Gynecologic Cancer Steering Committee
Ovarian Clinical Trial Planning Meeting
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Introduction/ Meeting Description: *The Ovarian Clinical Trials Planning Meeting convened in Philadelphia, PA at the Renaissance Hotel at the Philadelphia airport on October 28-29, 2011. The goals of this meeting were to:*

- ***Identify key tumor types, high-priority molecular pathways, and biomarkers for targeted intervention;***
- ***Undertake critical analysis of early-phase clinical trials for screening of new agents and combinations;***
- ***Identify the barriers and potential solutions for rapid evaluation of new agents, including comparative and combinatorial studies;***
- ***Optimize design of larger phase II-III trials to define new standards of care and facilitate drug registration, including international collaboration***
- ***Navigate the landscape of scientific priorities, regulatory compliance, funding and targeted accrual.***

The meeting was attended by clinical and translational investigators, international colleagues involved with clinical research, representatives from the pharmaceutical industry, FDA, and patient advocates. Most of the attendees were included on discussion panels for each of the three sessions, reflecting their expertise with the subject matter. There were approximately 96 attendees at the meeting.

Background and Summary of Discussions Leading to Recommendations:

- Epithelial Ovarian Cancer (EOC) is a generic term ascribed to tumors that involve the ovary. Most, if not all, are derived from Müllerian tissues, including the fallopian tube, ovarian surface, inclusion cysts, endometriotic foci or the peritoneal cavity.

- Approximately 75% of EOC is diagnosed at advanced-stage (III-IV), reflecting the biology of peritoneal implantation, which can occur as an early event in cancer development, and limiting the effectiveness of screening with available markers and imaging technologies.
- Clinical trials have demonstrated modest incremental improvements in median progression-free survival (PFS) and median overall survival (OS) for patients with advanced-stage disease, but this has not yet translated into a change in overall disease-related mortality rates in the United States or Canada.
- There are distinct histologic types of EOC, including high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), clear cell carcinoma (CCC), mucinous carcinoma (MuC), endometrioid carcinoma (EC), and carcinosarcoma (CS). In addition to characteristic microscopic and clinical features, each of these tumor types have been associated with distinct molecular findings, including specific gene mutations (loss of function and activating), gene expression profiles, pathway activation, and whole genome variations associated with genomic instability.
- Over 75% of patients with advanced-stage EOC have HGSC histology. Of these, nearly 100% have loss-of-function mutations or deletions of p53, and approximately 50% demonstrate homologous recombination deficiencies (HRD) in DNA repair, due to functional loss of BRCA1/2 and associated pathways. Together, these and other molecular changes contribute to genomic instability and chemotherapy resistance, which are hallmarks of EOC, and potential targets for clinical trials.
- There is an emerging perspective that many tumors previously classified as high-grade endometrioid ovarian tumors share many features such as immunohistochemcial and mutation profile with, and thus are actually HGSC. Such cancers should be included in planned studies of HGSC. In contrast, low-grade endometrioid tumors share features of typical endometrioid endometrial carcinomas

- The clinical and molecular features of LGSC, CCC, MuC, and CS are sufficiently distinct from HGSC to warrant the ongoing development of separate clinical trials to evaluate specific chemotherapeutic and molecular-targeted strategies.
- The potential for tumor molecular networks to evolve in response to treatment selection will increase, particularly as treatment interventions become more specifically targeted. This will require an emphasis on collection of serial tumor specimens from the same patient over a period of time.
- With increased molecular targeting of new agents, the lack of validated biomarkers, the heterogeneity of disease, and the use of drug combinations, it is more difficult to rely on historical data from mixed populations to establish thresholds of drug activity in non-randomized trials. As such, randomized phase II trials with multiple experimental arms, and appropriate internal reference (control) arms, should provide a more efficient paradigm for selection of promising treatment strategies.
- Comparative and combinatorial studies of new molecular targeted agents are needed, but this remains difficult to achieve across different pharmaceutical entities at early-stages of drug development (prior to FDA approval of a primary indication). Some studies can be conducted within a single corporate entity, or across entities, using a neutral broker (such as the Cancer Therapy Evaluation Program of the National Cancer Institute), but this applies to only a small subset of potential studies.
- Due to the impact of cytoreductive surgery and platinum-based chemotherapy, metrics do not exist for the clinical interpretation of front-line non-randomized phase II trials in patients with newly-diagnosed advanced-stage disease, and it has become common practice to move from exploratory phase I trials to fully-powered phase III trials without an opportunity for phase II confirmation and optimization.
- While phase III trials to change standard-of-care or obtain regulatory approval for a new treatment intervention are important, it is also necessary that NCI-supported research address high-priority scientific and clinical questions. In many cases, this could be best achieved using a hybrid funding model, involving collaborative

support from industry, NCI, and national cooperative groups. The current funding model is limited by the requirement for standardized per capita funding, and does not encourage more innovative collaborative agreements.

- The research focus of larger randomized trials should incorporate strategies that will increase the overall efficiency of our clinical trials program, such as multiple experimental arms with a single reference (control) arm, early analysis of futility to drop arms that appear non-promising, and secondary endpoints to promote development of useful biomarkers (including imaging technologies).
- National enrollment on high-priority clinical trials remains low, due to the risk of financial deficits related to inadequate reimbursement, as well as the increasing regulatory and administrative overhead associated with clinical research. Alternative embedded designs are needed to optimize the review process and the overall cost of study activation, accrual, and data management.
- Other barriers to clinical trials 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 front-line clinical trials (for treatment of newly-diagnosed disease), and unstructured utilization of advocacy resources.

Consensus & Recommendations:

Short term:

- Continued development of clinical trials for patients with EOC and high-grade serous histology involving international coordination through the Gynecologic Cancer InterGroup (GCIG).
- Recognition that distinct clinical trials should be developed for other tumor types, including LGSC, CCC, MuC, and CS.

- Greater utilization of randomized phase II designs (front-line and recurrent) with multiple experimental arms to more efficiently select promising agents and combinations for phase III evaluation, with appropriate benchmarks and thresholds for activity, including dual-endpoint designs.
- Increased flexibility to support the negotiation of collaborative agreements among CTEP-NCI, the pharmaceutical industry, and national cooperative groups, including partial sponsorship for clinical trials reimbursement (per capita payments).
- Greater utilization of multi-arm multi-stage design in the context of larger phase III trials to permit early analysis of futility and elimination of non-promising arms.

Long Term:

- Increased structured involvement of advocacy groups and resources to optimize the design and availability of clinical trials, and overcome barriers to accrual, including modular consent documents, and optimized cross-over designs to maximize the proportion of subjects able to receive experimental therapy.
- Request for NCI support to encourage clinical protocols that include serial tumor banking over a period of time from the same patient.
- Support for international observational studies to address tumor biology, including the role of the Fallopian tubes and salpingectomy.
- Expanded role of CTEP-NCI (or a Foundation) as a broker for multi-agent trials involving more than one sponsor