be a smaller trend for improvement associated with incorporation of new agents, which was not observed.

• Thirdly, it is possible that the effectiveness of primary therapy (as defined by short-term outcomes) may limit the opportunity to observe incremental benefit from a new agent. Ovarian tumors are initially platinum sensitive, and most patients achieve a complete remission following maximal cytoreductive surgery and primary chemotherapy, consistent with several logs of tumor kill, even though frequently followed by recurrence. It is possible that the addition of a third active (but non-curative) agent might contribute very little to this pre-existing pattern of tumor response and short-term outcomes.

The last argument is supported by two observations. In particular, it may explain the somewhat paradoxical benefit of platinum-based combinations in the setting of recurrent disease, when these same combinations have not demonstrated increased benefit in the front-line setting. Platinum-sensitive recurrence is simply not the same as newly diagnosed disease. While remissions do occur, it is less common to observe a complete remission, the time to further disease progression is generally shortened and a higher proportion of tumors will demonstrate rapid evolution of platinum resistance during treatment. In this setting, a second (or third) drug with additive benefit, particularly against tumors that are becoming platinum resistant, may show an advantage in clinical outcomes.

Limited supplemental benefit of additional cytotoxic drugs in the front-line setting could also reflect tumor biology. There are emerging data regarding stem-like behavior observed in subpopulations of ovarian cancer cells, including dormant cells with a low mitotic index that exclude cytotoxic drugs from their cytoplasm and demonstrate increased resistance to chemotherapy. These stem-like populations are generally enriched following primary chemotherapy, and could limit the effectiveness of any third agent [25, 26]. Potential molecular targets have been identified in stem cell populations, including pathways associated with differentiation, renewal and progenitor activities. It remains to be determined if these pathways can be specifically targeted in tumor populations.

If these biological and clinical observations have merit, it might indeed be quite difficult to improve further on the results of primary cytoreductive surgery and platinum-based chemotherapy without new therapies specifically targeted to fundamental molecular pathways with key relevance to ovarian cancer.

As an alternative strategy, some studies have evaluated a third agent as maintenance therapy for patients in remission after completion of primary therapy. In general, maintenance chemotherapy has not been associated with improved clinical outcomes in solid tumors, and is clearly associated with an increased risk of cumulative toxicity. In women with ovarian cancer, all studies using chemotherapy have been negative, with the exception of one study evaluating extended paclitaxel administered on a 3-week schedule [27–31]. In that study, there was an early difference in progression-free survival favoring extended therapy, and the trial was closed by recommendation of the data monitoring committee following a scheduled interim analysis. This observation remains controversial, due to the risk of toxicity, and uncertain clinical benefit associated with a modest improvement of progression-free survival (that was actually less than the difference in total treatment times), as well as an absence of any survival benefit (although the trial was not powered to determine overall survival). GOG is currently completing a phase III maintenance trial that will attempt to resolve the question, but other studies of maintenance paclitaxel have been negative, and there is not currently any established role for maintenance chemotherapy in women with ovarian cancer. Other studies are evaluating maintenance using newer molecular targeted agents in patients following primary therapy, or in patients with remission after therapy for recurrent disease.

The timing of cytoreductive surgery has also been prospectively evaluated in phase III trials. Interval cytoreduction in appropriate patients (after three cycles of
with serous or endometrioid subtypes [39, 40]. International platinum-based chemotherapy, and patients with advanced verified that mucinous tumors are not generally responsive to collaborative retrospective review of international data has of src kinase. prompting clinical evaluation of dasatinib and other inhibitors [38]. Core components of EMT are under control of src kinase, expression profiles, even without visible evidence of sarcoma features have also been identified through analysis of gene enzymes and invasive behavior. Aggressive mesenchymal contribute to cellular motility, production of proteolytic (such as epithelial membrane antigen) and up-regulation of (EMT) associated with down-regulation of epithelial markers ( aflibercept), blockade of the VEGF receptor-2 (VEGFR2) with monoclonal antibodies (IMC-1C11) or inhibition of receptor-associated tyrosine kinase with low molecular weight inhibitors (axitinib, cediranib, pazopanib, sorafenib or BIBF 1120). Indirect strategies include targeting genes involved in the regulation of VEGF expression, such as hypoxia-inducible factor 1-α (HIF1α), antibody-based blockade of angiopoietin-2 (CVX-060), inhibition of cytoplasmic tyrosine kinases that are activated following VEGF receptor-mediated phosphorylation, inhibition of protein kinase C β (enzastaurin) or interference with other convergence pathways, such as the serine-threonine-specific protein kinase (AKT) or the mammalian target of rapamycin (mTOR).

In contrast, high-grade serous tumors tend to have inactivation of p53 through chromosomal deletion and/or mutation, and are initially sensitive to platinum-based chemotherapy. Some high-grade ovarian cancers are associated with sarcomatous differentiation, recognized as carcinosarcomas or mixed Müllerian tumors. This is thought to occur through a process of epithelial–mesenchymal transition (EMT) associated with down-regulation of epithelial markers (such as epithelial membrane antigen) and up-regulation of mesenchymal markers (such as vimentin) [37]. These changes contribute to cellular motility, production of proteolytic enzymes and invasive behavior. Aggressive mesenchymal features have also been identified through analysis of gene expression profiles, even without visible evidence of sarcoma [38]. Core components of EMT are under control of src kinase, prompting clinical evaluation of dasatinib and other inhibitors of src kinase.

Although primary ovarian mucinous tumors are rare, collaborative retrospective review of international data has verified that mucinous tumors are not generally responsive to platinum-based chemotherapies, and patients with advanced mucinous tumors have inferior long-term survival, compared with serous or endometrioid subtypes [39, 40]. International collaborative trials have been initiated to evaluate alternative regimens modeled after colorectal adenocarcinoma.

Advanced stage clear cell tumors exhibit more aggressive patterns of metastatic spread and are frequently resistant to platinum-based chemotherapy. Analysis of gene expression profiles has identified characteristic patterns associated with clear cell tumors from other primary sites, but optimal treatment strategies for clear cell tumors of ovarian origin remain to be defined.

**targeting angiogenesis**

High-grade serous ovarian cancer is characterized by overexpression of vascular endothelial growth factor (VEGF), which drives dysfunctional tumor-associated angiogenesis, contributing to high interstitial pressure and production of ascites. Direct targeting of this pathway can be achieved by sequestration of VEGF protein using monoclonal antibodies (bevacizumab) or engineered binding site molecules (aflibercept), blockade of the VEGF receptor-2 (VEGFR2) with monoclonal antibodies (IMC-1C11) or inhibition of receptor-associated tyrosine kinase with low molecular weight inhibitors (axitinib, cediranib, pazopanib, sorafenib or BIBF 1120). Indirect strategies include targeting genes involved in the regulation of VEGF expression, such as hypoxia-inducible factor 1-α (HIF1α), antibody-based blockade of angiopoietin-2 (CVX-060), inhibition of cytoplasmic tyrosine kinases that are activated following VEGF receptor-mediated phosphorylation, inhibition of protein kinase C β (enzastaurin) or interference with other convergence pathways, such as the serine-threonine-specific protein kinase (AKT) or the mammalian target of rapamycin (mTOR).

Thus far, the most widely studied agent has been bevacizumab, initially as a single agent, and subsequently in phase III trials with concurrent chemotherapy and maintenance [41, 42]. When evaluated in combination with chemotherapy, bevacizumab was associated with improved long-term outcomes in other tumors, achieving regulatory approval in colon cancer, non-squamous lung cancer and breast cancer. These observations have been attributed to improved drug delivery as a result of pseudo-normalization of tumor vasculature and a reduction in interstitial pressure. However, this hypothesis has not actually been validated in clinical studies, and there are other actions associated with VEGF that could have an impact on tumor behavior.

Single-agent activity with bevacizumab in recurrent ovarian cancer is more substantial than previously observed in most other tumor types. As such, it is has been anticipated that combinations of bevacizumab with carboplatin and paclitaxel will improve long-term outcomes for women with ovarian cancer. These combinations are currently under evaluation in several phase III trials, in the setting of primary therapy for both newly diagnosed disease (GOG0218, ICON7) and recurrent disease (GOG0213). Each of these trials also includes maintenance administration of single-agent bevacizumab after completion of chemotherapy, based on experience in other clinical settings.

Only one phase III trial (GOG0218) is prospectively evaluating the role of maintenance bevacizumab (compared

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**biological advances with an impact on primary therapy**

In advanced stage serous tumors, distinct molecular profiles have been associated with low-grade (type I) compared with high-grade (type II) neoplasia [35, 36]. Low-grade invasive adenocarcinoma generally arises in conjunction with borderline tumors of low malignant potential. These tumors are not generally sensitive to platinum-based chemotherapy, retain functional p53 and harbor activating mutations of either B-raf or K-raf. Activated RAS triggers phosphorylation and activation of RAF kinase which then phosphorylates cytoplasmic mitogen-activated protein kinases (MAPKs) that include MEK-1/2. Activated MEK then phosphorylates ERK-1/2 which dimerizes and translocates to the nucleus, where it can regulate cellular proliferation. This important pathway is activated by a diverse group of extracellular signals including integrins, receptors for epidermal growth factor, platelet-derived growth factor and insulin-like growth factor-1, as well as various cytokines. Specific tyrosine kinase inhibitors, such as AZD6244, have been developed to target MEK-1/2, a central pathway component. GOG has completed a phase II study of AZD6244 in low-grade ovarian adenocarcinoma, and this may provide an important strategy to build new combinations.

In contrast, high-grade serous tumors tend to have inactivation of p53 through chromosomal deletion and/or mutation, and are initially sensitive to platinum-based chemotherapy. Some high-grade ovarian cancers are associated with sarcomatous differentiation, recognized as carcinosarcomas or mixed Müllerian tumors. This is thought to occur through a process of epithelial–mesenchymal transition (EMT) associated with down-regulation of epithelial markers (such as epithelial membrane antigen) and up-regulation of mesenchymal markers (such as vimentin) [37]. These changes contribute to cellular motility, production of proteolytic enzymes and invasive behavior. Aggressive mesenchymal features have also been identified through analysis of gene expression profiles, even without visible evidence of sarcoma [38]. Core components of EMT are under control of src kinase, prompting clinical evaluation of dasatinib and other inhibitors of src kinase.
with placebo), and only in patients randomized to receive bevacizumab during chemotherapy. Of interest, preliminary data indicate that the arm with concurrent followed by maintenance bevacizumab met the primary study objective for improvement of progression-free survival, but the arm with concurrent bevacizumab followed by maintenance placebo did not meet the primary objective [43]. Pending review of mature data, this appears to be an important finding, and suggests that VEGF blockade may have greater impact in preventing tumor regrowth, or in the management of recurrent disease, rather than augmentation of primary chemotherapy. From a biological perspective, microscopic peritoneal implants might not be an optimal target for VEGF blockade, as they can exist by simple diffusion, below the threshold that would require tumor angiogenesis.

**overcoming chemotherapy resistance**

The most important pattern of resistance observed in ovarian cancer is related to platinum compounds (cisplatin and carboplatin). Resistance is multifactorial, involving decreased active transport, increased efflux, rapid detoxification of platinum through glutathione conjugation, increased DNA damage tolerance, reduced detection of DNA damage, accelerated removal of platinum–DNA adducts, enhanced DNA repair and defective apoptotic signaling, often associated with loss of tumor suppressor protein p53, but also independent of p53. Resistance can be intrinsic, or evolve in response to selective pressures from chemotherapy exposure. As such, some components of resistance might be reversible, over a period of time. Preclinical models have suggested a variety of strategies to prevent or overcome resistance, but these ideas have not successfully translated to clinical practice.

Some chemotherapy agents, such as gemcitabine and topotecan, can interfere with DNA repair, and reliably increase platinum-mediated toxicity. However, these effects are not tumor specific, and are associated with increased hematological toxicity. A sterically hindered platinum compound (picoplatin) was developed to avoid thiol-mediated inactivation, but did not achieve superior clinical outcomes in patients with recurrent disease [44]. It was also thought that oxaliplatin might retain activity in resistant tumors because it forms DNA adducts that are not detected by the mismatch repair system, but only a 7% response rate was observed in patients with a platinum-free interval of <6 months [45]. Components of the mismatch repair system, such as MLH1, can be suppressed by promoter methylation in resistant tumors, prompting studies with a demethylating agent (decitabine) and carboplatin, but without improved efficacy at the expense of increased hematological toxicity [46].

Nucleotide excision repair (NER) is the primary mechanism to remove platinum–DNA adducts, and excision repair cross-complementing-1 (ERCC1) is a critical NER component. Resistance to platinum has been linked to ERCC1 mRNA expression in ovarian cancer and other tumors, and ERCC1 levels are predictive of clinical outcomes in lung cancer patients treated with platinum-based chemotherapy. Whether ERCC1, or other markers, could be used to guide chemotherapy selection in women with ovarian cancer is unknown.

Recent efforts have focused on the biology of platinum influx, largely mediated by copper transporter-1 (CTR1), which can be down-regulated after platinum exposure [47]. Strategies are also under evaluation to restore damage detection and apoptotic signaling in tumor cells via intrinsic or extrinsic pathways, such as restoration of the tumor suppressor gene protein p53, regulation of the antiapoptotic protein Bcl-2, activation of the receptor for tumor necrosis factor (TNF), and TNF-related apoptosis-inducing ligand (TRAIL) R1.

Ovarian tumors can also develop multidrug resistance (MDR) for natural products mediated primarily by drug efflux pumps, such as p-glycoprotein (pGP). Natural substrates for pGP include taxanes, anthracyclines and Vinca alkaloids. A number of inhibitors of pGP MDR function have been developed. The most extensively studied agent has been valspodar, an analog of ciclosporin A, which showed no clinical benefit in a phase III trial with paclitaxel and carboplatin [48]. While these agents can block drug efflux at the cellular level, the effects are not tumor specific, requiring a reduction in chemotherapy dosage, and potentially minimizing any therapeutic advantage. The breast cancer resistance protein (BCRP), or ATP-binding cassette protein G2 (ABCG2), dimerizes to form a membrane-associated energy-dependent efflux pump that is also associated with MDR, primarily to mitoxantrone and camptothecins, including topotecan.

Other cellular adaptations have been associated with resistance to individual cytotoxic agents. Perhaps most important are mutations in β-tubulin subunits, or reversible alterations in the ratio of tubulin β-III isoforms that have a direct impact on taxane sensitivity. Epothilone analogs, such as ixabepilone, appear less sensitive to changes in tubulin isoforms, and can be effective against tumors that are taxane resistant [49]. Down-regulation of topoisomerase I can prevent the formation of cleavable complexes with topotecan. Resistance to gemcitabine can be mediated by decreased active membrane transport, reduced phosphorylation related to depletion of deoxycytidine kinase, or amplification of the gene for the M2 subunit of ribonucleotide reductase.

Clearly, our understanding of the biology surrounding drug resistance has improved. However, drug resistance still remains a central problem in the treatment of advanced stage ovarian cancer, and these findings have not yet led to interventions with improved clinical outcomes.

**inhibiting DNA repair: synthetic lethality**

Poly [adenosine diphosphate (ADP)-ribose] polymerase (PARP) is a key component in the process of base excision repair of single-strand DNA breaks. Inhibition of PARP leads to the accumulation of DNA single-strand breaks, which can lead to potentially lethal DNA double-strand breaks at replication forks. However, these breaks are usually repaired by the double-strand homologous recombination pathway, which incorporates the tumor-suppressor proteins BRCA1 and BRCA2. Germline mutations in either BRCA1 or BRCA2 have been associated with an increased risk of developing ovarian cancer, and tumor cells that harbor loss-of-function BRCA mutations (affecting the remaining wild-type allele) are deficient in homologous repair. Importantly, this repair defect
is not shared by normal tissues in the same patient, due to the presence of the remaining wild-type allele.

Inhibition of PARP in a patient with a BRCA1/2 mutation has the potential to create a ‘synthetic lethal’ situation, generating unrepaired single-strand breaks, accumulation of double-strand breaks and collapse of the replication fork. This single-agent treatment strategy is well tolerated and effective in a proportion of women with BRCA1/2 mutations [50, 51]. Inheritable germline mutations only account for perhaps 5% of ovarian cancer. Additional patients may benefit if they have tumors with somatic mutations, or epigenetic silencing of key genes involved in DNA homologous recombination repair [52, 53]. Allowing for all possible scenarios might account for >30% of women with high-grade serous ovarian cancer. Of interest, laboratory studies have documented the appearance of secondary mutations in tumor-associated BRCA1 that can restore expression and overcome the effects of PARP inhibition [54, 55].

PARP inhibitors (olaparib, ABT-881 and BSI-201) can also be utilized to enhance the effects of cytotoxic chemotherapeutics that target DNA, such as carboplatin, gemcitabine and topotecan. However, as with other strategies to overcome drug resistance, there can be increased host toxicity, particularly bone marrow suppression, and randomized trials are in progress to evaluate clinical benefits.

**discussion**

Optimal primary therapy of advanced ovarian cancer has not substantially changed over the last few years, in spite of new cytotoxic agents and evaluation of diverse treatment strategies. Almost all patients undergo at least one attempt at maximal cytoreductive surgery, and the combination of carboplatin and paclitaxel remains a well-tolerated and widely utilized standard treatment regimen. Recent data favor the selected utilization of neoadjuvant chemotherapy in patients with bulky disease, and dose-dense weekly paclitaxel in combination with carboplatin appears superior to standard dosing of paclitaxel. Intraperitoneal cisplatin and paclitaxel can be administered to patients with small-volume residual disease, and new trials are evaluating intraperitoneal delivery of carboplatin to improve patient safety and tolerability.

The integration of emerging biological principles with the development of molecular targeted reagents is starting to achieve meaningful results, especially with regard to inhibition of angiogenesis and interference with PARP-mediated DNA repair. Biological observations have also contributed to our understanding of tumor classifications, and prompted the evaluation of individualized treatments. However, the rapid development of drug resistance remains a major clinical challenge for the majority of patients with advanced stage disease, prompting studies that target regenerative subpopulations of resistant cells.

The next few years will see mature data from phase III trials targeting VEGF, and numerous phase II trials with diverse molecular targeted agents. Comparative data among these agents are limited, and selection of high-priority combinations will remain challenging. Our conventional phase I–II–III paradigm was designed for the development of traditional cytotoxic agents with predictable dose-limiting toxicities, such as myelosuppression, and it is not well suited for the efficient evaluation of molecular targeted agents, especially when used in combination, or when designed for chronic administration.

Ideally, phase I trials should define more relevant end points, such as desired serum levels, duration of exposure, sequencing, feasibility of chronic administration at the selected dose, drug–drug interactions and saturation of biological targets. With few exceptions, single-agent phase II trials with targeted agents have not been very informative, and it would be preferable to broadly utilize randomized phase II designs with multiple arms to select promising agents (or combinations) and drop agents that fail to meet appropriate thresholds. In many cases, this would involve multiple pharmaceutical sponsors willing to work together with investigational agents on a single trial, which has been difficult. Finally, phase III trials should include multiple arms with a scheduled interim analysis of safety and futility, allowing the investigators to drop arms that appear non-promising or overly toxic. This type of adaptive research program would address key scientific questions, while efficiently selecting optimal regimens for fully powered phase III evaluation.

**disclosures**

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