

COMMENTARY

Better Therapeutic Trials in Ovarian Cancer

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The Ovarian Task Force of the Gynecologic Cancer Steering Committee convened a clinical trials planning meeting on October 28–29, 2011, with the goals to identify key tumor types, associated molecular pathways, and biomarkers for targeted drug intervention; review strategies to improve early-phase screening, therapeutic evaluation, and comparison of new agents; and optimize design of randomized trials in response to an evolving landscape of scientific, regulatory, and funding priorities. The meeting was attended by international clinical and translational investigators, pharmaceutical industry representatives, government regulators, and patient advocates. Panel discussions focused on disease types, early-phase trials, and randomized trials. A manuscript team summarized the discussions and assisted with formulating key recommendations. A more integrated and efficient approach for screening new agents using smaller selective randomized trials in specific disease-type settings was endorsed, together with collaborative funding models between industry and the evolving national clinical trials network, as well as efforts to enhance public awareness and study enrollment through advocacy.

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Recent years have witnessed important changes in our understanding of epithelial ovarian cancer (EOC), from that of one disease toward an appreciation of a set of unique diseases of diverse origin and biology, linked primarily by ovarian localization, with profound therapeutic implications.

A plateau in the slope of improvement achieved with conventional cytotoxic agents is apparent. The advent of targeted therapeutics raises challenges to existing clinical paradigms. The clinical trial milieu, despite improved intergroup cooperation, remains a financial and regulatory maze—daunting to pharmaceutical innovator, clinical investigator, and potential research subject. A collaborative planning meeting, with broad representation, was perceived as one strategy to promote innovative future trial design.

Reforming Pathology Concepts

Historically, EOCs were thought to arise from ovarian surface epithelial cells, with metaplasia leading to five major cell types: serous, endometrioid, clear cell, mucinous, and transitional. Although differences in biology and response to therapy were recognized, it was thought that these cell types reflected morphologic variants of the same disease, and cell type was not a treatment consideration.

Advances in pathology have demanded a change in this model (1). Serous carcinomas have been subdivided into high-grade (HGSC) and low-grade (LGSC) (2,3), with transitional carcinomas, apart from rare malignant Brenner tumors, now regarded as a variant of HGSCs (4). In addition, carcinomas diagnosed in the past as poorly differentiated, high-grade endometrioid, or mixed almost invariably exhibit p53 mutations and are best classified as HGSCs (5). The resulting five EOC cell types in descending frequency (HGSC,

endometrioid with or without clear cell components, pure clear cell, mucinous, and LGSC) differ in risk factors, precursor lesions, patterns of spread, underlying molecular abnormalities, and chemosensitivity (summarized in Table 1). These entities can be reproducibly diagnosed (6,7) and are best considered as separate diseases.

There is increasing evidence that EOC arises from distinct, often nonovarian, precursor lesions. The majority of peritoneal HGSCs are believed to arise from serous tubal intraepithelial carcinoma, usually located in the fimbriated distal portion of the fallopian tube. Among high-risk germline BRCA mutation carriers, these precursor lesions have been commonly identified in the tube, without ovarian precursors, as subsequently observed in some cases of sporadic HGSC (8–10). Ovarian endometrioid carcinoma (EC) and clear cell carcinoma (CCC) are associated with endometriosis (11,12). Atypical noninvasive endometriosis has been shown to be linked to adjacent CCC through demonstration of identical *ARID1A* mutations in both components (13), as well as *MET* amplification and mutations in *PIK3CA*.

Based on cell type, molecular features, and clinical characteristics, these entities represent discrete diseases, with implications for prevention, screening, and treatment, including the development of tailored subtype-specific approaches (14).

Evaluating New Treatments in the Age of Biomarkers

Recognition of unique types of EOC is already having an impact on clinical trials. Failure to consider accurate diagnosis could dilute any type-specific treatment benefits or imply benefit within a disease type where it does not exist while exposing all subjects to

Table 1. Disease types and characteristics*

Descriptors	HGSC	CCC	EC	MC	LGSC
Percentage of cases					
FIGO I–II	39%†	33%	22%	5%	1%
FIGO III–IV	86%†	2%	7%	2%	3%
Genetic risk factors	BRCA1/2	HNPCC	HNPCC	None known	None known
Environmental risk factors	↓Risk with OC and tubal ligation; ↑Risk with HRT	None known	↓Risk with OC and tubal ligation; ↑Risk with HRT	None known	None known
Precursor lesions	Serous tubal intraepithelial carcinoma	Endometriosis	Endometriosis	Unknown	Serous borderline tumor
Clinical presentation	Ascites, GI symptoms	Adnexal mass	Adnexal mass	Adnexal mass	GI symptoms
Pattern of spread	Peritoneal, nodal	Peritoneal, nodal, hematogenous	Peritoneal, nodal, hematogenous	Peritoneal +/- Pseudomyxoma peritonei	Peritoneal, nodal
Chemotherapy response	Sensitive, then resistant	Resistant	Sensitive	Resistant	Resistant
Molecular genetics (illustrative)	p53, BRCA1, BRCA2, HRD with genomic instability	PI3K, ARID1A, MSI	PTEN, beta catenin, ARID1A, MSI	KRAS, HER2	BRAF, KRAS, NRAS
Knowledge gaps	Overcoming drug resistance, targeting tumor stem cells	Risk modification, effective chemotherapy	Risk modification	Effective chemotherapy	Effective chemotherapy
Prevention	OC, tubal ligation, RRBSO	None known	OC, tubal ligation, RRBSO, avoid HRT	None known	None known
Screening	None known	None known	None known	None known	None known
Potential targets	PARPi, Angiogenesis	Angiogenesis	Hormone receptors, mTOR	HER2/neu	BRAF, MEK

* CCC = clear cell carcinoma; EC = endometrioid carcinoma; GI = gastrointestinal; HGSC = high-grade serous carcinoma; HRD = homologous recombination deficiency; HRT = hormone replacement therapy (postmenopausal); LGSC = low-grade serous carcinoma; MC = mucinous carcinoma; MSI = microsatellite instability; mTOR = mammalian target of rapamycin; OC = oral contraceptive; PARPi = poly-ADP-ribose polymerase inhibition; RRBSO = risk-reducing bilateral salpingo-oophorectomy.

† Includes mixed histology tumors with high-grade features.

potential toxicities. More selective trials will also more accurately characterize baseline type-specific clinical metrics.

There is a compelling need to identify valid clinically relevant biomarkers. Most biomarkers are prognostic, such as the extent of residual disease after cytoreductive surgery, and are associated with outcomes that are independent of any specific treatment. Factors associated with a reduced risk of recurrence, such as KRAS or BRAF mutation in LGSC, could also be used to minimize postsurgical interventions (15,16).

Predictive biomarkers define the potential for response to a specific treatment intervention. Often these represent genetic aberrations, for example, *HER2* amplification predicts clinical benefit from anti-*HER2* therapy in breast cancer (17). In non-small cell lung cancer, biomarkers related to *ALK* kinase rearrangements predict susceptibility to a class of *ALK* inhibitors (18), with similar data in melanoma for selected mutations in *BRAF*. Predictive markers in EOC have been more difficult to define. This is perhaps best illustrated by the dramatic response to VEGF inhibition observed in a minority of patients, which cannot be predicted on the basis of any validated molecular biomarker. Indeed, clinical biomarkers, such as the presence of ascites and

pleural effusions, have been used to help select patients for anti-VEGF therapy in the setting of recurrent disease.

In EOC, germline *BRCA1/2* mutations have demonstrated diagnostic, prognostic, and predictive significance. It is now appreciated that deleterious germline *BRCA1/2* mutations are present in at least 15% of women with HGSC, and these tumors have a better prognosis compared with sporadic HGSC, regardless of treatment (19). Although a diagnosis of HGSC, in and of itself, predicts for response to polyADP-ribose polymerase inhibition, there is greater predictive value when correlated with *BRCA1/2* mutation status (20–22). In addition, tumors with *BRCA1/2* mutations are also more likely to respond to nontargeted cytotoxic agents, such as doxorubicin (23,24). Based on these findings, there is agreement that HGSC, with or without *BRCA1/2* mutations, should be studied independently from other EOC types. In addition, a number of strategies to better identify tumors with more broadly defined defects in double-strand break repair are under development.

Validated biomarkers can be used for subject selection and stratification to enhance pharmacodynamic and outcome analysis. There is enthusiasm to stratify within a trial where a putative

biomarker is being evaluated. Caution is needed, as was observed in LGSC, where the MEK inhibitor selumetinib appeared less active in subjects with KRAS or BRAF mutations, which had initially been proposed to predict for increased activity (25). This emphasizes the importance of validating sensitivity, specificity, and predictive value of molecular markers before limiting therapy to a marker-positive population. Parallel molecular networks, feedback loops, and secondary mutations can also influence response over time.

Large-scale collaborative mining of molecular data has revealed unanticipated complexity within the HGSC family (26), with the emergence of four subtypes based on mRNA expression profiles (27). Although more study is needed to validate key pathways and potential targets within each subset, these data suggest that more consideration might be given to the selective use of immune modulators, angiogenesis- and stromal-targeted agents, and polyADP-ribose polymerase inhibition with chemotherapy, reflecting current areas of research.

Ovarian CCC has been shown to depend upon the IL6/JAK2/STAT3 pathway, and sunitinib, an agent that shows activity against renal CCC, has also shown activity against ovarian CCC xenografts (28,29). Trials open to CCC could corroborate this molecular signature while also determining whether CCC histology, irrespective of primary tumor site, reliably identifies patients for whom pathway-targeted therapy may have greater therapeutic relevance. In addition, efficient nontraditional strategies are needed to evaluate potential targets and therapies in rare tumor subsets, such as the overexpression of HER2 in a proportion of mucinous tumors (30), which is being studied through a consortium of investigators (<http://www.smartcancerproject.com>).

Appreciation of the different types of EOC, including subtypes of HGSC, as well as the targeting profiles of available agents, must inform clinical trial development. Clearly, collection of tumor and validation of potential surrogates (such as ascites, circulating tumor cells or microsome fragments, or free DNA), is crucial within the context of clinical trials, ideally with pre- and post-treatment samples to investigate targeting and evolution of resistance. Guided needle biopsy techniques have become safer, and high-quality molecular data can be obtained from small samples. However, the issue of intratumoral heterogeneity and the need for multiple specimens must be considered, as well as the substantial nonreimbursed costs of these minimally invasive procedures. Integration of specimen acquisition with routine treatment would be ideal and facilitated by strategies such as neoadjuvant chemotherapy with interval cytoreductive surgery.

Optimizing Design of Randomized Trials

We are in the midst of a transition to strategies incorporating targeted therapeutics. However, conventional cytotoxics retain a central role, and primary therapy will generally require sequential or combined regimens to maximize clinical benefit. Traditional approaches to drug development are being increasingly taxed by the multitude of potential targets and candidate drugs. Primary study endpoints, such as median overall survival (OS), were adopted at a time when few agents were effective in EOC and the management of recurrent disease had little impact on outcomes.

Newer agents may not demonstrate traditional dose-related toxicities and are frequently intended for chronic administration, with cumulative toxicity often more relevant than acute first-dose

events. Optimal biologic dose, that which achieves the desired effect upon receptor, gene expression, or signal transduction, can be difficult to determine. Modified phase I designs using expanded cohorts treated for multiple cycles, with laboratory correlates, will better guide subsequent randomized trials. Such schemes may confirm safety and targeting and provide an estimate of clinical activity. These integrated strategies conserve patient resources while accelerating overall development but with some risk of missing smaller treatment effects. Importantly, in the setting of HGSC, phase I trials may ethically enrol newly diagnosed patients because the experimental combinations generally incorporate standard cytotoxic agents in this chemo-responsive cohort.

Traditional phase II trials were developed to screen conventional cytotoxic agents against historical controls. This approach has obvious limitations when applied to targeted agents, which may not elicit a measurable response or may be designed to work in conjunction with conventional therapy; clinically important treatment effects could be missed. Additionally, historical data from mixed populations are unlikely to define meaningful thresholds of drug activity when applied to type-specific trials.

In view of the number of new agents that merit evaluation, it would be appealing to have a more efficient phase II paradigm that could incorporate multiple combinations (with a single reference arm) and offer the ability to compare and select among agents within the same general class or explore combinations of targeted agents. In practical terms, this has proven difficult because of the need to involve multiple sponsors with different investigational agents and intellectual property and financial interests. Some studies can be conducted using a neutral broker, such as the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute. One example, supported by CTEP through the national cooperative groups, was the BeST randomized phase II trial in renal cancer, which evaluated the addition of other targeted agents to bevacizumab (31). In the iSPY2 breast cancer trial (NCT01042379), case patient were randomized between a common standard reference arm and a biomarker-directed arm that also incorporates standard therapy (32). Successful biomarker/drug pairs can then move forward for phase III assessment. Of note, this trial is using pathologic complete response to neoadjuvant therapy as the primary endpoint, which facilitates rapid evaluation of each experimental arm.

When early-phase data appear interesting but might not be sufficient to support a fully powered phase III trial, there are randomized designs that incorporate an embedded phase II component (33). These designs include an interim analysis to confirm disease-specific activity and feasibility before enabling full phase III accrual. This avoids the need for two separate trials and allows patients enrolled on the phase II component to contribute to the final phase III endpoint, conserving clinical and financial resources. A logical extension of this approach is the multiarm, multistage design, perhaps beginning with a five-arm randomized phase II component, followed by an interim analysis, dropping arms that fail to reach predetermined thresholds for efficacy or tolerability (34). The final phase III component might only include two or three of the original arms. Applying such a strategy within a large, multicenter trial is challenging from an administrative and regulatory perspective but can be successfully managed, as illustrated by the STAMPEDE experience in prostate cancer (35). Enhanced coordination through

resources such as a centralized institutional review board can facilitate operations across multiple centers.

A hybrid randomized design could use a longitudinal reference arm, such as carboplatin and paclitaxel, which would remain continuously open as experimental arms are sequentially phased in and out. An unbalanced randomization (eg, 2:1) to the experimental arm would minimize the number of patients assigned to the reference arm and facilitate rapid evaluation of experimental arms based on predetermined activity thresholds. This would allow stratification of patients, overcoming time and treatment variation biases. Favorable arms would be selected for phase III expansion, fully powered to assess progression-free survival (PFS) or OS.

Exploiting opportunities in response to new knowledge comes with challenges (Table 2). Needed are methods to optimize identification of best in class and balance clinically meaningful activity with quality of life. We also need to determine optimal dosing for each agent and combination, which could exceed the capacity of our traditional research infrastructure. For example, in combination regimens, the minimal dose necessary to jointly modulate a common target, rather than maximal tolerated doses of each agent, may be sufficient.

The validity of the phase III endpoint of OS has been diminished by an increasing number of available treatment options for management of recurrent disease, with the majority of well-planned trials showing no survival advantage. One key confounder is crossover after progression, which can be incorporated within the trial design but more commonly occurs when identical (or similar) agents are commercially available external to a clinical trial. The impact of crossover is illustrated by the substantial 12-month improvement in median OS associated with incorporation of paclitaxel in GOG111, followed immediately by the lack of any improvement in OS when the exact same regimen was evaluated in GOG132, which permitted crossover (36,37). This has prompted greater consideration of PFS as the preferred primary endpoint because the timing of progression is not altered by secondary treatments. However, PFS is subject to detection bias, requiring better control over post-treatment monitoring. In recent years, progression has tended to be driven by minor changes in high-resolution serial radiographic

imaging rather than new symptoms or clinical findings. The impact of image-based progression in an asymptomatic population is readily illustrated by step-wise decrements within actuarial survival curves corresponding to the timing of scans at 6- to 8-week intervals. Although a relatively short advantage in PFS may achieve statistical significance, it may not translate into meaningful clinical benefit. In view of these uncertainties, most registration trials include sufficient accrual to evaluate both PFS and OS.

An alternative approach for determination of clinically meaningful disease progression could be through event-triggered imaging (Figure 1). Scheduled scans would still be obtained but at longer intervals, perhaps every 4 to 6 months. Trigger events would be predetermined (and might include a proportional increase in CA125, new physical findings, new symptoms related to disease, and/or changes in functional imaging) and would prompt traditional cross-sectional disease imaging. This would have the advantage of reducing the frequency of expensive scans and insurance copayments while defining more robust clinical endpoints but could introduce some minor variability in the timing of progression. Another approach would be to select more clinically relevant endpoints, such as control of disease-related symptoms or time to initiation of next treatment, rather than asymptomatic progression of small-volume disease.

With the push toward targeted and individualized treatments, there has also been increased pressure from regulatory agencies to use companion diagnostics predictive of response and to select appropriate patients. However, the relationship between prognostic and predictive markers can be complex, with some markers having both prognostic and predictive impact, such as germline *BRCA1/2* mutations. Because not all presumptive biomarkers will be validated, it is sometimes more useful to include a wider variety of patients with tumor specimens that can be studied for multiple markers and pathways. If the patient population is too narrowly defined based on putative targets, it may be more difficult to enroll patients and randomize to a treatment arm that does not include access to a particular drug because patients could perceive a risk of denied access to treatment. Furthermore, with heightened expectation of benefit from a new treatment, there can be increased

Table 2. Design challenges

Design elements	Challenges
Dose selection	Optimal biologic dose vs maximally tolerated dose vs dose density or cumulative dose delivery over time
Agent selection	Limited comparative data available to guide selection of agents for clinical trials on the basis of class, mechanism, specificity, preclinical activity, tolerability, convenience, cost, or industry sponsorship
Combination regimens	Optimized drug and dose selection to minimize toxicity, vertical pathway integration, lateral crosstalk between pathways, dual-targeting of the same component, and multitargeting of different components with a single agent
Schedule selection	Weekly dosing can be more effective and better tolerated for some agents but is generally more expensive and inconvenient. Chronic daily dosing requires an adjusted process for determination of optimal dose and monitoring of toxicity, including late effects, as well as the impact on quality of life.
Health-related quality of life and toxicity	Balance between activity and health-related quality of life needs to be considered, particularly with chronic dosing in the setting of recurrent disease.
Statistical power	Some ovarian cancer types (morphologic and molecular) fall into a rare disease category, limiting the ability to conduct phase III trials, even with international collaboration.
Outcomes measures	Postprogression treatment complicates overall survival endpoints, and historical benchmarks for progression-free survival may lack validation in smaller subpopulations.
Resources	Reduction in national funding for clinical trials with scientific endpoints, greater emphasis on industry collaboration toward drug registration

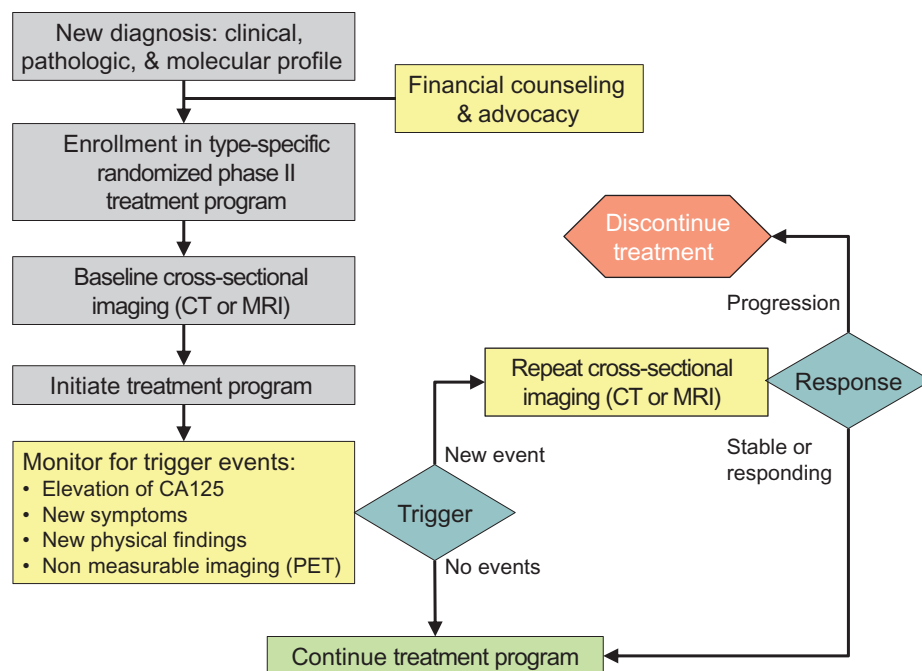


Figure 1. Idealized representation of clinical trials enrollment and assessment of tumor response according to an event-triggered process. CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

dropout (or early progression) on the standard arm, which can be difficult to control, even with administration of placebo. Some phase III trials have opted to incorporate asymmetric randomization, such as 2:1, to make the study more acceptable to patients, but this can reduce the power and increase the overall sample size.

Another important consideration is access to biospecimens, which are required to validate potential biomarkers, confirm targeting, and explore pathways of drug resistance. Most valuable are serial specimens from the same patient collected as sequential treatments are administered. The demand for serial sampling reflects the profound intratumoral heterogeneity of EOC and the importance of contemporary sampling to accurately reflect molecular dynamics over time (38). Without funding for such sampling, to include optimally-processed tumor and plasma, future trial designs should mandate specimen acquisition at the time of diagnosis, then at interval cytoreductive or other surgeries.

A challenging area related to biomarkers involves commercial laboratories that have achieved clinical laboratory certification to market tests that profile tumor or host molecular and genetic characteristics and have proposed that these assays can guide treatment selection. It is important to note that these assays have generally not been submitted to the US Food and Drug Administration for analysis of clinical benefit, nor have any yet been prospectively evaluated in a randomized trial. It remains to be seen whether collaborative strategies will evolve to validate these commercial profiling assays in the setting of newly diagnosed EOC, compared with more targeted evaluation of specific mutations, intracellular pathways, and functional paradigms, such as homologous recombination DNA repair.

Functional imaging can also provide a source of biomarker data, and studies should consider incorporation of perfusion-based computed tomography, diffusion-weighted magnetic resource imaging, and positron emission tomography, depending on the specific

clinical scenario and availability of resources. An important partner in these efforts has been the American College of Radiology Imaging Network.

National enrollment on high-priority clinical trials remains low, and this is partly attributable to the risk of financial deficit related to inadequate per capita reimbursement and the increasing regulatory and administrative overhead associated with clinical research. Other barriers to enrollment include geographic considerations (large academic centers vs community-based practice or rural populations), underserved and under-represented populations, language of informed consent and associated educational materials, a bias against enrollment in clinical trials for treatment of newly diagnosed disease, and unstructured use of advocacy resources. Finally, with implementation of the Affordable Care Act, potential ambiguities with regard to coverage and confusion among patients and providers could constitute yet another barrier to recruitment.

An opportunity exists to increase the utility of patient advocacy in the conduct of clinical trials. Advocates have been involved peripherally, serving on Department of Defense (DOD), Centers for Disease Control and Prevention, National Institutes of Health and Gynecologic Oncology Group (GOG) review committees and task forces, with the role of enhancing subject accrual and retention. Although they rarely endorse specific trials, advocate organizations provide information about EOC to their communities and assist in locating and encouraging participation in relevant trials. Advocate concerns about trial design mirror those of researchers, including access for underserved populations, recruitment and retention, time to completion, relevant quality-of-life measures, and effective, ongoing, transparent communication with trial participants. With structured effort and modest additional resources, patient advocates have the capacity to increase their impact and address areas of shared concern (Table 3).

Table 3. Advocacy and information sharing

Program/process	Comments
Internet-accessible trial descriptions	Accessible descriptions of currently enrolling trials, eligibility criteria, and contact information. Available through National Cancer Institute, national cooperative groups, individual cancer centers, advocacy groups, and foundations. Requires continuous updating, if not linked to an actual database
Internet-accessible educational programs	Interactive webinars repeated at specified intervals, and prerecorded sessions on-demand, particularly for newly diagnosed patients and their caregivers, to address the purpose of trials and the myths that constitute barriers to recruitment
Educational meetings	Collaborative educational sessions organized between advocacy and survivor groups together with established clinical trials and professional organizations, such as the Foundation for Women's Cancers and the Society of Gynecologic Oncology
"Patient-friendly" documentation	The key is early involvement of advocates in the design phase of a trial, throughout its development and implementation, with a focus on trial descriptions, additions to formal consent materials, supplemental materials to foster transparency, and foreign language resources.
Clinical research hot line	Tailored interaction and referral assistance for patients and family members
Trial alert system	Advocacy and support groups* hold a variety of community meetings and events that serve as forums to engage the community in learning about trials, in general, and about specific trials actively enrolling.
Sisters support network, trial ambassadors	Survivors are eager to help others diagnosed with epithelial ovarian cancer and to also identify treatment options for themselves. They can be organized into a resource network to identify potential trial participants and provide personalized information and education.
Online discussions	Online resources should not be used to advertise a particular trial, but list managers can provide information and questions to stimulate discussion. Of particular note are INSPIRE (http://www.inspire.com/groups/ovarian-cancer-national-alliance/) and ACOR (http://www.acor.org).
Caregiver resources	Caregivers frequently explore trial options and are eager for information and education.
Trial news	A structured "newsletter" for patients on a specific trial (or group of trials) with updated information about the study, including recruitment, presentation of results, and points of contact
Legislative advocacy	Collaboration between research and advocacy communities to help set research priorities, allocation of funding, treatment guidelines and access to new agents, and insurance coverage for therapeutic trials

* Groups include Foundation for Women's Cancer, National Ovarian Cancer Coalition, Ovarian Cancer Research Fund, Ovarian Cancer National Alliance, Ovarian Cancer Canada, Association of Cancer Online Resources, and their partners, local chapters, and affiliates, which encompass survivors, newly diagnosed patients, caregivers, families, and other interested parties.

Working Postulates and Recommendations

EOC is a generic term, ascribed to a variety of tumors that involve the ovary and arising from Müllerian tissues, including the distal fallopian tube (HGSC) and foci of endometriosis (CCC and EC). EOC consists of five distinct types: HGSC, CCC, EC, mucinous, and LGSC, with characteristic histologic and clinical features, as well as associated molecular findings (mutations, expression profiles, pathway activation, and whole genome variations).

The distinct profiles of CCC, mucinous carcinoma, and LGSC warrant the development of type-specific interventions. These are uncommon diseases, and international collaboration is required, with public and private partnerships to support clinical trials and acquisition of biospecimens, particularly in subjects with rare tumors and exploitable targets.

Clinical trials have led to meaningful improvements in PFS and OS for those with high-stage EOC, but have not yet improved disease-specific mortality, emphasizing the need to evaluate new biologic initiatives.

Most EOC presents at a high stage (stage III–IV), reflecting a preponderance of HGSC and early peritoneal dissemination, profoundly limiting the opportunity for screening to reduce mortality.

Less than one-third of EOC presents at a low stage (stage I), with a preponderance of CCC, EC, or mucinous carcinoma. In accurately staged patients without HGSC, surgical cure can often be realized, and a role for adjuvant chemotherapy has not been established.

Clonal tumor populations can evolve under pressure from targeted and nontargeted interventions, and studies should incorporate serial biospecimen acquisition, ideally with multiple specimens from different tumor sites within the same subject over time. The expanded use of neoadjuvant chemotherapy with interval cytoreductive surgery offers an attractive strategy for integration with pre- and post-treatment specimen collection.

Selective, multiarmed, randomized, phase II designs with appropriate internal reference arms are preferred to screen new agents and combinations because of the heterogeneity of EOC at a clinical and molecular level, which has limited the usefulness of historical data to establish meaningful decision thresholds for non-randomized trials.

Comparative and combinatorial studies of new targeted agents are sorely needed but are very difficult to achieve between different commercial sources at early stages of drug development before initial regulatory approval. Ideally, such studies can be conducted with a single corporate sponsor or across corporate entities using a neutral broker (such as CTEP).

Noncommercial (government and foundation) support is needed to address high-priority scientific and clinical questions. However, reductions in federal funding are already shifting the emphasis toward smaller trials within the National Clinical Trials Network. Flexibility is needed to promote the development of hybrid private–public collaborative agreements that could support larger registration trials with potential impact on standards of care.

When promising regimens are identified, the usefulness of larger randomized trials would also be improved by incorporating multiple experimental arms with an internal reference arm, dropping nonpromising arms through early futility analyses, and using secondary endpoints to develop biomarkers, including imaging.

National enrollment levels on high-priority trials will remain low unless the increasing costs and complexity of research (clinical, translational, regulatory, and administrative) are adequately managed and reimbursed, including sustainable partnerships with insurance providers for coverage of nonresearch components. Although improvements have been implemented in response to national panels and reports, the continuing goal must be to simplify and unburden, eliminating nonessential elements that detract from recruitment.

Substantial patient barriers exist to trial participation, including geographic access, underserved medical needs, language, insufficient educational resources, complexities of informed consent, and limited advocacy or navigation support. Resources directed to advocacy groups would promote improvements in trial design, development of educational materials, and barrier-free access. In the United States, reinforcement of coverage under the Affordable Care Act is essential.

In view of the limitations of screening, support is needed for international registration studies to address modified risk-reduction strategies, such as salpingectomy, in high-risk populations.

In conclusion, it is our hope that future clinical trials in ovarian cancer will use more efficient integrated designs to speed the evaluation of promising new interventions while embracing innovative partnerships between the pharmaceutical industry and the National Clinical Trials Network (supported by the National Cancer Institute) and engaging more actively with advocacy groups to enhance awareness and enrollment on high-priority clinical trials.

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