Published in final edited form as:
Int J Gynecol Cancer. 2010 October ; 20(7): 1290–1298. doi:10.1111/IGC.0b013e3181ee1c01.

Current academic clinical trials in ovarian cancer: Gynecologic Cancer Intergroup (GCIG) and United States National Cancer Institute (NCI) clinical trials planning meeting, May, 2009

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Abstract

Objective—To review the current status of large phase academic clinical trials for women with ovarian cancer, address cross-cutting issues, and identify promising areas for future collaboration

Materials/methods—In May, 2009, the Gynecologic Cancer Intergroup (GCIG), which represents 19 Cooperative Groups conducting trials for women with gynecologic cancer, and the United States National Cancer Institute convened a Clinical Trials Planning Meeting.

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Results—The topics covered included the impact of new developments in cancer biology upon molecular targets and novel agents, pharmacogenomics, advances in imaging, the potential benefit of diet and exercise to reduce risk of recurrence, academic partnership with industry, statistical considerations for phase II and III trials, trial endpoints, and symptom benefit and health-related quality of life issues. The clinical trials discussed spanned the spectrum of ovarian cancer from initial diagnosis, staging and cytoreductive surgery to consolidation chemotherapy, and treatment of recurrent disease.

Conclusions—Ongoing and effective collaboration with industry, government, and patients aims to ensure that the most important scientific questions can be answered rapidly. We encourage women with ovarian cancer and their oncologists to consider participation in the academic clinical trials conducted by the member groups of the GCIG.

Introduction

This one-day meeting was convened by the Gynecologic Cancer Intergroup and the United States NCI's Coordinating Center for Clinical Trials (CCCT) and Gynecologic Cancer Steering Committee (GCSC) to review the current status of clinical trials for women with ovarian cancer, address cross-cutting issues, and identify promising areas for future collaboration. To optimize the time of busy clinical trialists, translational research scientists, biostatisticians, and patient advocates, the conference was held immediately before the annual meeting of the American Society of Clinical Oncology in Orlando, Florida, USA, on May 29, 2009. The GCIG is an umbrella organization representing 19 Clinical Trials Cooperative Groups from Asia, Australia/New Zealand, Europe, and North America which conduct clinical trials for women with gynecologic cancer.[i] The NCI CCCT and GCSC are charged with providing scientific peer review for large-scale clinical trials, as well as working with cancer clinical trialists and NCI program staff to design a research agenda for clinical trials across the variety of gynecologic cancer types and the spectrum of cancer control.ii

New developments in cancer biology, molecular targets, and pharmacogenomics

Promising targets and agents in ovarian cancer are shown in Table 1. New research suggests that "epithelial ovarian cancer" may arise from two sources, the distal fallopian tube and the epithelial surface of the ovary.[iii] We do not yet know whether they are biologically equivalent nor whether they respond to treatment in similar fashion. Gene profiling indicates that clear cell ovarian cancer has a different genomic profile relative to serous and endometrioid types.[iv] Serous ovarian cancers can be broadly differentiated into high-grade tumors, which have p53 mutations, and low-grade tumors, which have mutations in B-raf, and K-ras.[v] Targets in endometrioid ovarian cancer would include beta catenin and pI3K/ PTEN.[vi] In almost all cells the repair of single-strand DNA breaks, known as base-excision repair, is executed by the PARP-1 enzyme. Inhibition of PARP-1 increases single-strand DNA damage. In normal cells, double-strand breaks are repaired via homologous recombination, which relies upon functional BRCA1 and BRCA2 enzymes. Cancer with BRCA mutations has difficulty repairing double-strand DNA damage. In tumors with BRCA-associated mutations, therefore, PARP-1 inhibition leads to increased tumor cell death. In addition, approximately 40% of sporadic serous ovarian cancers have BRCA1 or BRCA2 mutations or dysfunction, thus making them potential candidates for PARP-1 inhibitors. Treatment of patients with these tumors using PARP inhibitors has given promising results.[vii] PARP inhibitors might also be active in ovarian cancers with PTEN mutations. As with other highly proliferative cancer, the pIK/ Akt/ mTOR pathway also appears to be an attractive target in ovarian cancer. [viii] Finally, consideration should be

given to targeting the tumor microenvironment. Potential targets here include TNF-alpha, IL-6, and CCL2. Table 2 lists promising targets and the associated targeted agents.

In a number of diseases, emerging data suggest that responses to treatment and toxicity from treatment may vary according to both the genetic makeup of the individual cancer as well as genetic variation in different populations. We already know that there is significant inter-individual variation in drug metabolism, response to treatment, and incidence of toxicity. Prospective pharmacogenomic studies involving multiple GCIG groups could help us understand the role of population genetics in addition to individual tumor biology among women with ovarian cancer.[ix]

In the future, there is need to identify subgroups of patients based on genomic patterns and activated pathways, and to design trials appropriate for such subgroups. Future research must include the validation of prognostic and predictive markers, the identification and validation of small-molecule inhibitors and antibodies which target specific pathways, and determination of the molecular basis for resistance. Such studies will require the collection of large numbers of carefully annotated specimens, both at time of initial diagnosis and at time of recurrence. Valid prognostic and predictive makers that can be assessed in blood and urine specimens would be particularly useful.

Clinical trials

Recently closed and current large-scale trials span the trajectory of ovarian cancer as shown in Table 2.[x,xi,xii, xiii] The single-agent activity of bevacizumab in non-randomized phase II trials among women with ovarian cancer had lead to the evaluation of the addition of this agent to standard chemotherapy in two upfront-phase III trials (ICON 7, GOG 218) and three trials for women with recurrent disease (GOG 213, OCEANS, AURELIA). Both front-line trials (GOG 218 and ICON 7) and GOG 213 are also evaluating the impact maintenance bevacizumab may have in patients without progression following chemotherapy. The GOG reported a significant 4-month improvement in PFS associated with the addition of concurrent and maintenance bevacizumab in GOG 218. [xiv]In addition, phase I and II trials have demonstrated that bevacizmab can be safely combined with relevant intraperitoneally-administered chemotherapeutics, such as cisplatin, carboplatin, and paclitaxel. The GOG has launched a new trial, GOG252, which compares IV chemotherapy with carboplatin and weekly paclitaxel to two different IV/IP regimens, includes bevacizumab in all three arms. In addition, as the mature analysis of the PFS endpoint for GOG 218 demonstrates a statistically significant benefit for the bevacizumab triplet followed by maintenance bevacizumab (Arm III), the GOG is opening a new trial in women with suboptimal primary cytoreduction, which will investigate the role of weekly paclitaxel. Both arms of this trial will include bevacizumab during primary and maintenance treatment phases.

Phase II studies have also demonstrated activity for several other agents targeting angiogenesis, including sorafenib, sunitinib, cediranib, and aflibercept. Of these, cediranib and pazopanib is currently under evaluation in phase III trial (ICON 6, AGO-OVAR-16). Phase II trials evaluating combinations of anti-angiogenesis agents, as well as anti-angiogenesis agents with other biologic agents, are currently underway. In addition, the EORTC has undertaken a phase III trial evaluating the role of erlotinib, which targets epidermal growth factor receptor (EGFR) as consolidation therapy after primary chemotherapy (EORTC 55041)

The Japan Gynecologic Oncology Group (JGOG) recently reported demonstrated statistically significant improvements in both progression-free survival (PFS) and overall survival (OS) associated with weekly paclitaxel compared with paclitaxel given every 3 weeks.[xv] Women on both arms received carboplatin every 3 weeks. The Italian MITO group

has since opened a study comparing weekly carboplatin/ paclitaxel to the same agents given every 3 weeks(MITO 7). The UK NCRI has proposed a three-arm phase III trial comparing carboplatin/paclitaxel given every three weeks to the same drugs given weekly to the combination of carboplatin given every three weeks and paclitaxel given weekly (ICON 8). Unanswered questions include the optimal dosing for paclitaxel in dose-dense treatments, as well as the efficacy of a dose-dense approach when used in combination with anti-angiogenesis agents or when the RAF-1 pathway is impaired.

Another key issue is the timing of primary surgical cytoreduction.[xvi] The consensus in the United States continues to support primary surgery, for staging and cytoreduction, followed by chemotherapy, with neoadjuvant chemotherapy reserved for those women deemed unfit for initial surgery. This opinion is based primarily on the results of GOG 152, which showed no survival benefit associated with interval cytoreduction.[xvii] To date, North American investigators have not undertaken a phase III trial randomizing patients to primary surgery followed by chemotherapy versus neoadjuvant chemotherapy followed by interval cytoreduction. Based on data from EORTC 55971, many investigators have advocated neoadjuvant chemotherapy for 3 cycles, followed by surgical cytoreduction, then additional chemotherapy. Both sides agreed, however, on the need to stratify for the timing of surgery in those trials which ask a chemotherapeutic rather than a surgical question.

Multiple randomized phase III trials suggest that a combination of intraperitoneal and intravenous chemotherapy significantly improves survival among women with optimally debulked epithelial ovarian cancer. Current trials seek to evaluate the efficacy and toxicity of regimens of IP/IV chemotherapy which include dose-dense paclitaxel and intravenous bevacizumab (GOG 252), as well as the role of IP/IV chemotherapy after neoadjuvant chemotherapy (NCIC CTG OV 21). The JGOG has proposed a trial comparing IP to IV carboplatin, both given with weekly IV paclitaxel (JGOG 3019).

Meta-analysis of cooperative group data has confirmed clinical observations, namely that women with advanced-stage mucinous and clear cell epithelial ovarian cancer experience less benefit from standard chemotherapy and poorer survival than those with serous and endometrioid ovarian cancer.xviii As mentioned above, recent developments in molecular biology have shown clear differences in genetic profiles between mucinous, clear cell, and serous/endometrioid adenocarcinomas of the ovary. As shown in Table 2, separate phase III trials have now been developed for both clear cell and mucinous epithelial carcinomas, as well as a randomized phase II trial for women with chemotherapy-naïve sex-cord and stromal ovarian tumors. In addition, the GOG has undertaken phase II trials in such less common ovarian histologies as recurrent low-grade serous cancers (AZD 6244, a MEK inhibitor), and clear cell cancer (sunitinib).

Imaging advances in ovarian cancer

Perfusion imaging, either with dynamic-contrast-enhanced (DCE) CT or DCE MRI, may prove useful in determining prognosis at time of diagnosis. DCE MRI, for example, has been shown in other tumor types to correlate with pathologic prognostic indicators such as tumor grade, microvessel density, and VEGF expression, as well as predict clinical response to treatment with anti-VEGF antibody and tyrosine kinase inhibition. For detection of metastatic disease in lymph nodes, especially those less than 1 cm in size, ultra-small superparamagnetic iron oxide (USPIO) MRI is a promising new approach. For evaluation of women with recurrent ovarian cancer, PET-CT appears to demonstrates higher sensitivity and specificity than CT alone. PET-CT also appears useful as part of the primary evaluation of women with ovarian cancer. To date, however, there have been no phase III trials directly comparing PET-CT to CT.[xix] In addition, one must consider both the additional cost of PET-

CT, as well as access to centers in which PET-CT is readily available. Finally, percutaneous tumor ablation (thermal, cryo, high-intensity ultrasound, etc) may be useful for the local treatment of primary or recurrent disease not amenable to surgical resection.

Diet and physical activity to reduce recurrence

Epidemiologic studies and large clinical trials, such as the Women's Health Initiative, suggest that high vegetable intake, including green leafy vegetables, and a low-fat diet are associated with decreased risk of ovarian cancer. In addition, women with higher waist-hip ratios face a higher risk of ovarian cancer development, as well as enhanced survival for women with advanced disease. The influence of increased exercise upon risk of ovarian cancer is not clear clear. Several studies have found an increased risk of ovarian cancer associated with vigorous physical activity, while others have found reduction in risk associated with moderate physical activity. Based on these findings, GOG investigators have proposed an interventional trial for women with stage III-IV epithelial ovarian cancer who have no evidence of disease following primary surgery and chemotherapy. They would be randomized to standard care or an intervention promoting increased intake of fruits and vegetables, including at least one cruciferous vegetable, per day, a low-fat diet overall, and increased exercise (at least 4000 extra steps per day). This intervention has been piloted and appears to be feasible.[xx] The primary outcome of interest would be recurrence of cancer. To date, funding for this trial remains in limbo, in part due to the cost of the intervention.

Working with industry

Pharmaceutical companies and academic cooperative groups both bring different strengths to potential collaboration. Companies, for example, bring novel molecules, experience with trials in various diseases, and the potential for financial support. Academic research networks bring disease expertise, access to patients, experience in the design and conduct of clinical trials, and independence in reporting results. Companies and academic groups, however, do have different objectives, which can lead to tension and misunderstandings. The primary goal for companies, in general, is to get initial or expanded licensing approval for the novel agent they have developed. Due to financial and legal imperatives, companies generally strive to meet strict timelines as well as to ensure that trial conduct and data collection meets the Good Clinical Practice standards developed by the International Conference on Harmonization. In addition, the decision to proceed with development of an agent or the evaluation of that agent for a specific type of tumor may be made on the basis of financial and market judgments, not scientific opportunities. Academic investigators, on the other hand, may wish to evaluate the addition of the novel agent to standard therapy, as well as evaluate combinations of several novel agents, which may well have different corporate sponsors. In addition, academic investigators often want to study new agents in less common cancers, whose small market potential may make them less attractive to industry.

Nonetheless, there are many examples of successful collaboration between academic investigators and pharmaceutical companies. These span preclinical, phase I, II, and III trials. Definitive trials conducted by academic groups have been used as support of licensing applications for many anti-cancer agents. The extensive clinical drug development program conducted by the US NCI has also facilitated collaborations between industry and academic cooperative groups in North America. In Europe, academic investigators and industry have established the baseline requirements for collaboration to facilitate the rapid development of new drugs while maintaining mutual respect of their respective values.[xxi]

Statistical considerations

One of the critical issues in evaluating new agents is setting the bar for efficacy in order to determine which agents to advance to phase III trials. Only 25–30% of phase III trials based on phase II outcomes are positive. Clearly, improving the reliability of phase II trials to predict outcomes in phase III trials would be extremely useful, both to reduce the overall costs of drug development and to spare patients exposure to drugs which are not likely to benefit them. Single-arm phase II studies can reduce the number of patients required in drug development, if and only if the specified null rate is correct. If the null bar is set too low, then one may make the decision to go to a phase III trial too often and thus increase the expected sample size. If one sets the null bar too high, then phase IIII investigations will not be pursued often enough, and thus decrease the power of finding a treatment benefit at the end of drug development. This balance may be better exploited in randomized phase II designs, particularly in patient cohorts where the background null rate is not well described. From the perspectives of patient resources and investigative timeline, combination phase II/ III design are most efficient , as “go” versus ‘no go” decisions rules are building in to the same protocol. These designs should include a futility analysis based on PFS, as well as adequate power for a conclusion based on OS.[xxii] ICON 6 is a good example of this type of trial design. One can also incorporate multiple experimental arms, not all of which will necessarily go on to the phase III stage. The design of GOG 182/ICON 5, for example, used an intermediate phase II outcome (PFS) to decide which of the experimental arms to continue to phase III. This multi-arm, multi-stage design provides a rapid and reliable way to assess a large number of promising combinations simultaneously. GOG 182/ ICON 5, for example, assessed 4 new treatments in 3.5 years. There are, however, several disadvantages to such a design, however. First, its very complexity requires lengthy preparation. Second, the need for large sample sizes requires effective intergroup collaboration, which further requires much time for negotiation, agreement on trial design, and the coordination of trial logistics.

Trial endpoints

The conclusions of the 3rd ovarian cancer consensus conference regarding endpoints for front-line studies remain valid.xxiii As the participants in that meeting concluded, “both PFS and OS are important endpoints to understand the full impact of any new treatment. Thus, either may be designated as the primary endpoint. Regardless of which is selected, the study should be appropriately powered so both PFS and OS can be appropriately evaluated.” There is good evidence that PFS is a surrogate for OS in the front-line setting. For phase III trials which involved maintenance therapy, however, the participants recommended that OS, not PFS, be the primary endpoint. One unresolved issue is the use of CA 125 for documentation of progression of disease in large-scale trials.[xxiv] In the NCIC CTG OV.16 trial, for example, of 650 patients who experienced progression of disease, 359 had progression based on objective and CA 125 criteria, 229 on the basis of objective criteria only, and only 41 on the basis of CA 125 alone. Data from other front-line studies are needed to determine the added value of CA 125 alone as a marker of progression. In addition, more data is needed to evaluate the benefit of CA 125 alone to determine tumor response in phase II trials.[xxv] There remains ongoing tension between oncologists, who use CA 125 routinely in clinical practice, and regulatory authorities, who have made clear their preference for the diagnosis of recurrent or progressive cancer based on imaging studies. For patients with recurrent disease, the participants in the 3rd ovarian cancer consensus conference recommended that symptom benefit or overall survival serve as the primary endpoint. Nonetheless, progression-free survival is often used as the primary endpoint for large-scale trials for women with recurrent disease. Additional data is needed to establish whether PFS is a surrogate for OS in the setting of recurrent disease. With the availability of

multiple agents with activity in recurrent disease, it is possible that an active new agent might show an improvement in PFS but not impact OS. In addition, whether improvements in PFS parallel improvements in symptom benefit remains an important question for future research.

Symptom benefit and health-related quality of life issues

Health-related quality of life (HRQOL) measurement in ovarian cancer is evolving to include disease and symptom-specific measures, added to a global HRQOL rating. To enhance symptom monitoring and measurement in the setting of platinum-refractory and platinum-resistant ovarian cancer, accurate and clinically meaningful assessment of symptoms which are of highest priority to patients is essential. One promising approach is the FACT-O Symptom Index, comprised of 18 questions encompassing physical and emotional disease-related symptoms, treatment side effects, function, and well-being. The ANZGOG, US GOG, and MITO are all working on studies evaluating HRQOL in patients with platinum-resistant ovarian cancer. A related issue of high priority is the identification of effective treatment approaches for older women with ovarian cancer, particularly those with comorbidities, who may need additional evaluation to determine how well they will tolerate both surgery and chemotherapy. This cohort has been under-represented in many clinical trials, despite the higher prevalence of ovarian cancer among older women. The GOG is designing a prospective cohort study for older patients with ovarian cancer. Pretreatment evaluation will include assessment of activities of daily living, instrumental activities of daily living, nutritional status, the Charlson Index of co-morbidity, health-related quality of life, and performance status.

Conclusions

This paper has described a number of major challenges in the development and design of clinical trials needed to improve care in ovarian cancer, as summarized in Table 3. The GCIG is uniquely placed to achieve the framework of international collaboration by leading research groups, which is required to meet these challenges. Ongoing and effective collaboration with industry, government, and patients aims to ensure that the most important scientific questions can be answered rapidly. In addition, future studies should consider both the costs and the cost-effectiveness of new interventions. We encourage women with ovarian cancer and their oncologists to consider participation in the academic clinical trials conducted by the member groups of the GCIG.

REFERENCE

i. Gynecologic Cancer Intergroup. [accessed June 18, 2010]. www.gcig.igcs.org

ii. NCI Coordinating Center for Clinical Trials. [accessed June 18, 2010]. http://ccct.cancer.gov/

iii. Roh MH, Kindelberger D, Crum CP. Serous tubal intraepithelial carcinoma and the dominant ovarian mass: clues to serous tumor origin. Am J Surg Pathol 2009;33:376–383. [PubMed: 19011565]

iv. Zorn KK, Bonome T, Gangi L, et al. Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. Clin Cancer Res 2005;11:6422–6430. [PubMed: 16166416]

v. Tothill RW, Pinker AV, George J, et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin Cancer Res 2008;14 5198-08.

vi. Salvesen HB, Carter SL, Mannelqvist M, et al. Integrated genomic profiling of endometrial carcinoma associates aggressive tumors with indicators of PI3kinase activation. PNAS 2009;106:4834–4839. [PubMed: 19261849]

vii. Gien LT, Mackay HJ. The emerging role of PARP inhibitors in the treatment of epithelial ovarian cancer. J Oncol. 2010 (epub 2009 Dec 16).

viii. Campos SM, Ghosh S. A current review of targeted therapeutics for ovarian cancer. J Oncol. 2010 (Epub 2010 Jan 3).

ix. Paige AJ, Brown R. Pharmaco(epi)genomics in ovarian cancer. Paige AJ, Brown R. Pharmacogenomics 2008;9:1825–1834.

x. Herstedt, J.; Huober, J.; Priou, F., et al. A randomized, phase III study (AGO-OVAR-9, GINECO-TSG, NSGO-OC-0102): gemcitabine-paclitaxel-carboplatin versus paclitaxel-carboplatin as first-line treatment of ovarian cancer: survival of FIGO stage I-IIA.. J Clin Oncol; 2009 ASCO Annual Meeting Proceedings (post-meeting edition); 2009. p. 15SLBA5510

xi. Kaye, SB.; Vasey, P.; Rustin, G., et al. Randomized trial of intrapatient dose escalation of single-agent carboplatin as first-line treatment for advanced ovarian cancer: an SGTCG study (SCOTROC 4). J Clin Oncol; 2009 ASCO Annual Meeting Proceedings (post-meeting edition); 2009. 15S:5537

xii. Harter P, du Bois A, Hahmaann M, et al. Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR Trial. Ann Surg Oncol 2006;13:1702–1710. [PubMed: 17009163]

xiii. Pujade-Lauraine E, Wagner U, Avall-Lundqvist E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol. 2010 May 24; [Epub ahead of print].

xiv. Burger RA, Brady MF, Bookman MA, et al. Phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer: a Gynecologic Oncology Group study. J Clin Oncol 2010;28 suppl:7s. abstr LBA1.

xv. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-lable, randomised controlled trial. Lancet 2009;374:1331–1338. (9698). [PubMed: 19767092]

xvi. Vergote I, van Gorp P, Amant F, et al. Timing of debulking surgery in advanced ovarian cancer. Int J Gynecol Cancer 2008;18 Suppl 1:11–19. (review). [PubMed: 18336393]

xvii. Rose PG, Nerenstone S, Brady MF, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. N Engl J Med 2004;351:2489–2497. [PubMed: 15590951]

xviii. Mackay HJ, Brady MF, Oza AM, et al. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. Int J Gynecol Cancer. (in press).

xix. Prakash P, Cronin CG, Blake MA. Role of PET/CT in ovarian cancer. AJR Am J Roentgenol 2010;194:W464–W470. [PubMed: 20489063]

xx. Thomson CA, Alberts DS. Diet and survival after ovarian cancer: where are we and what's next? J Am Diet Assoc 2010;110:366–368. [PubMed: 20184986]

xxi. Vergote I, Pujade-Lauraine E, Pignata S, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and pharmaceutical companies. Int J Gynecol Cancer 2010;20:476–478. [PubMed: 20375816]

xxii. Bast RC, Thigpen JT, Arbuck SG, et al. Clinical trial endpoints in ovarian cancer: report of a FDA/ASCO/AACR public workshop. Gyn Oncol 2007;107:173–176.

xxiii. du, Bois A.; Quinn, M.; Thigpen, T., et al. Ann Oncol; 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004); 2005. p. viii7-viii12.

xxiv. Rustin GJ, Quinn M, Thigpen T, et al. Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Nat Cancer Inst 2004;96:487–488. [PubMed: 15026475]

xxv. Azad NS, Annunziata CM, Steinberg SM, et al. Lack of reliability of CA125 response criteria with anti-VEGF molecularly targeted therapy. Cancer 2008;112:1726–1732. [PubMed: 18300236]

Figure 1.
Disease trajectory

Table 1

Novel targets and agents in epithelial ovarian cancer

Targets	Agents under study in ovarian cancer
Angiogenesis	bevacizumab, cediranib, sorafenib, sunitinib, aflibercept, pazopanib, BIBF-1120
Epidermal growth factor receptor (EGFR)	erlotinib
Fibroblast growth factor receptor (FGFR)	BIBF-1120
Mammalian target of rapamycin (mTOR)	Temsirolimus, everolimus, deforolimus, sirolimus
Phosphatase and tensin homolog (PTEN)/ AKT protein kinase family	perifosine, PBI-05204, GSK 2141795
Phosphoinositide 3-kinase (PI3K)/ Mammalian target of rapamycin (mTOR)	XL147, PX-866, PI-103, GDC-0941, BKM120
Platelet-derived growth factor receptor (PDGFR)	Cediranib, pzapanib, BIBF-1120
Poly (ADP-ribose) polymerase (PARP)	ABT-888 (veliparib), AZD 2281 (olaparib), AG014699, BSI-201 (iniparib), INO-1001, MK 4827, GPI 21016

Table 2

Current GCIG phase III and randomized phase II clinical trials for women with ovarian cancer (included recently closed trials, trials open to accrual, and trials in final design)

Disease trajectory	Name of study	Lead and collaborating groups	Clinical question	Outcome
Disease trajectory	Name of study; trials registry #	Lead & collaborating groups	Clinical question	Current status; Outcome; N= sample size
Initial surgery	EORTC 55971	EORTC, NCIC CTG	Primary surgery vs. neoadjuvant chemotherapy & interval cytoreduction	Closed to accrual; no signicant difference in OS; N= 718
	CHORUS	MRC/NCRI	Primary surgery vs. neoadjuvant chemotherapy & interval cytoreduction	Open to accrual 2006; N= 550
	AGO-OVAR OP.3 (LION)	AGO-OVAR, AGO-Austria, KGOG, MITO	Primary surgery +/− pelvic & para-aortic lymphadenectomy	Open to accrual 2009; N=640
Initial chemotherapy for women with epithelial ovarian cancer, tubal carcinoma, and primary peritoneal carcinoma	AGO-OVAR-9	AGO-OVAR, GINECO, NSGO	Carboplatin/ paclitaxel +/− gemcitabine	Significant improvement in PFS; no significant difference in OS (10); N=1567
	SCOTROC 4	SGCTG, ANZGOG	Flat dosing of carboplatin vs intrapatient dose escalation	No significant difference (11)
	JGOG x	JGOG	Carboplatin + paclitaxel weekly vs every 3 weeks	Significant improvement in PFS and OS (14)
	JGOG 3019	JGOG	Carboplatin (AUC 6) IV vs IP, both with IV weekly paclitaxel	Open to accrual 2010; N= 754
	ICON-7	MRC/NCRI, AGO-OVAR, ANZGOG, EORTC, GINECO, GEICO, NCIC CTG, NSGO	Carboplatin/ paclitaxel +/− bevacizumab (7.5 mg/kg)	Closed to accrual; data maturing; N=1528
	GOG 218	GOG, GOG-Japan, ECOG, KGOG, NCCTG, NSABP, SWOG	Carboplatin/ paclitaxel +/− bevacizumab (15 mg/kg)	Closed to accrual; significant improval in PFS; N=1800
	MITO-7	MITO, AGO-OVAR, MaNGO	Weekly vs every 3 week carboplatin/ paclitaxel	Open to accrual 2009; N=400
	GOG 252	GOG	Carboplatin/ weekly paclitaxel/ bevacizumab vs. IP carboplatin/ weekly paclitaxel/ bevacizumab vs. IP cisplatin/ IV & IP paclitaxel / bevacizumab	Open to accrual; N=1250
	NCIC CTG OV 21	NCIC CTG, ANZGOG, GEICO, NCRI, SWOG	Neoadjuvant chemotherapy-> interval cytoreduction -> carboplatin / paclitaxel weeks 1 & 2 vs. IP carboplatin every / paclitaxel weeks 1 &	Open to accrual 2009; N=830

Disease trajectory	Name of study	Lead and collaborating groups	Clinical question	Outcome
			2 vs cisplatin IP/ paclitaxel IV week 1 & IP week 2/ bevacizumab	
	AGO-OVAR-12	AGO-OVAR, AGO-Austria, BGOG, GINECO, MANGO, MITO, NSGO, and select US sites	Carboplatin/ paclitaxel +/− BIBF 1120 (Vargatef)	Open to accrual 2009; N= 1300
	ICON 8	NCRI	Carboplatin/paclitaxel both every 3 weeks vs. carboplatin every 3 weeks + weekly paclitaxel vs carboplatin/ paclitaxel both weekly	In review; N= 1485
Initial chemotherapy for clear cell ovarian cancer	JGOG 3017	JGOG, GINECO, KGOG, MITO, SGCTG	Carboplatin/paclitaxel vs. cisplatin/irinotecan in clear cell cancer	Open to accrual 2007; N=652
Initial chemotherapy for mucinous ovarian cancer	mEOC/GOG 241	NRCI/ SGCTG & GOG, AGO-OVAR, GINECO, KGOG, MANGO, NSGO	Carboplatin/paclitaxel +/− bevacizumab vs oxaplatin/ capecitabine +/− bevacizumab in mucinous cancer	Open to accrual 2010; N=332
Initial chemotherapy for primary or recurrent sex-cord stromal tumors of the ovary	GOG 264 (randomized phase II)	GOG	Carboplatin/ paclitaxel vs. bleomycin/ etoposide/ platinum for chemotherapy-naïve primary or recurrent sex-cord stromal tumors of the ovary	Open to accrual; N dependent on events in control arm
Consolidation	EORTC 55041	EORTC, AGO-Ausria, ANZGOG, GINECO, MANGO, MRC/NCRI,	Primary chemotherapy +/− erlotinib × 2 years	Accrual complete; data maturing; N=835
	GOG 218	GOG, GOG-Japan, ECOG, KGOG, NCCTG, NSABP, SWOG	Primary chemotherapy +/− bevacizumab, both during chemotherapy and in consolidation	Accrual complete; significant improvement in PFS; N=1800
	AGO-OVAR-16	AGO-OVAR, AGO-Austria, ANZGOG, BGOG, GEICO, GINECO, ICORG, JGOG, KGOG, MANGO, MITO, NSGO, SWOG, and select US sites	Primary chemotherapy +/− pazopanib × 1 year	Open to accrual 2009; N= 900
	GOG 225	GOG	Improved diet & exercise vs normal lifestyle in women disease-free after primary treatment	Funding pending; N= 1400
Platinum-sensitive recurrence	AGO-OVAR-OP.2 DESKTOP II	AGO-OVAR, AGO-Austria, MITO	Evaluation of predictive factors for complete surgical resection	Validation of AGO-DESKTOP I Score (12); N= 412
	CALYPSO	GINECO, AGO-Austria, AGO- OVAR, ANZGOG, EORTC, MANGO, MITO, NCIC CTG, NSGO	Carboplatin/ paclitaxel +/− pegylated liposomal doxorubicin	Significant different in favor of doxorubicin arm (13); N=976
	GOG 213	GOG	Carboplatin/ paclitaxel +/− bevacizumab, +/− cytoreductive surgery	Open to accrual; N= 660 for bevacizumab question; N= 360 for surgical questions

Disease trajectory	Name of study	Lead and collaborating groups	Clinical question	Outcome
	ICON 6	MRC/NCRI, NCIC CTG, ANZGOG	Carboplatin/paclitaxel +/− cediranib both with chemotherapy and in maintenance	Open to accrual 2007; stage I, N=50; stage 2, N=600; stage 3, N=2000
	AGO-OVAR-OP.4 DESKTOP III	AGO-OVAR	Cytoreductive surgery vs no surgery	Open to accrual 2009; N= 385 (12)
	HECTOR	NOGGO/ AGO-OVAR, AGO- Austria, GEICO	Carboplatin/ topotecan vs carboplatin/ paclitaxel or carboplatin/ gemcitabine	Closed to accrual; N=550
	MITO-8	MITO, AGO-OVAR, BGOG, MANGO	Liposomal doxorubicin vs carboplatin/ paclitaxel, with cross-over at progression	Open to accrual 2009; N=253
	DDPC-PREOC (randomized phase II)	SGCTG	Liposomal doxorubicin vs weekly carboplatin/ paclitaxel	In review; N= 130
	OVATYON	MANGO	Lipsomal doxorubicin + carboplatin vs liposomal doxorubicin + trabectidin	Open to accrual; N=588
Platinum-resistant/ refractory ovarian cancer	MITO-11 (randomized phase II)	MITO	Weekly paclitaxel +/− pazopanib	Open to accrual 2009; N=72
	AURELIA	GINECO, AGO-OVAR, GEICO, MITO, NSGO	Chemotherapy +/− bevacizumab	Open to accrual 2009; N=332

Table 3

Unanswered questions in the treatment of advanced epithelial ovarian cancer

Can we identify better predictors of risk for recurrence or chemoresistance?
Can we identify individual variation in gene expression governing drug metabolism which affect both toxicity and efficacy?
Can we identify genomic patterns which are prognostic or predictive or response to specific drugs or treatment combinations?
Which patients are best served by neoadjuvant chemotherapy followed by interval cytoreduction?
How can we best use targeted biologics in combination with initial chemotherapy to improve outcome?
How can we reduce the toxicity and improve the efficacy of intraperitoneal chemotherapy?
Does the use of dose-dense (weekly) paclitaxel obviate the benefit of intraperitoneal chemotherapy?
Should we administer both carboplatin and paclitaxel weekly?
Does the use of targeted biologics obviate the benefit of intraperitoneal chemotherapy?
Should consolidation therapy be offered to all patients after initial treatment with debulking surgery and chemotherapy?