Published OnlineFirst May 24, 2019; DOI: 10.1158/1078-0432.CCR-19-0619

CCR Perspectives in Regulatory Science and Policy

Clinical Cancer Research

Advancing Drug Development in Gynecologic Malignancies

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Abstract

Gynecologic malignancies continue to be a major cause of morbidity and mortality in the United States despite recent advances in oncologic therapies. To realize the promise of immunotherapy and biomarker-driven approaches to improve clinical outcomes for patients, better communication among stakeholders in the drug development and approval pathways is needed. To this end, the FDA-AACR-SGO Drug Development in Gynecologic Malignancies Workshop brought together clinicians, patient advocates, researchers, industry representatives, and regulators in June 2018, to review the state of the science in gynecologic cancers and explore how scientific advances impact approval processes. Topics of discussion and key takeaways are summarized in this *Perspectives in Regulatory Science and Policy* article. Single-agent immunotherapies have demonstrated variable and often modest response rates among gynecologic cancers. Combination therapies and other novel approaches, such as cell-based therapies, may show improved efficacy compared with single-agent immunotherapies; however, utilizing innovative clinical trial designs will be necessary to progress further. Companion and complementary diagnostics inform physicians of potential benefits of specific therapeutics for patients; however, they serve different functions that have important regulatory implications, thus trialists should understand the distinctions between diagnostic types. PARP inhibitors hold great promise for treating ovarian cancers, both as monotherapies and in combination with chemotherapeutics, other targeted agents, and immunotherapies. Rare gynecologic cancers often exhibit unique molecular characteristics that can serve as effective targets to which novel therapeutics can be developed. This workshop highlighted the importance of future open discussions on scientific and regulatory challenges in drug development for gynecologic malignancies.

Introduction

It is critical for stakeholders to understand the interaction between scientific advances and the regulatory approval process in order to optimize the development of novel agents to advance outcomes for patients with gynecologic cancers. Although new targeted therapies, including anti-angiogenic drugs, poly (ADP-ripose) polymerase (PARP) inhibitors, and immunologic agents have been approved for gynecologic cancers, further development and advances are needed.

To this end, the FDA hosted a workshop that was cosponsored by the American Association for Cancer Research (AACR) and Society of Gynecologic Oncology (SGO) entitled "Drug Development in Gynecologic Malignancies." The purpose of this workshop was to review the current state of the science in gynecologic cancers and to explore how recent scientific advances potentially impact regulatory approval processes. On this issue, the recent regulatory targeted gynecologic approvals of four different agents resulted from translational breakthroughs in gynecologic and other malignancies, and they have spurred additional developments. Namely, there have been large investments in combination trials, especially in ovarian cancer, with trials in progress with combinations of anti-angiogenics, PARP inhibitors, and immunotherapeutics in all lines of therapy. Specific goals of the workshop are highlighted in Box 1.

Biological Rationale and Challenge of Immunotherapy for Gynecologic Cancers

Multiple studies have postulated a biological rationale for immunotherapy across gynecologic malignancies, focusing on: (i) immunoreactive ovarian cancers with higher numbers of tumor-infiltrating lymphocytes having superior survival; (ii) the presence of foreign human papilloma virus (HPV) epitopes in cervical cancer–enhancing tumor immune recognition; and (iii) the abundance of neoepitopes in mismatch repair (MMR)-deficient patients with endometrial cancer promoting tumor immune recognition.

Although responses to immunotherapy among gynecologic malignancies are frequently durable, one critical challenge is determining *a priori* benefit utilizing biomarkers considering the

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Clin Cancer Res 2019;25:4874–80

doi: 10.1158/1078-0432.CCR-19-0619

Published OnlineFirst May 24, 2019; DOI: 10.1158/1078-0432.CCR-19-0619

Box 1: Workshop Goals

To review the state of the science in gynecologic malignancies and to discuss, in an open forum among regulators, clinicians, patient advocates, industry, and researchers, in the context of gynecologic malignancies, how to:

- Explore how scientific advances impact approval processes;
- Incorporate rational immunotherapy combinations into study designs;
- Understand and utilize biomarkers effectively for both incorporation into clinical trials and patient selection in clinical practice;
- Develop novel study designs for rare gynecologic tumors and subtypes of common tumors;
- Optimize patient outcomes by most efficiently identifying novel therapeutics for potential regulatory approval; and
- Accelerate the development of immunotherapies, targeted therapies, and combination therapies.

low percentage of responders, severe side effects, and cost. Existing biomarkers are not yet sufficient to guide gynecologic patient selection for immunotherapy; optimal patient selection will depend on integration of tumor, blood, host, and environmental factors, and will require validation via clinical trials. Another challenge is that single-agent immunotherapies often are not highly efficacious in this patient population; successful treatment will likely require combinations of therapies in most patients.

Efficacy/Safety of Single-Agent Immunotherapy in Gynecologic Cancers

Development of immunotherapeutics in gynecologic malignancies has explored both single agents and combinations. In endometrial cancer, DNA MMR loss leading to microsatellite instability (MSI) is common, with up to 35% of tumors showing defects in MMR genes. Most of these alterations are somatic, due largely to epigenetic silencing via methylation. However, pathogenic mutations can also occur. Lynch syndrome is defined by these MMR gene mutations occurring in the germline. MMR-deficient tumors, including endometrial cancer, have response rates exceeding 30% with single-agent anti-PD-1 therapies. Durable responses can also occur in heavily-pretreated patients. PD-L1 expression alone appears less robust than MSI as a biomarker for response to pembrolizumab in endometrial cancer. MMR immunohistochemistry (IHC) or MSI testing is recommended for all endometrial cancers and can be considered in all gynecologic cancers.

Cervical cancer is a rational target for immunotherapy based on foreign HPV viral antigen presence, higher expression of PD-L1 documented in virus-associated cancers, and the upregulation of PD-1 seen in early cervical lesions such as cervical intraepithelial neoplasia. However, single-agent immune checkpoint inhibitors (ICI) have variable response activity in cervical cancer (range 3%–26%; refs. 1, 2). PD-L1 expression alone does not appear to be a robust, independent biomarker for response. Lymphocyte depletion after chemoradiation and T-cell exhaustion associated with chronic viral infection may blunt response to ICI therapy in cervical cancer.

Ovarian cancer is characterized by limited expression of biomarkers of response to ICI, including low levels of PD-L1 expression and MSI, and the lowest tumor mutation burden of all gynecologic cancers. Effective immunotherapy in ovarian cancer will likely require combinatorial approaches using multiple ICIs, cancer vaccines, or adoptive cell therapy. Sensitization with radiation, targeted therapy, or chemotherapy may be required to deliver effective responses to immunotherapy.

Efficacy/Safety of Combination Immunotherapy in Gynecologic Cancers

Understanding how immunotherapies interact with agents that increase antigen presentation and T-cell activation such as chemotherapy, radiation, and the plethora of novel targeted agents is critical. Four specific combination strategies were highlighted at the workshop: (i) PARP inhibitors + immunotherapy, (ii) vascular endothelial growth factor (VEGF) inhibitors + immunotherapy, (iii) chemotherapy + immunotherapy, and (iv) complementary immune therapies.

The combination of PARP inhibitors and immunotherapy is promising in platinum-resistant patients lacking mutations in the DNA damage repair pathway. Although PARP inhibitors enhance antigen presentation and T-cell activation, they can also increase DNA damage, innate immune responses, and mutational burden (3). VEGF is immunosuppressive via numerous mechanisms, including direct and indirect effects on dendritic cells, T cells, and myelodysplastic cells, as well as induction of abnormal tumor vasculature that reduces tumor T-cell trafficking. Thus, VEGF blockade can increase the tumor T-cell population.

Rational immuno-oncology combinations enhance stimulatory and block inhibitory interactions and require understanding of cancer-specific immune-inhibitory mechanisms, such as CTLA-4 and PD-1 pathways, that prevent overwhelming immune self-attack but can be leveraged as therapeutic targets in cancer. For example, dual immuno-blockade of inhibitory receptors with anti-PD-L1 and anti-CTLA-4 reverses dysfunctional tumor-infiltrating lymphocytes by increasing antigen-specific $CD8^+$ and $CD4^+$ T cells that increase cytokine release, while decreasing suppressive T-regulatory cell function. Furthermore, triple and even quadruple biologic therapy is currently being explored (Table 1). Vaccines and epigenetic therapies represent new frontiers as both likely increase neoantigen load, thereby optimizing immuno-oncologic efficacy.

Novel Immunotherapy Approaches and Cell-Based Therapy for Gynecologic Oncology Patients

Other novel immunotherapy approaches discussed at the workshop included cell-based therapies and delivery timing (i.e., optimal sequential administration). The overall goal of immunotherapy is to develop a cellular immune response against tumor-associated antigens, which is a multistep process that offers numerous opportunities for therapeutic intervention. For example, immunization can result in tumor-associated antigen presentation to dendritic cells, and immunosuppressive factors

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Table 1. Combination therapies for gynecologic malignancies in recent clinical trials

Combination	Indication	Trial size	Trial phase	Primary endpoint	Trial completion date
Atezolizumab + bevacizumab	2L+PR, CRC, RCC, NSCLC, TNBC, gastric	*N* = 240	Phase I, safety expansion cohort 2L+PR ovarian added 7-2015	DLT	Dec 2018
Vanucizumab + atezolizumab	2L + AST incl. PR/Ref ovarian	*N* = 132	Phase I	ORR	Dec 2016
Atezolizumab ± bevacizumab ± aspirin vs. bevacizumab vs. atezolizumab	2-4L PR ovarian	*N* = 160	Phase II/III	6m PFS	Jan 2021
Pembrolizumab + ziv-aflibercept	2-3L PR	*N* = 36	Phase I	DLT	Dec 2018
Pembrolizumab + bevacizumab + Cyclophosphamide	2L + ovarian	*N* = 40	Phase II/III	PFS	Dec 2018
Nivolumab+ bevacizumab	2-4L ovarian	*N* = 38	Phase II/III	ORR	Feb 2020
Durvalumab + olaparib + cediranib	AST	*N* = 384	Phase I/II	ORR	Dec 2018
Olaparib + tremelimumab	2L PR or PPSR ovarian	*N* = 68	Phase II/III	Safety	Sept 2019
Olaparib + tremelimumab	2L + gBRCAm ovarian	*N* = 50	Phase II/III	ORR	Feb 2020
Durvalumab+ tremelimumab+ olaparib	PSR/PRR BRCAm ovarian	*N* = 39	Phase II/III	PFS	Aug 2019
Pembrolizumab + niraparib	TNBC, 3-5L (P1) or 3-4L (P2) PRR ovarian	*N* = 121	Phase II/III	ORR	May 2018
TSR-042 + niraparib or paclitaxel/carboplatin vs. TSR-042 + bevacizumab vs. TSR-042 + bevacizumab + paclitaxel/carboplatin	AST	*N* = 168	Phase I	Safety	Oct 2019
BGB-290 + BGB-A317 (PD1)	AST	*N* = 230	Phase I	ORR	Apr 2019
Rucaparib + atezolizumab	BRCAm/HRD+ PSR OC, TNBC	*N* = 48	Phase II/III	DLT	Jan 2019
Rucaparib + nivolumab vs. Rucaparib vs. nivolumab vs. placebo	1L mtx all-comers	*N* = 1,012	Phase II/III	PFS	Dec 2024
Talazoparib + avelumab	NSCLC, BC, PSR ovarian, bladder, prostate	*N* = 316	Phase II/III	ORR	Mar 2020
BMS-986016 (LAG3) ± nivolumab	AST, ovarian cohort only in the dose escalation arm	*N* = 1,000	Phase I	Safety	Aug 2020
Nivolumab + varlilumab (CD27)	2-6L ovarian, NSCLC, mel, CRC, SCCHN	*N* = 175	Phase II/III	ORR	Dec 2018
Nivolumab vs. nivolumab + ipilimumab (CTLA-4)	2-4L PR or PPSR ovarian	*N* = 96	Phase II/III	ORR	Dec 2020
FPA008 ± nivolumab (CSF1R)	2L+ ovarian, NSCLC, SCLC, SCCHN, panc, RCC, Gliomas	*N* = 295	Phase I	Safety, ORR	Mar 2019
Nivolumab + IFN-gamma	2L+ AST	*N* = 15	Phase I	Safety	Dec 2019
nivolumab + WT1 (vaccine)	2L + maintenance ovarian	*N* = 11	Phase I	DLT	Apr 2019
ABBV-428 ± nivolumab (CD40)	2L+ AST incl. ovarian	*N* = 172	Phase I	Safety	Apr 2019
Atezolizumab + GDC-0919 (IDO1)	AST, ovarian cohort added in aug 206	*N* = 158	Phase I	DLT	Dec 2019
Atezolizumab ± guadecitabline ± CDX-1401 vaccine (HMA)	2L+ PRR ovarian	*N* = 78	Phase II/III	PFS	Mar 2020
Avelumab + defactinib (FAK)	4-7L ovarian	*N* = 98	Phase I	ORR	Nov 2018
Durvalumab + tremelimumab (CTLA-4)	2L+ ovarian, RCC, CRC and cervical	*N* = 106	Phase I	Safety	Jun 2019
Durvalumab + VTX-2337 (TLR8) + Pegylated Liposomal Doxorubicin	2-3L PRR or PPSR ovarian	*N* = 53	Phase II/III	PFS	Dec 2018
Durvalumab + AZD1775 (wee1)	AST	*N* = 55	Phase I	DLT	Apr 2019
Durvalumab + tremelimumab + chemotherapy (CTLA-4)	1L AST	*N* = 42	Phase I	Safety	Jun 2019
Durvalumab + TPIV200 (vaccine)	2L + PRR ovarian	*N* = 29	Phase II/III	ORR	May 2019
Durvalumab + tremelimumab (CTLA-4)	PRR ovarian	*N* = 100	Phase II/III	irPFS	May 2021
Durvalumab + trabectedin (DNA groove)	gBRCAm ovarian/sarcoma	*N* = 50	Phase I	MTD	May 2020
Durvalumab + ONCOS-102 (T-cell adenovirus)	AST incl. PRR ovarian	*N* = 78	Phase II/III	Safety	Jul 2020

secreted from tumors can be blocked by specific small-molecule inhibitors.

T-cell expansion is necessary for immune response and can be augmented by adoptive transfer of activated antitumor T cells that are collected from the patient, expanded or genetically modified in culture, and then re-administered to the patient to facilitate tumor-antigen recognition to effect cancer cell destruction. This response can be further enhanced by using specific "immunostimulatory" monoclonal antibodies (i.e., agonists of CD40/CD137/OX40) and/or cytokines (i.e., IL12/IL15/IL21).

Further progress in these areas will require use of innovative clinical trial designs including translational endpoints that assess

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dynamic changes using on-treatment biopsies assessing tumor and surrounding microenvironment.

Innovations in Immuno-oncology Clinical Trial Designs and Statistical Considerations for Immuno-oncology Trials

The significant promise of immune-targeted therapy is countered by efficacy heterogeneity among different tumor types and complexity of potential therapeutic partners (e.g., biologics, chemotherapeutics, and radiation).

Although investigation of traditional endpoints, such as objective response rate and progression-free survival (PFS), still serve as immune therapy primary objectives, these endpoints may not be fully representative of efficacy, serve as good surrogates for overall survival, or be amenable to interpretation under standard assessment practices such as RECIST (4–7). These difficulties are due to tumor response characteristics with immune-targeted interventions, such as early progression before response ("pseudo-progression"); overall survival benefit without improvement in objective response or PFS; and loss of statistical power for inference of intermediate (i.e., futility) endpoints due to prolonged times to disease progression (8–10).

In light of these observations, new approaches to clinical trial design could better assess a regimen's toxicity profile, as well as its efficacy/futility. Because there are many potential novel combinations to explore, adaptive trial designs offer not only the ability to assess toxicity and efficacy based on prior knowledge during the trial's conduct, but also the opportunity to expand a cohort or rotate in new agents upon futility without suspending the trial. A key advantage of Bayesian trial designs over the traditional "3+3" phase I safety assessment is a much more efficient and accurate algorithm to identify a predetermined safety benchmark. In-tumor efficacy evaluation, such as receptor engagement or microenvironment immune cell infiltration, can be contemporaneously measured with toxicity by utilizing dual endpoints. These combined assessments of safety and efficacy can be used to optimize the most promising cohort into later development. Multiple different tumor types can be evaluated in the same trial, and different "go/no-go" decisions and safety signals can be explored simultaneously as demonstrated in the Keynote-001 trial, whereby pembrolizumab received approval in several indications (11). With trials needed to assess dosing, schedule, disease-type, biomarkers, and multiple drug combinations, adaptive designs may be the optimal clinical trial construct. Although these adaptive designs are being used more commonly, they have not been widely adopted in gynecologic malignancies.

Another design issue originates from the increased use of immunotherapy in combinations. When assessing efficacy with multiple drug combinations, it may not be possible to isolate the effect of each individual agent in the combination. In these cases, important information regarding contribution of effect can be obtained from separate trials that are often conducted earlier in drug development where a smaller combination of agents could be studied.

FDA Perspective on Biomarker Development

In the era of precision medicine, biomarker selection of patients for treatment with a specific therapeutic requires development of an *in vitro* diagnostic device (IVD) in concert with the development of the investigational drug such that the therapeutic product and device may be approved contemporaneously. Recent approvals for the treatment of ovarian cancer across various lines of therapy with PARP inhibitors illustrate some important approaches to the co-development of an IVD and determination of a companion or complementary diagnostic.

The initial approval of olaparib for patients who had received 3 or more prior lines of chemotherapy included only those with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer. This accelerated approval coincided with the approval of the companion diagnostic BRACAnalysisCDx, an IVD developed to correctly identify patients in this clinical setting who would benefit from treatment with olaparib. Similarly, the approval of rucaparib for the treatment of patients with gBRCAm advanced ovarian cancer who had received 2 or more prior lines of chemotherapy occurred contemporaneously with the first next-generation sequencing (NGS)-based companion diagnostic device, the FoundationFocusCDX$_{BRCA}$ test. In these specific clinical situations, the diagnostic devices were deemed essential for the safe and effective use of the associated drugs, and thus were approved as companion diagnostics.

In contrast to companion diagnostics, a complementary diagnostic device can inform patients and prescribers about the potential benefit from treatment with a specific therapy, but the device, and thus the presence of the biomarker, is not required for use of the drug. When rucaparib was approved for the maintenance treatment of women with recurrent ovarian cancer, the clinical data submitted to the new drug application (NDA) supported a broad indication, not limited by biomarker to a specific subpopulation. However, on the ARIEL3 study that supported this approval, patients were stratified by germline/somatic BRCA mutation, genomic loss of heterozygosity (LOH), and biomarker negative using a clinical trial assay and bridged to the NGS-based FoundationFocus CDx$_{BRCA\ LOH}$. This device was approved as a complementary diagnostic whereby prescribers can make an informed decision about the potential benefit of using rucaparib based on patients' biomarker status, but the device is not required for the safe and effective use of the drug in this setting.

PARP Inhibitors: Therapeutic Use and Resistance

PARP inhibitors (PARPi) came into focus due to their synthetic sickness (or functional synthetic lethality) with aberrations in homologous recombination (HR) initially based on aberrations in the BRCA1/2 tumor suppressors that predispose individuals to breast and ovarian cancers (12). A significant part of the activity of PARP is mediated by its role in protecting replication forks. PARPi induce replication fork collapse, resulting in accumulation of DNA damage. This activity may be accentuated in cancer cells due to ongoing replication stress. Following the implementation of PARPi as agents of synthetic sickness through inhibition of PARP enzyme activity, it was found that PARPi trap PARP on DNA, creating difficult-to-repair lesions. Indeed, the concentration dependence of PARPi activity in patients correlates better with their ability to trap PARP than with their ability to inhibit PARP enzyme activity.

Multiple PARPi have been approved in ovarian cancer due in part to the high frequency (approximately 50% of high-grade

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Table 2. Mechanisms of resistance to PARPi

Constitutive	Acquired
Ras mutation	Reconstitution of HR
	• Healing of BRCA1/2, Rad51C, Rad51D
	• Demethylation of BRCA1/2 promoter
	• Upregulation of hypomorphic mutant BRCA1/2 allele
	• Loss of shield complex
GPB1 loss	Replication fork protection
	• Loss of MLL3/4 or PTIP (MRE11 effector)
	• Loss of EZH2 (MUS81 effector)
	• Decreased proliferation
	Other
	• Loss of PARP
	• PARP mutations
	• PARG-mediated reversal of ADP ribosylation of PARP
	• Overexpression and fusion of P glycoprotein/MDR/ABC transporters
	• Loss of SLFN11
	• EMT
	• Removal of ribonucleotides by ribonuclease H2

serous ovarian cancers) of aberrations in HR in high-grade serous ovarian cancers. Although companion diagnostics are not required by the FDA for the use of PARPi in all ovarian cancer indications, benefit is most clearly manifest in patients with HR defects (HRD) which can be identified through a number of approaches. Indeed, the approval of PARPi for maintenance in patients who respond to platin-based chemotherapy may derive from the observation that platinum sensitivity, and particularly repeated platinum sensitivity, may be a surrogate for HRD. The sensitivity of cells with HRD to PARPi has opened up novel therapeutic opportunities associated with the induction of HRD or extensive DNA damage in tumor cells that are normally HR competent. Indeed, there are ongoing and planned combination studies of PARPi with radiation and chemotherapy; anti-angiogenesis agents; HDAC, BRD4, MAPK, and PI3K pathway inhibitors; and inhibitors of DNA damage repair. As noted above, the ability of PARPi to increase DNA damage could potentially increase the numbers of neoantigens present and activate STING responses that could augment the activity of immune oncology agents (3).

Unfortunately, like many targeted therapies, the responses of most patients to PARP inhibitors are transient. This has created a need to identify and reverse both preexisting and emerging mechanisms of resistance to PARPi (Table 2). Most resistance mechanisms have been identified in model systems and, with the exception of reconstitution of HR, which accounts for up to 20% of observed PARP resistance, appear to occur rarely in patients. Thus, the majority of the causes of PARP resistance in patients remain to be elucidated.

Emerging Opportunities in Rare Gynecologic Cancers

The definition of "rare cancer" is based on disease prevalence. The NCI defines rare cancers as those with prevalence of <15 per 100,000 people/year, whereas the European Society for Medical Oncology defines their prevalence as <6 per 100,000 people/year. For orphan status designation by FDA for rare disease, the disease must affect fewer than 200,000 people in the U.S. However, even among the more common cancers, there are subtypes that are relatively rare. For example, *POLE* mutations are present in only about 7% of endometrial cancers (13). For ovarian cancers, high-grade serous is the most common histologic subtype whereas others, such as low-grade serous (LGSC), clear cell (OCCC), endometrioid, and mucinous, represent frequencies of 2% to 25% (14). Many of these rare subtypes have unique molecular features that may offer therapeutic vulnerabilities (14–17). For example, ovarian small cell carcinomas can be classified as "pulmonary type" or "hypercalcemic type" (18); the hypercalcemic type had remarkable responses to PD-L1 blockade (19). In OCCC, PIK3CA and ARID1A alterations may occur in roughly 50% of cancers, which could make them uniquely vulnerable to some of the targeted therapies (15).

Progress in Drug Development for Rare Epithelial Ovarian Cancers: The NRG Oncology (GOG) Experience

Challenges for clinical studies related to rare cancers include: small numbers of cases, long accrual times, less attention by the scientific community, lower availability of funding, fewer patient advocates, and lower priority by pharmaceutical companies. Novel therapy development for rare malignancies in the gynecologic oncology group (GOG) has been facilitated by establishment of the Rare Tumor Committee in 2005. Examples of clinical trials include GOG-240, a randomized controlled trial of paclitaxel/topotecan versus paclitaxel/cisplatin with or without bevacizumab in patients with metastatic, recurrent, persistent cervical cancer. Patients receiving bevacizumab in addition to chemotherapy displayed significantly improved overall survival

Box 2: Key Workshop Takeaways

- Single-agent immunotherapies have demonstrated variable and often modest response rates among gynecologic cancers.
- Combination therapies and other novel approaches, such as cell-based therapies, may show improved efficacy compared with single-agent immunotherapies.
- Preclinical, mechanistic models support testing combinations of anti-angiogenics, PARPi, and immunologic agents.
- Determination of the relative contribution of each component of combination therapies is necessary to understand observed efficacy and toxicity.
- Innovative clinical trial designs evaluating 3 or more cohorts will be necessary to effectively and efficiently assess novel strategies.
- Trialists should understand the distinctions between companion and complementary diagnostics, whose different functions have important regulatory implications.
- PARPi hold great promise for treating ovarian cancers, both as monotherapies and in combination with chemotherapeutics, other targeted agents, and immunotherapies.
- Rare gynecologic cancers often exhibit unique molecular characteristics that can serve as effective targets to which novel therapeutics can be developed.

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Box 3: Future Directions

- Recent activity in the development of new therapies for ovarian, uterine, and cervical cancers has created a robust portfolio of clinical trials in gynecologic malignancies that will produce results over the next few years and could lead to new standards of care.
- Continued advances in molecular biology will reveal new potential targets that will generate novel therapeutic platforms, particularly for rare gynecologic cancers and tumors.
- Implementing novel clinical trial designs that include adaptive constructs and addressing barriers to clinical trial participation will improve efficiencies and maximize resources.

(17.0 months vs. 13.3 months) and PFS (8.2 months vs. 5.9 months) compared with those receiving chemotherapy alone (20). For LGSC, GOG-239 (phase II) demonstrated an objective response rate of 15% and a clinical benefit rate of 80% for selumetinib (21). For OCCC, multiple phase II trials have been conducted or initiated. Several other trials (e.g., MILO, GOG-281, NRG-GY-019) are either planned or underway.

Conclusions

The topics covered in this workshop—combination strategies, immunotherapy, biomarkers, therapeutics development in rare subtypes, and more—are critical to advancing stakeholder understanding and facilitating expeditious development of safe and effective drugs for gynecologic malignancies. Box 2 provides more detail on Key Takeaways, and Box 3 outlines future directions and goals for the field. Although progress has been made over the last 5 years, continued open discussions such as the FDA–AACR–SGO workshop will further advance the science and encourage rational development of effective novel therapeutics to benefit women afflicted with gynecologic cancers.

Disclosure of Potential Conflicts of Interest

R.L. Coleman reports receiving commercial research grants from Abbvie, AstraZeneca, Gateway Foundation, Clovis, Genentech, Genmab, Janssen, Merck, and V-Foundation, and is a consultant/advisory board member for Abbvie, Agenus, Aravive, AstraZeneca, Clovis, Gamamab, Genentech/Roche, Genmab, Janssen, Merck, Oncomed, and Tesaro. R.C. Arend is a consultant/advisory board member for Clovis, Tesaro, Pfizer, PUMA, and AstraZeneca. G.B. Mills reports receiving other commercial research support from AstraZeneca, Ionis, Karus Therapeutics, Nanostring, Pfizer, Tesaro, and Takeda/Millenium Pharmaceuticals, has licensed technologies to Myriad (HRD Assay) and Nanostring (DSP), holds ownership interest in Catena Pharmaceuticals, ImmunoMet, SignalChem, Spindletop Ventures, and Tarveda, and is a consultant/advisory board member for AstraZeneca, Chrysalis, ImmunoMET, Ionis, Mills Institute for Personalized Care, Nuevolution, PDX Pharma, Signalchem Lifesciences, Symphogen, and Tarveda. A.K. Sood reports receiving commercial research grants from M-Trap, holds ownership interest in BioPath, and is a consultant/advisory board member for Merck and Kiyatec. T.J. Herzog is a consultant/advisory board member for AstraZeneca, Caris, Clovis, Genentech, Tesaro, and Johnson & Johnson. No potential conflicts of interest were disclosed by the other authors.

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Acknowledgments

R.L. Coleman receives support from the Judy Reis/Al Pisani, MD Ovarian Cancer Research Fund, the Ann Rife Cox Chair in Gynecology, NCI grant P50CA217685, and CPRIT RP210214. G.B. Mills received support from a kind gift from the Adelson Medical Research Foundation, support from the Ovarian Cancer Research Foundation and NCI grants: 1P50CA217685, 1U01CA217842, and P50CA098258. A.K. Sood received support from the NCI grants P50CA217685, P50CA098258, and R35CA209904; American Cancer Society Research Professor Award; and the Frank McGraw Chair in Cancer Research.

Received February 22, 2019; revised April 18, 2019; accepted May 21, 2019; published first May 24, 2019.

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Published OnlineFirst May 24, 2019; DOI: 10.1158/1078-0432.CCR-19-0619

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Clin Cancer Res 2019;25:4874-4880. Published OnlineFirst May 24, 2019.