Update of randomized trials in first-line treatment

Michael A. Bookman*
Arizona Cancer Center, Tucson, AZ, USA

Advanced-stage epithelial ovarian cancer remains a highly lethal malignancy, in spite of effective cytoreductive surgery and primary chemotherapy. Randomized phase III trials have provided the most consistent platform for the evaluation of new treatment interventions. Recently completed and ongoing international phase III studies in the primary disease setting, summarized and analyzed in the present review, have evaluated multidrug combinations, weekly scheduling, intraperitoneal delivery, neoadjuvant chemotherapy, maintenance therapy and targeting of angiogenesis. The data from these studies have supported the consideration of intraperitoneal cisplatin, dose-dense weekly scheduling of paclitaxel or neoadjuvant chemotherapy with interval cytoreductive surgery in appropriate patient populations.

Contrary to this, the use of three-drug combinations or maintenance chemotherapy is not supported by phase III data. Encouraging data have emerged using antiangiogenic agents, but with questions regarding optimal dose, timing and duration. Ongoing and planned trials will evaluate the inhibition of DNA repair and tailored treatment in accordance with tumor molecular profiles.

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

introduction

Advanced-stage epithelial ovarian tumors are generally managed with cytoreductive surgery and chemotherapy consisting of carboplatin and paclitaxel, achieving clinical complete remission in the majority of patients. Incremental improvements in median progression-free or overall survival have been documented in phase III trials with the incorporation of paclitaxel, the utilization of intraperitoneal therapy in selected patients and dose-dense weekly scheduling of paclitaxel. In addition, the use of neoadjuvant therapy with interval cytoreductive surgery has been shown to be a safe and better-tolerated approach for patients with more advanced disease [1]. However, in the USA, none of these strategies has yet been shown to have an impact on overall mortality from ovarian cancer (Figure 1), which has not appreciably changed over the last 30 years [1].

Approximately 80% of advanced-stage tumors demonstrate high-grade serous histology, and these tumors can arise from the distal (fimbriated) fallopian tube, peritoneal cavity or surface epithelium of the ovary. While high-grade serous tumors can also arise from the endometrium, these tumors have a somewhat different biology, are generally managed as endometrial cancer and are not included in clinical trials of ovarian cancer. As such, most of our current data are derived from extrauterine high-grade serous tumors.

Advances in molecular profiling have contributed to a better understanding of the diversity of ovarian cancer, including prognostic information and potential molecular targets. At this point, we can categorize tumors and obtain prognostic information according to stage, extent of residual disease following cytoreductive surgery, primary histology (serous, endometrioid, clear cell or mucinous), grade (low grade and borderline versus high grade) and presence of epithelial-mesenchymal transition (carcinosarcoma). However, currently, there are few comparative trials and none of the newer regimens have yet to demonstrate superiority to platinum–taxane combinations in any tumor subset. Clearly, as our understanding of molecular pathways continues to advance, we will have new opportunities to specifically target key subsets, including mucinous, clear cell, carcinosarcoma and low-grade invasive serous cancer.

Efforts to improve on the long-term results of primary therapy through the addition of a third cytotoxic agent have not been successful, including triplet combinations, sequential doublets, alternative taxanes and extended maintenance (with taxanes or other agents). Over the last 15 years, multiple international collaborative phase III trials, collectively enrolling >12 000 women, have been completed without showing clinical benefit from new combinations in primary therapy. Accrual data from many of the published trials are summarized in Table 1. The majority of studies only included two treatment arms and it is worth noting that >38% of the patients were assigned to a reference arm [3–10].

Chemotherapy resistance can emerge rapidly, through multiple molecular pathways, and it has not yet been possible to successfully translate single-pathway preclinical models to achieve clinical benefit in either primary therapy or recurrent
disease. However, emerging data with inhibitors of poly(adenosine diphosphate-ribose) polymerase (PARP), particularly in tumors with pre-existing defects in homologous recombination DNA repair, are encouraging and await phase III randomized trials.

There has been considerable interest in targeted and biological agents that interfere with growth factors, membrane-bound receptors and intracellular signal transduction cascades. Efforts to target the epidermal growth factor receptor family, including HER2 and EGFR, with antibodies and small-molecule inhibitors of the receptor-associated tyrosine kinase (rTKI) have not been particularly encouraging in recurrent ovarian cancer, and these strategies have not been evaluated in primary phase III trials.

In contrast, tumor-associated angiogenesis has emerged as a prominent area of investigation over the last 5 years, based on the role of vascular endothelial growth factor (VEGF) in normal ovarian physiology, as well as VEGF-mediated production of ascites and overexpression of VEGF by the majority of high-grade tumors. Two phase III randomized trials have been completed with bevacizumab administered during and following primary chemotherapy, which achieved a modest, and transient, benefit in progression-free survival, but without early evidence of an advantage in overall survival [11]. These interesting results raise questions about balancing potential clinical benefit with treatment-related toxicities and the overall financial cost associated with long-term drug administration. Additional randomized trials are in progress with other antiangiogenic agents, including multitransgenic rTKIs, but data are pending and there are no ongoing trials directly comparing rTKIs with bevacizumab.

### Optimized Primary Treatment

After >30 years, platinum compounds remain dominant as the most active primary cytotoxic chemotherapy. Historical improvements have been achieved through the development of better-tolerated analogues (carboplatin), together with targeted dosing, sequence and duration of treatment. 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 [13]. Newer platinum conjugates have not yet proven to be superior to carboplatin, although oxaliplatin is undergoing evaluation as primary therapy for mucinous carcinomas in the context of an international phase III trial (Figure 2).

Intraperitoneal delivery of cisplatin has been shown to improve overall survival in phase III randomized trials and is an appropriate option for selected patients [14]. However, the dose of cisplatin in phase III trials has been high (100 mg/m²), with an impact on host toxicity, including nausea, vomiting, abdominal pain and neuropathy. It has become common practice to utilize a better-tolerated dose of 75 mg/m² in clinical practice and this is now being prospectively evaluated in a phase III Gynecologic Oncology Group (GOG) trial (Figure 3). There has also been interest in the substitution of intraperitoneal carboplatin. Both cisplatin and carboplatin are rapidly absorbed from the peritoneal cavity; however, carboplatin requires a much longer time for activation via aquation, due to the larger size of the organic leaving groups. As such, it remains unproven if intraperitoneal carboplatin will be equivalent to cisplatin. This is also being prospectively evaluated in phase III trials conducted by the GOG, in

![Cancer Death Rates: (US 1930-2006)](image)

**Figure 1.** Overall cancer-related mortality for women in the USA over a period of 75 years. In spite of significant advances in the management of ovarian cancer, we have not yet observed an impact on disease-related mortality [2].

<table>
<thead>
<tr>
<th>Groups and study designation</th>
<th>CP</th>
<th>CPG</th>
<th>CD ± P</th>
<th>CT ± P</th>
<th>CG</th>
<th>CDoc</th>
<th>CE</th>
<th>Total</th>
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<td>864</td>
<td>863</td>
<td>861</td>
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<td>4312</td>
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<td>MITO-2 [10]</td>
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<td>410</td>
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<td>Regimen total</td>
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<td>1426</td>
<td>861</td>
<td>539</td>
<td>1090</td>
<td>11265</td>
</tr>
</tbody>
</table>

*age-adjusted to the 2000 US standard population.

**Table 1.** Summary of overall accrual of international phase III trials through the Gynecologic Cancer InterGroup to evaluate new cytotoxic agents in the primary therapy of ovarian cancer

C, carboplatin or cisplatin; P, paclitaxel; G, gemcitabine; D, PEG-liposomal doxorubicin; T, topotecan; Doc, docetaxel; E, epirubicin.

Volume 22 | Supplement 8 | December 2011
doi:10.1093/annonc/mdr466 | viii53
Paclitaxel 175 mg/m² (3 h)

Recently, several GOG intraperitoneal cisplatin, compared with the benefit observed in residual disease did not experience additional benefit from analysis of GOG104 suggested that patients with microscopic residual disease has never been prospectively evaluated in a randomized trial. However, a provocative retrospective study of GOG104 suggested that patients with microscopic residual disease did not experience additional benefit from intraperitoneal cisplatin, compared with the benefit observed in patients with macroscopic disease [15]. Recently, several GOG and JGOG pilot studies have enrolled patients with larger-volume residual disease, and demonstrated the safety and feasibility of this approach. Two ongoing phase III trials (GOG0252 and JGOG3109) subsequently permitted enrollment of patients with suboptimal residual disease, with analysis pending.

In view of the importance of paclitaxel, a number of studies have evaluated the dose, schedule, sequence and route of administration, as well as alternative formulations, taxane analogues and nontaxane antimicrotubule agents. In a phase III trial, a prolonged infusion of paclitaxel (96 h) increased mucosal and bone marrow toxicity, but without improved efficacy [16]. Shorter infusions (<3 h) are generally better tolerated from a hematologic perspective, although higher individual doses can increase the risk of arthralgia-myalgia and neuropathy. Weekly scheduling permits higher cumulative dose delivery, while avoiding hematologic toxicity and alopecia, and has demonstrated consistent activity in patients who had recurrence within 6 months of primary therapy with conventional carboplatin and paclitaxel. The JGOG conducted a phase III trial in women with newly diagnosed advanced-stage ovarian cancer (Figure 5), demonstrating superiority of weekly dose-dense paclitaxel in combination with standard doses of carboplatin compared with three-weekly scheduling of the same drugs [17]. This is an important finding, illustrating the need to carefully examine how we use established agents, in addition to strategies to incorporate new 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 [14]. Ongoing phase III trials through GOG and other groups aim to extend the JGOG findings, including integration with intraperitoneal chemotherapy and molecular-targeted agents (Figures 4 and 6), as well as weekly dosing of carboplatin (Figure 7). However, there is some concern that carboplatin is not particularly schedule-sensitive and fractionating the dose will reduce peak drug levels, with a potential impact on tumor delivery.

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**GOG 0252: Dose Dense and IP Therapy**

- **Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer**
- **Optimal and Suboptimal Disease (through April 2011)**
- **Primary Endpoint: PFS**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Paclitaxel 175 mg/m² (3 h) Carboplatin AUC 6</td>
</tr>
<tr>
<td>II</td>
<td>Oxaliplatin 850 mg/m² BD x14d Paclitaxel 130 mg/m²</td>
</tr>
<tr>
<td>III</td>
<td>Paclitaxel 175 mg/m² (3 h) Carboplatin AUC 6 Bevacizumab 15 mg/kg Q21d x 16</td>
</tr>
<tr>
<td>IV</td>
<td>Oxaliplatin 135 mg/m² IP (d1, 3h) Paclitaxel 60 mg/m² IP (d8) Bevacizumab Q21d x 16</td>
</tr>
</tbody>
</table>

*Open: JUN-2009
Closed: OCT-2011 (projected)
Target Accrual: 1250 pts (1200 optimal; 250 suboptimal)*

**JOG 3109: Dose-Dense, IP Carboplatin**

- **Epithelial Ovarian or Peritoneal**
- **Stratified: residual disease, stage, and global region**
- **Stage II – IV, No prior therapy**
- **Primary endpoint: PFS**
- **Secondary endpoint: OS**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Paclitaxel 80 mg/m² (D1,8,15) Carboplatin AUC = 6 IV</td>
</tr>
<tr>
<td>II</td>
<td>Oxaliplatin 130 mg/m² BD x14d Paclitaxel 130 mg/m²</td>
</tr>
<tr>
<td>III</td>
<td>Bevacizumab 15 mg/kg Q21d x12</td>
</tr>
</tbody>
</table>

*Open: MAY-2010
Closed: APRIL-2013 (projected)
Accrual: 746 pts (120 Phase II)*

**Figure 3.** Design of the ongoing phase III trial within the GOG to evaluate intraperitoneal carboplatin with dose-dense weekly paclitaxel, without incorporation of bevacizumab.
chemotherapy with interval cytoreductive surgery (NACT-ICS). The study also permits patients to receive neoadjuvant dense weekly paclitaxel, with optional election to receive bevacizumab [17].

Figure 6. Design of the ongoing phase III GOG trial to evaluate dose-dense weekly paclitaxel in combination with standard three-weekly carboplatin [17].

GOG 0262: Dose-Dense Integration

- Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer
- Suboptimal residual disease, amended to permit NACT-ICS
- Primary endpoint: PFS
- Amended to incorporate perfusion-based CT imaging (ACRIN)

Open: SEP-2010
Closed: OCT-2011 (ongoing)
Target Accrual: 1100 pts

Figure 7. Design of the ongoing phase III GOG trial to evaluate dose-dense weekly paclitaxel with optional election to receive bevacizumab (GOG0262). The study also permits patients to receive neoadjuvant chemotherapy with interval cytoreductive surgery (NACT-ICS).

incorporating a third cytotoxic agent (primary and maintenance)

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 to evaluate topotecan, gemcitabine, PEG-liposomal doxorubicin and epirubicin, the addition of a third cytotoxic agent has not been shown to improve long-term clinical outcomes [3]. Some agents, such as topotecan and gemcitabine, exhibit schedule- and sequence-dependent hematologic toxicity, particularly when combined with carboplatin. These agents can interfere with the repair of platinum–DNA adducts, but often at the expense of increased hematologic toxicity. In contrast, combinations of paclitaxel with carboplatin are well tolerated, with 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 [18]. Indeed, one potential advantage of weekly paclitaxel could be the temporal separation from carboplatin, optimizing the tumor-related cytotoxicity of both agents.

In reviewing the cumulative results of these phase III trials, one is struck by the consistent lack of benefit, including in subpopulations with more favorable prognostic features, such as microscopic optimal disease after primary cytoreductive surgery. At some level, this is perplexing, in view of the 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 and PEG-liposomal doxorubicin. There are several potential explanations for these observations:

- First, perhaps the dose or schedule of chemotherapy was not optimal. It is difficult to refute this argument. However, 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 dosing was suboptimal.

- Second, perhaps only a subset of patients is sensitive to each new agent, but this effect is lost in the setting of a trial with a randomized allocation of drugs among the entire population. In theory, this could be evaluated by tumor profiling prior to randomization. While potentially important, this explanation also seems unlikely, as there should still be an overall trend for improvement associated with the incorporation of new agents, which was not observed.

- Third, it is possible that the short-term effectiveness of primary surgery and standard chemotherapy may limit the opportunity to observe incremental benefit from a new agent. Ovarian tumors are initially platinum sensitive and the majority of patients begin chemotherapy following optimal cytoreductive surgery, rapidly achieving clinical complete remission. It is possible that the addition of a third noncurative agent, even though active, might contribute little to the observable clinical outcomes during primary therapy.

- Fourth, emerging data regarding stem-like behavior has been 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 [19]. These stem-like populations are generally enriched following primary chemotherapy and could limit the effectiveness of any third cytotoxic agent.

The last two arguments could explain the somewhat paradoxical benefit of platinum-based combinations in the setting of recurrent disease, when these same combinations have not always demonstrated increased benefit in the frontline setting. Recurrent tumors, even if platinum-sensitive, are not the same as newly diagnosed (untreated) disease. While remissions do occur in the setting of recurrent disease, it is less common to observe complete remissions and the time to further disease progression is generally shortened, associated with a more rapid evolution of drug resistance. In this setting, providing a second nonplatinum drug, particularly against tumors that are already becoming platinum resistant, may show an advantage.

A number of trials have evaluated a third agent as maintenance therapy for patients in remission after completion of primary therapy [21]. 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 [26]. 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 uncertain clinical benefit associated with a modest improvement of PFS (that was substantially less than the difference in total treatment times) without any benefit in overall survival. The 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, currently, there is not any established role for maintenance chemotherapy in women with ovarian cancer.

Several cytotoxic agents have recently been developed with encouraging activity in recurrent disease, including epothilone analogues (ixabepilone and patupilone), alternative taxane formulations (nanoparticle albumin-bound paclitaxel), multtargeted antifolates (pemetrexed), a DNA minor groove binding agent (trabectedin), folate–vinca alkaloid drug conjugates (EC145), irinotecan–polymer conjugates (NKTR-102) and inhibitors of aurora kinases (MLN-8237). However, in view of this substantial body of negative phase III trials, the threshold for moving a new cytotoxic agent to primary therapy appears quite high.

**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. 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-ras or K-raf [27]. 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, and is associated with the down-regulation of epithelial markers (such as epithelial membrane antigen) and up-regulation of mesenchymal markers (such as vimentin) [29]. These changes contribute to cellular motility, the production of proteolytic enzymes and invasive behavior. Aggressive mesenchymal features have also been identified through the analysis of gene expression profiles, even without visible evidence of sarcoma [30].

Although primary ovarian mucinous tumors are rare, a collaborative retrospective review of the international data has verified that mucinous tumors are not generally responsive to platinum-based chemotherapy [31] and patients with advanced mucinous tumors have inferior long-term survival, compared with those with serous or endometrioid subtypes. An international collaborative phase III trial has been initiated to evaluate alternative regimens modeled after colorectal adenocarcinoma (Figure 2).

Advanced-stage clear cell tumors exhibit more aggressive patterns of metastatic spread and are frequently resistant to platinum-based chemotherapy. Expression profiles have identified the activation of hypoxia-associated genes and other characteristic findings, sharing some features with clear cell tumors from other primary sites (such as renal) and suggesting new treatment strategies to be tested in future trials. Accrual has
targeting angiogenesis

High-grade serous ovarian cancer is characterized by the overexpression of VEGF, which drives dysfunctional tumor-associated angiogenesis, contributing to high interstitial pressure within tumors and an increased production of ascites. Direct targeting of this pathway can be achieved by sequestration of the VEGF protein using monoclonal antibodies (bevacizumab) or engineered binding-site molecules (aflibercept). Blockade of VEGF receptor-2 can be achieved with monoclonal antibodies (IMC-1C11) or inhibition of receptor-associated tyrosine kinases using low molecular weight agents (axitinib, cediranib, pazopanib, sorafenib and vargatef). Indirect strategies include targeting genes involved in the regulation of VEGF expression, such as hypoxia-inducible factor 1-α (HIF1α). It is also possible to target other angiogenic factors, such as angiopoietin-2, and their associated receptors. Much attention has also been focused on the inhibition of cytoplasmic tyrosine kinases that are activated following VEGF receptor-mediated phosphorylation, or inhibition of other downstream 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. Single-agent activity with bevacizumab in recurrent ovarian cancer is more substantial than previously observed in most other tumor types. As such, it was anticipated that combinations of bevacizumab with carboplatin and paclitaxel would improve long-term outcomes for women with ovarian cancer. Thus far, two phase III trials for newly diagnosed ovarian cancer have reported a nonsustained and modest improvement in progression-free survival, but with less impact on overall survival [11]. Both of these trials incorporated maintenance administration of single-agent bevacizumab after completion of chemotherapy.

These positive results have attracted considerable attention. Although both trials met their primary endpoints for improvement in PFS, the magnitude of benefit was not as great as what had been anticipated on the basis of phase II data in patients with recurrent disease. Due to the design of the trials, it is not possible to determine how much of the improvement in PFS is related to the total duration of therapy, the integration with concurrent chemotherapy or maintenance following chemotherapy. However, maximal benefit was achieved in the population that received bevacizumab during and following chemotherapy. In addition, both trials demonstrated a trend for greater benefit in patients with more extensive disease, based on either the results from cytoreductive surgery (ICON7), or through exclusion of patients with small-volume disease and CA-125 progression (GOG0218). In this regard, an updated analysis from a subset of 465 high-risk patients with more extensive disease in the ICON7 trial showed a statistically significant 7.8 month improvement in median overall survival, achieving a hazard ratio of 0.64 (95% confidence interval: 0.48–0.85) [34]. The magnitude of this effect appears greater in ICON7, compared with GOG0218, and it is possible that a higher proportion of patients on the GOG trial were able to obtain commercial bevacizumab (or other related agents) after completion of protocol-directed therapy.

Expected toxicities from bevacizumab were observed (including thromboembolic events and hypertension). However, most of the serious events tended to occur during primary chemotherapy and within the perioperative period, with fewer dose-limiting events noted during maintenance therapy. Initially, based on phase II single-agent data, there was concern regarding the potential risk of bowel perforation, but this did not emerge as a significant bevacizumab-related toxicity in either randomized trial.

In other tumor settings, improvements in survival have been attributed to enhanced drug delivery as a result of pseudonormalization 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. In addition, most patients with ovarian cancer undergo optimal cytoreductive surgery and then receive platinum-based chemotherapy prior to receiving any bevacizumab. The combined impact of surgery and chemotherapy would tend to minimize tumor-associated VEGF production, as well as the size of any residual disease, which is quite different from the management of large-volume metastatic disease in other settings. Taken together, these effects could theoretically reduce the impact of bevacizumab during primary chemotherapy and might favor using bevacizumab in the setting of recurrent disease, as illustrated by data from the OCEANS trial in platinum-sensitive recurrent disease [35].

Important questions remain regarding the optimal dose, schedule, timing and integration of anti-VEGF therapy. Thus far, it appears that VEGF blockade may have greater impact in preventing tumor regrowth or in the management of recurrent disease, rather than in the augmentation of primary chemotherapy. Mature data are awaited from these completed studies.
overcoming chemotherapy resistance

The most important pattern of resistance observed in ovarian cancer is related to the 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 a 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 been successfully translated to clinical practice.

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 [36]. Whether ERCC1 or other markers could be used to guide chemotherapy selection in women with ovarian cancer is unknown.

Emerging data with inhibitors of PARP, particularly in tumors with pre-existing defects in homologous recombination DNA repair, are encouraging and phase III randomized trials are being initiated. There are at least two distinct strategies for the incorporation of PARP inhibitors and each approach merits evaluation. First, concurrent combination with platinum-based chemotherapy can increase platinum-mediated cytotoxicity, regardless of genetic defects in homologous recombination. However, this has generally been associated with increased hematologic toxicity, requiring adjustments in the dose and schedule to safely administer multiple cycles. Second, PARP inhibitors can be administered as a single-agent following completion of primary therapy, creating a synthetic lethal paradigm for tumors with defects in homologous recombination DNA repair. In this regard, it is important to note that these defects are not simply limited to inherited mutations of BRCA1 or BRCA2, but include somatic mutations, the methylation status of gene regulatory elements and mutations in a large number of candidate genes associated with DNA repair, approaching 50% overall incidence in patients with high-grade serous or endometrioid histology, as reflected in emerging data from The Cancer Genome Atlas project [37]. It is likely that at least two phase III trials with similar PARP inhibitors will be initiated, and that these trials will evaluate concurrent and extended maintenance therapy, but designs are still under development (Figure 11).

AGO OVAR12: CP +/- BIBF1120

- Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer
- Optimal or Suboptimal Cytoreduction, Stage IIB - IV
- Primary Endpoint: PFS

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<th>Dose</th>
<th>NNR or concurrent chemotherapy</th>
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<td>BIBF1120 200 mg PO bid</td>
<td>x 6</td>
</tr>
<tr>
<td>Placebo PO bid</td>
<td>BIBF1120 (120 wks max)</td>
<td></td>
</tr>
</tbody>
</table>

- Multi-targeted TKI (VEGF-R1,2,3; FGF-R1,3; PDGF-Rα,β)
- Favorable toxicity profile (GI, sx, fatigue, reversible transaminase elevation)

Open: Jan-2010
Closed: Aug 2010
Target Accrual: 1300 pts (2 Y)

Figure 9. Ongoing phase III GCIG trial (with leadership from AGO) evaluating concurrent and extended maintenance therapy with a multitargeted oral tyrosine kinase inhibitor (BIBF-1120, Vargetef).

AGO OVAR16: Pazopanib Maintenance

- Epithelial Ovarian, Primary Peritoneal, or Fallopian Cancer
- Primary platinum-based therapy (IV, IP, Neoadjuvant permitted)
- CR, PR, or SD after initial therapy
- Primary Endpoint: PFS
- Secondary Endpoint: OS (with interim analysis)
- Amended to permit 2 years of post-primary treatment on-study

Primary Rx: Platinum and Taxane

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<td>Pazopanib 800 mg PO qd (15 m)</td>
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<tr>
<td>Placebo PO qd (15 m)</td>
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Open: May 2009
Closed: Aug 2010
Accrual: 900 pts (under analysis)

Figure 10. Accrual has been completed on this phase III GCIG trial (with leadership from AGO) to evaluate extended maintenance therapy (up to 2 years) with an oral tyrosine kinase inhibitor (pazopanib).

GOG PARPi: Proposed Phase III

- High-grade extraterine serous and endometrioid tumors, Stage I-C, II, III, IV
- Election for neoadjuvant therapy with interval cytoreduction (biopsimens)
- Election for intraperitoneal (IP) cisplatin or intravenous (IV) carboplatin
- Primary endpoint OS incorporating interim analysis (PFS)

<table>
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<tr>
<th>Schedule</th>
<th>Dose</th>
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<td>Placebo d -1 to 4 PO</td>
<td>Placebo daily PO</td>
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<tr>
<td>Parpi daily PO</td>
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<tr>
<td>Paclitaxel 175 mg/m² (3 h) Carboplatin AUC 6 (IV)*</td>
<td>PARPi d -1 to 4 PO</td>
</tr>
<tr>
<td>Placebo d -1 to 4 PO</td>
<td>Placebo daily PO</td>
</tr>
<tr>
<td>Parpi daily PO</td>
<td>Placebo daily PO</td>
</tr>
</tbody>
</table>

* Patients electing intraperitoneal therapy will receive cisplatin 75 mg/m²
* Dose and schedule of PARPi with concurrent chemotherapy pending

Figure 11. Proposed design for the GOG phase III trial to evaluate concurrent and maintenance therapy with an oral PARP inhibitor.
discussion
The optimal primary therapy of advanced ovarian cancer has not substantially changed over the last few years, in spite of new cytotoxic agents and the 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, which 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 the intraperitoneal delivery of carboplatin to further improve patient safety and tolerability.

The integration of emerging biologic principles with the development of molecular-targeted reagents is starting to achieve meaningful results, especially with regard to the inhibition of VEGF-mediated angiogenesis and interference with PARP-mediated DNA repair. Biologic observations have also contributed to our understanding of tumor classifications and prompted the evaluation of individualized treatments for patients with clear cell, mucinous and low-grade histologies. However, the rapid development of drug resistance remains a major clinical challenge for the majority of patients with advanced-stage disease, prompting studies designed to target regenerative subpopulations that are resistant to conventional cytotoxic agents.

The next few years will see mature data from phase III trials targeting VEGF and related components of angiogenesis. Comparative data among these agents are limited and the selection of high-priority combinations will remain challenging. Ideally, phase I trials should define more relevant endpoints, such as desired serum levels, duration of exposure, sequencing, feasibility of chronic administration at the selected dose, drug–drug interactions and saturation of biologic targets. With few exceptions, single-agent phase II trials with targeted agents have been not very informative and it would be preferable to broadly utilize randomized phase II designs with multiple arms to select promising agents (or combinations) that meet appropriate thresholds. Finally, phase III trials should include multiple arms with selective and adaptive designs based on interim analysis, allowing the investigators to drop arms that appear nonpromising 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.

acknowledgements
The author is grateful to the symposium organizers and participants for their dedication to international research and education related to ovarian cancer.

disclosures
The author serves as Chair of the GOG Ovarian Cancer Committee and as a member of data-monitoring committees for phase III trials sponsored by Genentech-Roche and Boehringer-Ingelheim. In addition, he has participated as an independent consultant for multiple pharmaceutical advisory boards without financial holdings.

references


