Society Position Statement/White Paper

FDA ovarian cancer clinical trial endpoints workshop: A Society of Gynecologic Oncology White Paper☆

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Thomas J. Herzog [a], Gwynn Ison [b], Ronald D. Alvarez [c], Sanjeeve Balasubramaniam [b], Deborah K. Armstrong [d], Julia A. Beaver [b], Annie Ellis [j], Shenghui Tang [e], Peg Ford [f], Amy McKee [b], David M. Gershenson [h], Geoffrey Kim [b], Bradley J. Monk [h], Richard Pazdur [i], Robert L. Coleman [g,*]

[a] University of Cincinnati Cancer Institute, Dept. of Ob/Gyn, University of Cincinnati, United States
[b] Office of Hematology Oncology Products, OND, CDER, FDA, United States
[c] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN, United States
[d] Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, United States
[e] Division of Biometrics V, OB, OTS, CDER, FDA, United States
[f] Ovarian Cancer Alliance of San Diego, United States
[g] Department of Gynecologic Oncology & Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[h] U.S. Oncology, Phoenix, AZ, United States
[i] Oncology Center of Excellence, OMPT, FDA, United States
[j] Ovarian Cancer Survivor, White Plains, New York

1. Introduction

Optimizing clinical trial endpoint selection is an important goal that has significant implications for multiple constituencies. For clinical trialists, endpoints inform study design and conduct, and foster the most efficient use of resources while providing the most valid framework for critical analyses of results. For regulators and industry partners, endpoints define the roadmap for investigational product development and approvals. For clinicians, endpoints define the framework for practice-based decisions informing or defining new standards of care based on true clinical benefit. Most importantly, for our patients, endpoints

reflect treatment impact and strive to portray outcomes in a meaningful clinical context, thereby enhancing patient care.

Several years ago, the Society of Gynecologic Oncology (SGO) embarked on a dialogue with the key officials from the Food and Drug Administration (FDA) and others to better understand the regulatory approval process as it pertains to patients with ovarian cancer [1]. Driving the effort was the observation that new drug regulatory approvals in ovarian cancer were nearly absent over the previous decade. The dialogue was fruitful, informative, and constructive, and highlighted the need to develop clinical trials with endpoints that best address the unique features of the disease's biology and the affected patients. Ultimately, the raison d'etre was to expand drug development to address the high overall mortality associated with this disease. A key tenet of the endpoints discussion was understanding which clinical trial endpoints could be used for regulatory intent [2,3]. The FDA posited that endpoints other than overall survival (OS), such as progression-free survival (PFS) or overall response rate (ORR) with sufficient context-dependent response duration, could be acceptable for regulatory

Table 1
Efficacy endpoint considerations.

	Frontline	Platinum-sensitive	Platinum-resistant	Clear cell mucinous LG-serous
OS	Approve	Approve	Approve	Approve
PFS (statistically significant) + other (QoL/PRO)	Approve	Approve	Consider	Consider
PFS (statistically significant) with clinically meaning MOE[a] (median difference)	Consider (MOE: 6 mos?)	Consider (MOE: 4 mos?)	Consider (MOE: 3 mos?)	Consider
Objective response rate (with supportive duration of response)	No	No	Consider	Consider

[a] MOE, Magnitude of Effect, median difference between the experimental arm(s) relative to control.

decisions. The impact of this posture has recently greatly impacted clinical trial design and has facilitated drug development. Table 1 contextualizes the efficacy endpoint considerations. Suggested "minimal" treatment effects were purposefully vague, but in general, were meant to reflect not only a convincing difference between treatment arms to stakeholders (patients, clinicians, regulatory bodies, industry), but also an unbiased difference in treatment effect (e.g. 2 assessment or imaging cycles for studies mandating measurable disease). However, the impact must be couched by observed treatment-related toxicity. It was the intent of both organizations to provide stakeholders with a less opaque understanding of the regulatory requisites for ovarian cancer therapeutic approvals.

This productive discourse culminated in the FDA hosting a "Clinical Trial Endpoints In Ovarian Cancer" workshop in 2015. Stakeholders invited to participate included the American Association for Cancer Research (AACR), American Society of Clinical Oncology (ASCO), patient advocates, and SGO. The goals of this workshop were to review the current state of the science of ovarian cancer biology and implications for clinical trial design. Specific aims included: 1) to better understand the role of the neoadjuvant chemotherapy platform as an investigational opportunity and as a potential regulatory approval pathway; 2) to explore emerging classification systems for recurrent disease and measures of treatment effect, including circulating factors, tissue and imaging biomarkers; 3) to gain insight into the patient's perspective relative to current and future trial designs; 4) to discuss relevant endpoints reflective of the diversity of disease and patient populations and how these factors impact trial designs and determine endpoint selection; 5) to explore innovative trial designs and strategies for population enrichment relative to discovery and within the context of rare tumors, and the emergence of immune-oncology; and 6) to review common procedural pitfalls that undermine the validity of clinical trials.

1.1. Can neoadjuvant chemotherapy serve as a platform for discovery and regulatory action?

Neoadjuvant chemotherapy (NACT) as a treatment strategy for newly diagnosed primary ovarian cancer is practiced in a highly variable manner throughout the world. Despite two prospective, phase III, non-inferiority clinical trials demonstrating equal (and consistent) treatment effects on progression-free (PFS) and overall survival (OS), routine use is still a matter of intense debate [4,5]. However, general consensus has been reached that NACT is appropriate for patients considered medically unfit for surgery and for those in whom an optimal cytoreduction (defined as no visible residual disease or a complete gross resection) is not likely [6]. In these cases, induction chemotherapy, preferably 3–4 cycles, is administered followed by an attempted surgical resection in those not demonstrating overt progression.

Despite the inherent patient selection bias, NACT as a platform offers a unique opportunity to evaluate in-tissue treatment effects of therapy in an unbiased manner. Depending on the pre-chemotherapy assessment for NACT candidacy, this tissue sampling can also be anatomically directed, matched and paired within the same patient when surgical intervention is undertaken. Given the noted tumor heterogeneity of ovarian cancer, this type of tissue assessment reduces the potential for sampling error in hypothesis testing and provides a unique opportunity to assess pharmacodynamic treatment effects. Of particular value is the opportunity to study not only on-target treatment effects in the tumor cells but also the entire tumor microenvironment in local and metastatic sites. Documented alterations could be used for pre- or on-treatment biomarkers to better define populations gaining benefit or no benefit from a specific intervention and could pave the way for developing new integral biomarkers. Further, since tumor response can be formally assessed, unusual response (pathological complete response, pCR) could be investigated for regulatory purposes, much as it has in breast cancer trials [7]. However, it was noted that pCR rates in ovarian cancer are poorly described (ranging from 4%–7% under the strictest definitions) [4,5,8,9]. Our deliberations in the session on NACT, sought to explore these principles and to initiate a dialogue through which such investigation should proceed.

While using NACT as a platform for biomarker discovery and validation was highly supported and encouraged among the participants, its use as a regulatory tool was felt to be premature warranting further work to address the following issues:

- How do we define a cohort from which pCR rates under control therapy would be consistent?
- What methodology should be used to determine in whom NACT is offered?
- Should induction chemotherapy (type, amount, duration, etc.) be standardized?
- How should interval surgery be approached? What tissue sampling is necessary to declare a pCR (e.g. do the ovaries need to be histologically negative)? How many and what tissues need to be sampled? What evaluation is necessary for Stage IV patients, particularly for those with document chest disease (effusion and/or evaluable parenchymal disease)?
- What is the true prevalence of pCR in patients offered NACT currently?
- What is the magnitude of effect that would be considered "interesting" or "necessary" for regulatory filing?
- Does pCR need to serve a surrogacy role? For PFS? For OS? For both?

Additionally, while preliminary data support that pCR has prognostic value in respect to both PFS and OS (like breast cancer), such effects may not reflect value of a specific intervention. This was observed in a study of nearly 12,000 heterogeneous breast cancer patients receiving NACT in 12 international clinical trials [10]. While pCR rates were prognostic for PFS and OS at an individual level, there was poor correlation with the relative treatment effect compared to control treatment as measured by odds ratio with respect to pCR and by hazard ratio with respect to event-free survival. Thus, the predictive value of pCR was not observed at a population level. If this were observed for ovarian cancer, this discordancy could challenge the regulatory implications of experimental treatment within the NACT platform. However, it has been hypothesized that the poor surrogacy of pCR to survival in breast cancer trials may be due the limited focus on the tumor primary alone [11]. This is quite different than what would be proposed in ovarian cancer trials where pCR would be defined by tissue acquisition from the primary and the multiple metastatic sites within the abdominal-pelvic cavity. In this context, pCR would better reflect a systemic effect and, thus, may be a more meaningful surrogate endpoint for ovarian cancer.

The principal action item from this discussion was to develop language, standards, and strategy in response to the highlighted questions for further consideration.

1.2. How do we better classify ovarian cancer patients and enrich patient populations for clinical trials?

For many decades, there has been a "one-size-fits-all" policy for the conduct of clinical trials in patients with epithelial ovarian cancer. Traditionally, clinical trials for patients with newly diagnosed ovarian cancer have only incorporated surgical stage (i.e., early vs. advanced) and the results of primary cytoreductive surgery (i.e., optimal vs, suboptimal) as the basis for determining patient eligibility. Likewise, clinical trials for patients with recurrent ovarian cancer have largely focused on the treatment- or disease-free interval (< 6 mos. vs. ≥ 6 mos.) and the number of prior lines of therapy as principle eligibility criteria. Nomenclature reflecting these criteria have at times inappropriately labeled patients as "platinum-resistant" or "platinum-sensitive", based on arbitrarily defined time intervals from prior platinum-based therapy. Accordingly, there is a clear need to recognize that "ovarian" cancer represents a constellation of distinct subtypes of neoplasia, involving the ovary and related structures (i.e., the fallopian tube and peritoneum). This was also emphasized in the recently released Institute of Medicine's report entitled "Ovarian Cancers: Evolving Paradigms in Research and Care [12]."

Discussion at the conference highlighted that further classification of ovarian cancer into distinct subgroups will be key to the future of drug development in ovarian cancer. Conducting trials in distinct histologic subgroups of epithelial ovarian cancer is an important first step in better categorizing and enriching patient populations in this disease context. High-grade serous carcinoma (HGSC), the largest contributor to ovarian cancer mortality, has distinct biologic and clinical features from other epithelial types of ovarian cancer, such as low-grade serous, mucinous and clear cell adenocarcinoma [13]. (See Fig. 1) Indeed, clinical trials in these distinct subpopulations are ongoing and unique therapeutic approaches based on the biology of these distinct subtypes are being developed. (see Table 2)

Identification and incorporation of relevant biomarkers also represents another important step towards better classification of ovarian cancer patients and enrichment of clinical trials. For example, BRCA mutation status is known to correlate with long-term outcome and should be an important consideration when designing clinical trials for patients

with ovarian cancer. Specifically, BRCA mutation status was key to the approvals of the poly (ADP-ribose) polymerase (PARP) inhibitors, olaparib, in 2014 and rucaparib, in 2016 [14,15]. Similarly, recurrent ovarian cancer patients with a "BRCA-like" genotype have also been demonstrated to respond better to PARP inhibitors than those ovarian cancer patients with wild-type BRCA status. This suggests that a "BRCA like" genotype may also be an important biomarker to utilize when designing ovarian cancer clinical trials particularly for patients with HGSC, a patient population known to harbor genetic defects that affect homologous recombination repair in up to 50% of patients. A recently completed Phase III trial of another PARP inhibitor niraparib, approved in 2017, demonstrated significant reduction in the hazard for progression when administered as maintenance therapy to recurrent ovarian cancer patients responding to platinum-based chemotherapy [16].

There has also been increasing evidence over the past decade that the tumor immune microenvironment significantly impacts outcomes in ovarian cancer patients, and there are a number of immunotherapy trials that are ongoing or in development for patients with recurrent ovarian cancer [17]. Characterizing the tumor microenvironment with an immunoscore, such as that determined to be useful in colon cancer, or with alterations identified in early on-treatment biopsies or imaging, as has been recently discovered in melanoma, might be a factor to consider adding once validated in ovarian cancer [18,19].

Of note, categorizing patients with recurrent ovarian cancer strictly on the basis of a time line is a limiting and potentially flawed approach to determining ultimate prognosis and eligibility for clinical trials, particularly given the variability in surveillance strategies utilized to monitor ovarian cancer patients for recurrence and the increased sensitivity of modern day imaging technology. Factors such as histology and BRCA mutation status also play a major prognostic role in this clinical context. Utilizing a multiplex system that incorporates potentially multiple variables (i.e., histologic subtype, treatment free interval, number of prior therapies, biomarker or composite of biomarkers status, etc.) into the development of trials for patients with recurrent ovarian cancer should facilitate enrichment of study populations and allow for the selection of appropriate controls and clinical trial endpoints unique for the patient population and clinical scenario being investigated [20].
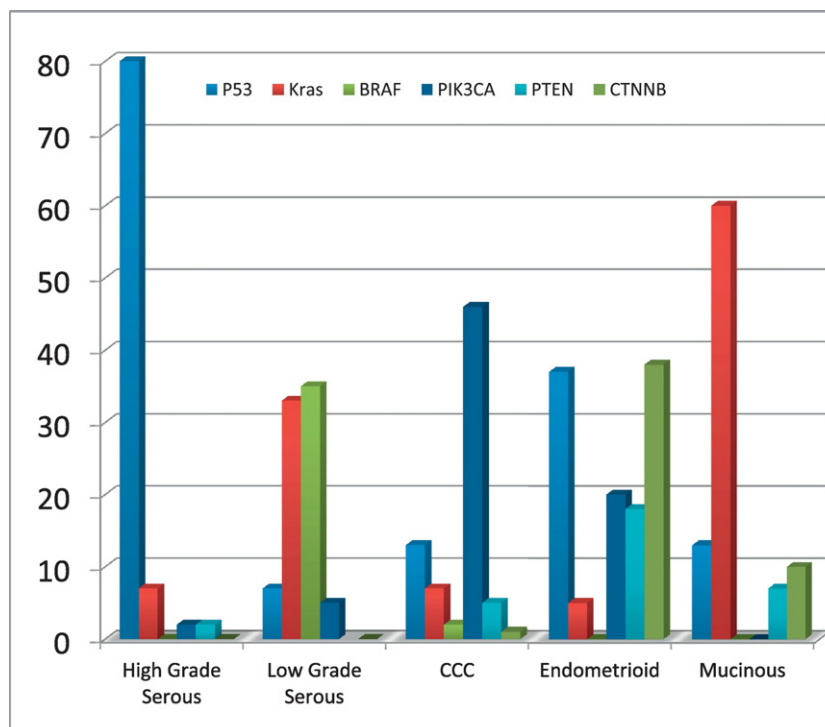

Fig. 1. Frequent mutational alterations in different ovarian cancer histological subtypes.

Table 2
GOG/NRG Oncology Trials for Rare Epithelial Ovarian Cancers.

Clinical trial	Phase	Disease setting	Investigational drug	Histologic subtype	Results
GOG 0241	III	Newly diagnosed	Oxaliplatin Capecitabine Bevacizumab	Mucinous	Pending (closed prematurely)
GOG 0239	II	Recurrent	Selumetinib	Low-grade serous	RR = 15%
GOG 0281	II/III	Recurrent	Trametinib	Low-grade serous	Ongoing
GOG 0268	II	Newly diagnosed	Temsirolimus	Clear cell	Pending
GOG 0254	II	Recurrent	Sunitinib	Clear cell	RR = 7%
GOG 0283	II	Recurrent	Dasatinib	Clear cell	Ongoing
GY-001	II	Recurrent	Cabozantinib	Clear cell	Ongoing

An extension of the discussion on updating the classification of recurrent ovarian cancer patients led to proposals for clinical trial enrichment. These strategies consisted of the following:

- Acknowledgement that epithelial ovarian cancer represents a constellation of diseases and thus a "one-size-fits-all" approach to treatment should be abandoned.
- Development of new classification systems for patients with both newly diagnosed and recurrent ovarian cancer that incorporate multiple descriptive factors with prognostic impact to facilitate enrichment of patient populations for clinical trials.
- Integration of the number and type of prior chemotherapy regimens, which influence drug clinical activity and tolerability.
- Selection of controls and endpoints for clinical trials should consider the unique patient populations being investigated.

1.3. Can tissue, circulatory, or imaging based biomarkers serve as independent clinical trial endpoints?

As our understanding of ovarian cancer as a heterogeneous and genomically unstable cancer evolves and as technologies advance, there is a greater potential to incorporate biomarkers into ovarian cancer diagnosis, prognosis, and treatment decisions [21]. From a drug development perspective there are four common biomarker categories: diagnostic, prognostic, predictive, and response biomarkers. There are many ways to incorporate biomarkers into an ovarian cancer clinical trial. Randomization of a trial could be stratified based on a biomarker and information obtained in both the marker negative and marker positive populations. A trial could also be enriched based on a biomarker if there was prior knowledge about a biomarker being only useful in a particular population or prior knowledge that demonstrated the biomarker identified a high-risk population to decrease heterogeneity [22]. A biomarker could also be used as an early indicator of drug activity informing a decision to move forward with a trial or switch treatments ahead of traditional imaging.

CA-125 is the most commonly used biomarker in ovarian cancer. However, despite widespread use, CA-125 response has not been used as an independent endpoint for drug approval in ovarian cancer. Over the years, multiple criteria describing CA-125 response have been proposed, some which incorporate Response Evaluation Criteria in Solid Tumors (RECIST v1.1) Criteria [23–26]. Although CA-125 sampling is convenient for patients, and may allow for an assessment of biochemical recurrences particularly in non-measurable disease patients, there is a low concordance of CA-125 with complete response. Furthermore, direct clinical utility of CA-125 has not been established [27]. The role of CA-125 is unclear with targeted therapies and the magnitude of reduction needed to predict clinical benefit is imprecise. There is a potential for CA-125 to be used in the incorporation of pharmacodynamic and pharmacokinetic endpoints to estimate optimal dose or inform upon prior assumptions in Bayesian designs. CA-125 requires further validation as an independent endpoint, but it potentially could be informative if presented in the context of RECIST v1.1 response rate.

Multiple novel tissue biomarkers that incorporate genetic signatures of ovarian cancer have been analyzed, but diverse data and methods make these difficult to compare or utilize in a clinically meaningful way. Liquid biomarkers, such as circulating cell-free tumor DNA (ctDNA), circulating tumors cells (CTC) and exosomes hold great potential in clinical investigation as they are easy to obtain, can be obtained repeatedly and may represent a molecular proxy of overall disease, thus avoiding concerns of intra-tumor and inter-metastatic tumor heterogeneity associated with tissue sampling.

Other non-invasive strategies include functional imaging modalities, such as PET, dynamic MRI and contrast CT. Although a detailed description of the state of the science for these modalities was beyond the scope of this workshop, it was noted that each of these tools is already under investigation in translational trials. While metabolic assessment with FDG PET—CT is used *qualitatively* in non-solid-tumor trials, *quantitative* standardized uptake value (SUV) measurements await multicenter validation. Among imaging biomarkers under development, modalities that image the tumor micro-environment (e.g. perfusion imaging and diffusion MRI) show the most promise in their availability, reproducibility and applicability to a wide range of tumor types and agents. In particular, perfusion CT scans as assessed at an early time point just one week into treatment have demonstrated the potential to predict progression free survival of patients treated with bevacizumab in combination with paclitaxel and carboplatin [28].

From a regulatory standpoint, a biomarker could be used in a single drug development program and become accepted for use through the Investigational New Drug (IND), New Drug Application (NDA) or Biologics License Applications (BLA) drug approval process along with a companion diagnostic device. In this pathway, Center for Drug Evaluation and Research and Center for Devices and Radiological Health work together to advise the development and ultimately approve a therapeutic product along with a companion diagnostic device deemed essential for the safe and effective use of the therapeutic product. The biomarker qualification program is a potentially complementary pathway in which a biomarker can become established for use in multiple development programs [29].

1.4. Lessons from the past: What are the perils and pitfalls of ovarian cancer clinical trials?

Systematic bias and confounding variables easily contaminate the results of clinical trials and erode confidence in both the interpretation of the results as well as the clinical validity of the findings. Five common errors were discussed in detail within the context of ovarian cancer clinical trials including:

1) Findings from clinical trials other than the primary endpoint.
"Study 19" was a randomized phase II study of maintenance olaparib in patients with platinum-sensitive relapsed serous ovarian cancer. Unfortunately, the germline *BRCA* mutation (gBRCAm) status in those enrolled was not prospectively collected [30]. This omission contributed to a negative vote by the FDA Oncology Drug Advisory Committee in 2014 because the retrospective identification of the gBRCAm population might have led to an imbalance of known prognostic factors in the treatment arms [31].

Even though exploratory analyses (and even secondary endpoints) are generally not sufficient for regulatory approval, occasionally they can significantly alter clinical practice. For example, the exploratory analyses of a predefined subgroup in ICON7, a phase III study of front-line bevacizumab, [32] has led many to preferentially use bevacizumab in only those newly diagnosed patients with high risk prognostic factors [33].

2) Over interpretation of strata analyses.

AURELIA was an open-label randomized phase III trial of chemotherapy with or without bevacizumab with PFS as its primary endpoint [34]. In addition to reporting the data in aggregate, the bevacizumab US package insert [35] presents efficacy and toxicity information on the three individual physician choice chemotherapy options [36]. A legitimate concern is inference of the treatment effect differences between these subgroups, where power to do so is limited. Another challenge raised in this trial was determining the independent effect that might have been realized from bevacizumab alone. Differences between the European and FDA approvals of bevacizumab potentially create uncertainty as to the appropriate setting for integrating bevacizumab into clinical practice [37].

Although anti-angiogenic agents seem to provide more clinical benefit in the setting of ascites, [38] this stratum in a phase III trial of trebananib in recurrent ovarian cancer was not sufficient for regulatory approval and requires prospective confirmation [39].

3) Challenges in "sensitivity" analyses and open-label trials

Prior to 2014, it had been eight years since the FDA approved a new agent in treating ovarian cancer. In 2006, a phase III trial of gemcitabine plus carboplatin versus carboplatin in patients with platinum-sensitive recurrent ovarian cancer led to FDA approval of this combination. This open label trial only showed a 2.8-month improvement in the median PFS. Being an open label trial, a sensitivity analysis was required to address potential bias in assessing progression [40]. A similar requirement was seen in AURELIA [36]. These analyses were complicated by missing radiologic scans prior to progression and by the fact that many patients began a new treatment regimen prior to documented protocol-defined progression, thus requiring censoring. Additionally, subjects who died or did not progress did not contribute to the assessment of efficacy. Although sensitivity analyses can add confidence to clinical endpoints of open-label trials, they frequently include small numbers of patients and are difficult to interpret. What if the sensitivity analysis contradicts the primary conclusions or is just borderline? Does it overcome the bias of not having a placebo or a blinded independent central review of the radiologic findings?

4) Incomplete patient-reported outcome data

Patient reported outcomes (PROs) are important components of randomized clinical trials and contextualize toxicity, PFS and OS. However, collection and interpretation may be challenging. Additionally, the optimal timing and methods of assessments are frequently unclear and often depend on the setting and agent being studied. Further research and consensus is needed in order to validate this tool. Specifically, what is the threshold for missing data that would preclude data interpretation? A frequent shortcoming of trials that rely on PRO's is missing data, which can introduce bias often seen with open label studies.

How should future trials integrate PROs? Separating disease versus treatment related effects on quality of life is important. Finally, maintenance trials differ in the assessment of PROs as the comparator is no treatment placebo.

5) Mid-trial amendments and their impact on Special Protocol Assessments (SPA)

SPA is a process in which sponsors may request to meet with FDA to reach agreement on the design and size of certain clinical trials, clinical studies, or animal trials to determine if they adequately address scientific and regulatory requirements. This enables the FDA to be aware of the developmental context in which the protocol is being developed and the questions being answered. However, because the SPA process adds time to the development process and substantial amendments

prior to the primary endpoint of the study design may invalidate the SPA, they are uncommon [41].

1.5. How do we assess efficacy with immunotherapeutics?

The development of effective immunotherapy has seen the beginnings of a dramatic shifting of the landscape of approved therapies for several types of cancer. While long held to be active only in melanoma and renal cell carcinoma, two cancers felt to be specifically immunogenic, newer immune agents have demonstrated efficacy in several clinical trials and so far have led to additional regulatory approval for use in urothelial, head and neck, bladder, as well as non-small cell lung cancer. Efficacy has also been demonstrated in a wide variety of malignancies in smaller studies, heralding the impending arrival of the immunotherapy era in oncology. The agents furthest along in development are antibodies targeting the immune checkpoint programmed death-1 (PD-1) receptor or its ligand, PD-L1; inhibition of this pathway is thought to reduce a suppressive signal that dampens endogenous antitumor T-cell activity, with expected autoimmune toxicities.

Several research programs have demonstrated both the presence of tumor-infiltrating lymphocytes (TILs) in ovarian cancer specimens and the association between TIL infiltration and patient outcome but immune activity has not yet been shown to be curative in this disease [42]. Immunotherapy for the treatment of ovarian cancer requires two basic components: the elaboration of anti-cancer specific immune effector cells, and intact pathways for those effectors to engage with and kill target tumor cells. The basic mechanism, often referred to as an immunologic synapse, requires the specific interaction of the T-cell receptor with the major histocompatibility complex (MHC) presenting the recognized antigen, in the context of several co-stimulatory signals, and without being over-dampened by tolerance-inducing inhibitory signals; when self-tolerance predominates, tumors effectively evade immune detection and killing.

Two broad approaches of anticancer immunotherapies are in development in numerous academic and industry research programs: the use of cellular-based therapies, such as T-cell transfer, and the use of molecules to modify immune interactions, such as checkpoint inhibitors and vaccines.

Cell transfer therapies hold the promise of personalized, specific treatments for cancer, and have several potential advantages that may be achieved once the technology is further developed: cells (TILs, tumor cells or peripheral blood lymphocytes) can be selected or manipulated outside of the patient to increase anti-cancer specificity, such as by genetic engineering of specific recognition receptors, and transferred to patients in large numbers. Several small trials have been performed and reported since the late 1990s, but the technology is undergoing rapid transformation.

Manipulation of a patient's immune system using antibodies has already demonstrated efficacy in many cancer types, including ovarian cancer; other types of therapies, such vaccines and small-molecule receptor inhibitors, are under development in this space as well. One early success [43] reports an expansion cohort in which 75 women with refractory/resistant ovarian cancer, 51 of whom had at least 3 prior regimens, were treated with the anti-PD-L1 antibody avelumab. Eleven patients (15%) had PR, including both patients enrolled with clear-cell ovarian cancer, a demonstration of the efficacy of immunotherapy in this disease. In another study, pembrolizumab, an anti-PD-1 antibody, achieved CR in 1 patient and PR in 2, in a small trial of heavily pre-treated women [44].

These initial successes highlight the importance of developing a better understanding of the immune system in its role in treating cancer—many aspects of these interactions are still poorly understood, even in disease settings where immunotherapy has already demonstrated a survival advantage. One hallmark of effective immunotherapy is the prolonged duration of response, despite relatively modest response rates; attempts at using biomarkers of immune recognition to

predict responding patients have been unsuccessful. Because of the natural history of ovarian cancer and its current treatment paradigm, additional questions arise as to the optimal application of immunotherapy: women who have had several lines of treatment will potentially have immune systems that are less robust due to prior antineoplastic exposure, but rounds of chemotherapy may also increase mutational load and therefore increase the unique antigenicity of tumors. Further questions surround appropriate patient selection, such as characteristics of disease burden; the utility of additional immune pathways; whether biomarkers may be useful as predictive markers; and, later, the optimization of combination therapies in order to fine-tune the breaking of self-tolerance, once single-agent efficacy is better understood.

Clinical trials designed to answer questions that will lead to drug approval must take into consideration key patient characteristics such as tumor burden, extent of initial surgical debulking (R0 resection rate) or results of neoadjuvant chemotherapy/pathologic complete response rate, and line of therapy. Key endpoints are generally prolonged durations of response, but promising response rates, especially in refractory disease settings, would also be feasible for regulatory consideration. Additional, novel endpoints for regulatory studies are under discussion, including landmark analyses and tumor growth kinetics. Strategies for accelerated approval can include planned, single-arm analyses, provided follow-up durations are adequate, but confirmatory endpoints must be carefully considered in the initial stages of trial design.

The era of anticancer immunotherapy promises to uncover a variety of new, effective treatment options for patients suffering from a variety of cancers. We have seen the early signs that these agents will also demonstrate efficacy for patients with ovarian cancer. A deeper understanding of immunology, coupled with careful clinical trial design specific to the nuances of validating metrics that define efficacy with immunotherapeutics, will accelerate the delivery of novel, safe, and effective agents to women with this disease.

1.6. What is the patient's perspective?

During the FDA Patient Representatives session, ovarian cancer survivors Peg Ford and Annie Ellis reviewed the recruiting, training and service of patient advocates and the survivor perspective on endpoints and side effect tolerability.

Although there has not been an increase in cure rates, women diagnosed with ovarian cancer are living longer with recurrent disease [45]. The 2012 SGO/OCNA survey revealed patient expectations of PFS and OS higher than physician expectations, as well as variability in toxicity thresholds [46]. A focus group to provide context for survivors' perceptions of endpoints conducted by New York University (NYU) and SHARE clarified that while initially the goals of treatment are cure and OS, quality of life measures become more important over time through multiple recurrences [47].

The SGO/OCNA survey further revealed that tolerance for toxicity is higher when patients expect cure than when treatment is considered palliative [48]. An August 2015 ovarian cancer survivorship survey likewise indicated an increase in tolerability of toxicity with patient expectation of cure, regardless of recurrence status [49]. (See Table 3 for survey participant comments.)

Discussion during the NYU/SHARE focus group elucidated unintentional reasons for underreporting of side effects, such as forgetfulness,

and intentional reasons, including desire to avoid additional tests, fear of cessation of treatment or dose reductions. Partnering with patients to increase PRO compliance would be extremely valuable since it is vitally important for patients to have accurate information regarding toxicities in order to make informed decisions as treatment priorities change with long-term management of recurrent disease. A suggested first step is to include patient advocates and adapt existing tools, such as NCI's PRO-CTCAE, to collect PRO data in real-time [50].

Engaging patient advocates to be informed and involved participants in the review process and cooperative groups is essential to the delivery of patient-centered care. A collaborative effort is necessary to meet the challenge, financial and otherwise, of recruiting and training patients from all ethnic and social-economic groups to ensure all voices are heard and represented.

1.7. How do we best study Rare Ovarian Tumors? Innovative clinical design strategies

Prior to the establishment of the GOG Rare Tumor Committee in 2005, all epithelial ovarian cancers in the US were largely treated identically, and there was essentially no prospective data for rare subtypes. Over the past decade, our understanding of the molecular biology and the clinical features of these rare epithelial subtypes have significantly expanded. Rare ovarian cancers present several challenges for clinical trial design, including small number of cases, long accrual times, less attention by the scientific community, low funding priorities, fewer patient advocates, and lack of standard bioinformatics methods and trial designs.

Rare ovarian cancers for which trials have been activated include clear cell carcinoma, low-grade serous carcinoma, and mucinous carcinoma, with varying degrees of success. See Table 2. Because all three subtypes share the feature of relative chemoresistance, a search for novel therapeutics is critical. An overarching barrier is feasibility. Essential elements for such trials include prospective pathology review, use of surrogate endpoints (response, DFS or PFS), translational research endpoints, and potential integration of pre- and post-treatment biopsies.

Rare ovarian cancer trials generally require national or international networks (e.g. Gynecologic Cancer InterGroup, GCIG), the use of cancer registries (for very rare cancers), innovative trial designs, quality tumor repositories, and regular consultations between regulatory bodies, industry, patient advocates, and investigators. Such clinical trials should seek large benefits with small sample size and tolerance of a higher degree of uncertainty. Whenever feasible, adaptive designs should be considered. Establishing trial networks with adequate infrastructure and use of common protocol can address many challenges. These master protocol design strategies can optimize trial design and conduct to realize efficiencies and improve data quality through centralization processes, systems and training. Such a platform can enable use of complicated innovative and adaptive trial designs. These types of designs require further exploration for rare ovarian cancers.

2. Conclusions

The FDA "Ovarian Cancer Clinical Trial Endpoints" workshop brought relevant stakeholders together to critically analyze the current state of the science, identify knowledge gaps, and predict the future

Table 3
Survivor comments by goal of treatment[a].

Cure	Remission	Stable disease
"I would accept any side effect for a CURE!!!" "I'd take anything that has less than a 20% chance of killing me immediately."	"I would tolerate these side effects if they were temporary." "I'd rather not tolerate any side effects." "None!"	"It depends on the severity and quality of life trade-offs." "This is a much bigger issue 'stable disease' is the best you can get." "Facing this now [I would accept this] learning that my tolerance for side effects is pretty low"

^a Reference 48.

a   Reference 48.

landscape concerning regulatory approval considerations in ovarian cancer. A consensus opinion was that surrogate endpoints such as PFS and even ORR could be viable primary endpoints for accelerated approval of novel agents in certain circumstances. These conditions include the magnitude of effect of the efficacy endpoints including duration of response as well as consideration of toxicities and impact on quality of life. PRO's can be particularly valuable in providing context of true patient net benefit when validated and sufficiently robust in terms of minimizing missing data. Ongoing communication among stakeholders and continual improvement in clinical trial designs that consider innovative designs incorporating real-world data to best reflect true patient benefit will best serve our ovarian cancer community.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2017.08.012.

References

[1] R.C. Bast, J.T. Thigpen, S.G. Arbuck, K. Basen-Engquist, L.B. Burke, R. Freedman, S.J. Horning, R. Ozols, G.J. Rustin, D. Spriggs, L.B. Wenzel, R. Pazdur, Clinical trial endpoints in ovarian cancer: report of an FDA/ASCO/AACR Public Workshop, Gynecol. Oncol. 107 (2) (2007 Nov) 173–176.

[2] T.J. Herzog, et al., Ovarian cancer clinical trial endpoints: Society of Gynecologic Oncology white paper, Gynecol. Oncol. 132 (1) (2014 Jan) 8–17, http://dx.doi.org/10.1016/j.ygyno.2013.11.008.

[3] T.J. Herzog, R.D. Alvarez, A. Secord, B.A. Goff, R.S. Mannel, B.J. Monk, R.L. Coleman, SGO guidance document for clinical trial designs in ovarian cancer: a changing paradigm, Gynecol. Oncol. 135 (1) (2014 Oct) 3–7, http://dx.doi.org/10.1016/j.ygyno.2014.08.004.

[4] Ignace Vergote, on behalf of the European Organization for Research and Treatment of Cancer–Gynaecological Cancer Group and the NCIC Clinical Trials Group* — a Gynecologic Cancer Intergroup Collaboration, Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer, N. Engl. J. Med. 363 (2010) 943–953.

[5] S. Kehoe, J. Hook, M. Nankivell, G.C. Jayson, H. Kitchener, T. Lopes, D. Luesley, T. Perren, S. Bannoo, M. Mascarenhas, S. Dobbs, S. Essapen, J. Twigg, J. Herod, G. McCluggage, M. Parmar, A.M. Swart, Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial, Lancet 386 (9990) (2015 Jul 18) 249–257, http://dx.doi.org/10.1016/S0140-6736(14)62223-6.

[6] A.A. Wright, et al., Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline, J. Clin. Oncol. (2016 Aug 8) (pii: JCO686907. [Epub ahead of print]).

[7] A. De Michele, et al., The neoadjuvant model is still the future for drug development in breast cancer, Clin. Cancer Res. 21 (13) (2015 Jul 1) 2911–2915.

[8] M. Petrillo, G.F. Zannoni, L. Tortorella, L. Pedone Anchora, V. Salutari, A. Ercoli, P.A. Margariti, G. Scambia, A. Fagotti, Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy in primary unresectable ovarian cancer, Am. J. Obstet. Gynecol. 211 (6) (2014 Dec) 632.e1–8 http://dx.doi.org/10.1016/j.ajog.2014.06.034.

[9] A.M. Nick, R.L. Coleman, P.T. Ramirez, A.K. Sood, A framework for a personalized surgical approach to ovarian cancer, Nat. Rev. Clin. Oncol. 12 (4) (2015 Apr) 239–245, http://dx.doi.org/10.1038/nrclinonc.2015.26 Epub 2015 Feb 24.

[10] P. Cortazar, L. Zhang, M. Untch, K. Mehta, J.P. Costantino, N. Wolmark, H. Bonnefoi, D. Cameron, L. Gianni, P. Valagussa, S.M. Swain, T. Prowell, S. Loibl, D.L. Wickerham, J. Bogaerts, J. Baselga, C. Perou, G. Blumenthal, J. Blohmer, E.P. Mamounas, J. Bergh, V. Semiglazov, R. Justice, H. Eidtmann, S. Paik, M. Piccart, R. Sridhara, P.A. Fasching, L. Slaets, S. Tang, B. Gerber, C.E. Geyer Jr., R. Pazdur, N. Ditsch, P. Rastogi, W. Eiermann, G. von Minckwitz, Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis, Lancet 384 (9938) (2014 Jul 12) 164–172, http://dx.doi.org/10.1016/S0140-6736(13)62422-8 (Review).

[11] K.R. Broglio, M. Quintana, M. Foster, M. Olinger, A. McGlothlin, S.M. Berry, J.F. Boileau, C. Brezden-Masley, S. Chia, S. Dent, K. Gelmon, A. Paterson, D. Rayson, D.A. Berry, Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes: a meta-analysis, JAMA Oncol. 2 (6) (2016 Jun 1) 751–760, http://dx.doi.org/10.1001/jamaoncol.2015.6113.

[12] Ovarian cancers evolving paradigms in research and care; national academies of sciences, engineering, and medicine, Ovarian Cancers: Evolving Paradigms in Research and Care, The National Academies Press, Washington, DC, 2016http://dx.doi.org/10.17226/21841.

[13] A. Gurung, T. Hung, J. Morin, C.B. Gilks, Molecular abnormalities in ovarian carcinoma: clinical, morphological and therapeutic correlates, Histopathology 62 (1) (2013) 59–70.

[14] G. Kim, G. Ison, A.E. McKee, H. Zhang, S. Tang, T. Gwise, R. Sridhara, E. Lee, A. Tzou, R. Philip, H.J. Chiu, T.K. Ricks, T. Palmby, A.M. Russell, G. Ladouceur, E. Pfuma, H. Li, L. Zhao, Q. Liu, R. Venugopal, A. Ibrahim, R. Pazdur, FDA approval summary: Olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced

[15] E.M. Swisher, K.K. Lin, A.M. Oza, C.L. Scott, H. Giordano, J. Sun, G.E. Konecny, R.L. Coleman, A.V. Tinker, D.M. O'Malley, R.S. Kristeleit, L. Ma, Bell-McGuinn KM, J.D. Brenton, J.M. Cragun, A. Oaknin, I. Ray-Coquard, M.I. Harrell, E. Mann, S.H. Kaufmann, A. Floquet, A. Leary, T.C. Harding, S. Goble, L. Maloney, J. Isaacson, A.R. Allen, L. Rolfe, R. Yelensky, M. Raponi, McNeish IA, Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial, Lancet Oncol. 18 (1) (2017 Jan) 75–87, http://dx.doi.org/10.1016/S1470-2045(16)30559-9 (Epub 2016 Nov 29).

[16] ENGOT-OV16/NOVA Investigators, Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, N. Engl. J. Med. (2016 Oct 7).

[17] T.B. Turner, D.J. Buchsbaum, J.M. Straughn Jr., T.D. Randall, R.C. Arend, Ovarian cancer and the immune system - the role of targeted therapies, Gynecol. Oncol. 142 (2) (2016 Aug) 349–356.

[18] J. Galon, B. Mlecnik, G. Bindea, H.K. Angell, A. Berger, C. Lagorce, A. Lugli, I. Zlobec, A. Hartmann, C. Bifulco, I.D. Nagtegaal, R. Palmqvist, G.V. Masucci, G. Botti, F. Tatangelo, P. Delrio, M. Maio, L. Laghi, F. Grizzi, M. Asslaber, C. D'Arrigo, F. Vidal-Vanaclocha, E. Zavadova, L. Chouchane, P.S. Ohashi, S. Hafezi-Bakhtiari, B.G. Wouters, M. Roehrl, L. Nguyen, Y. Kawakami, S. Hazama, K. Okuno, S. Ogino, P. Gibbs, P. Waring, N. Sato, T. Torigoe, K. Itoh, P.S. Patel, S.N. Shukla, Y. Wang, S. Kopetz, F.A. Sinicrope, V. Scripcariu, P.A. Ascierto, F.M. Marincola, B.A. Fox, F. Pagès, Towards the introduction of the 'immunoscore' in the classification of malignant tumours, J. Pathol. 232 (2) (2014 Jan) 199–209.

[19] Pei-Ling Chen, Whijae Roh, Alexandre Reuben, Zachary A. Cooper, Christine N. Spencer, Peter A. Prieto, et al. Analysis of immune signatures in longitudinal tumor samples yields insight into biomarkers of response and mechanisms of resistance to immune checkpoint blockade. Cancer Discovery, doi: http://dx.doi.org/10.1158/2159-8290.CD-15-1545 (Published August 2016).

[20] R.D. Alvarez, U.A. Matulonis, T.J. Herzog, R.L. Coleman, B.J. Monk, M. Markman, Moving beyond the platinum sensitive/resistant paradigm for patients with recurrent ovarian cancer, Gynecol. Oncol. 141 (3) (2016 Jun) 405–409.

[21] The Cancer Genome Atlas Research Network, Integrated genomic analyses of ovarian carcinoma, Nature (2010).

[22] Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products Guidance http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/.

[23] G. Rustin, et al., J. Clin. Oncol. 18 (2000) 1733–1739.

[24] G. Rustin, et al., JNCI 96 (2004) 487–488.

[25] G. Rustin, et al., Int. J. Gynecol. Cancer 21 (2011) 419–423.

[26] E. Eisenhauer, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer (2009).

[27] G.J. Rustin, M.E. van der Burg, C.L. Griffin, D. Guthrie, A. Lamont, G.C. Jayson, G. Kristensen, C. Mediola, C. Coens, W. Qian, M.K. Parmar, Swart AMEarly versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial.; MRC OV05; EORTC 55955 investigators, Lancet 376 (9747) (2010 Oct 2) 1155–1163.

[28] Lee TY et al. CT perfusion as an early biomarker of treatment efficacy in advanced ovarian cancer: an ECOG-ACRIN and NRG GOG study. J. Clin. Oncol. 2015 ASCO Annual Meeting (May 29–June 2, 2015). http://hwmaint.meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/5522 Accessed on March 17, 2016.

[29] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm.

[30] J. Ledermann, P. Harter, C. Gourley, M. Friedlander, I. Vergote, G. Rustin, C. Scott, W. Meier, R. Shapira-Frommer, T. Safra, D. Matei, E. Macpherson, C. Watkins, J. Carmichael, U. Matulonis, Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer, N. Engl. J. Med. 366 (15) (2012 Apr 12) 1382–1392.

[31] http://www.fda.gov/AdvisoryCommittees/Calendar/ucm394126.htm.

[32] A.M. Oza, A.D. Cook, J. Pfisterer, A. Embleton, J.A. Ledermann, E. Pujade-Lauraine, G. Kristensen, M.S. Carey, P. Beale, A. Cervantes, T.W. Park-Simon, G. Rustin, F. Joly, M.R. Mirza, M. Plante, M. Quinn, A. Poveda, G.C. Jayson, D. Stark, A.M. Swart, L. Farrelly, R. Kaplan, M.K. Parmar, T.J. Perren, Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. ICON7 trial investigators, Lancet Oncol. 16 (8) (2015 Aug) 928–936.

[33] J.A. Ledermann, F.A. Raja, C. Fotopoulou, A. Gonzalez-Martin, N. Colombo, C. Sessa, Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. ESMO Guidelines Working Group, Ann. Oncol. (2013 Oct) (24 Suppl 6:vi24–32).

[34] E. Pujade-Lauraine, F. Hilpert, B. Weber, A. Reuss, A. Poveda, G. Kristensen, R. Sorio, I. Vergote, P. Witteveen, A. Bamias, D. Pereira, P. Wimberger, A. Oaknin, M.R. Mirza, P. Follana, D. Bollag, I. Ray-Coquard, Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial, J. Clin. Oncol. 32 (13) (2014 May 1) 1302–1308.

[35] http://www.avastin-hcp.com/?cid=ava_PS_00004103.

[36] A.M. Poveda, F. Selle, F. Hilpert, A. Reuss, A. Savarese, I. Vergote, P. Witteveen, A. Bamias, N. Scotto, L. Mitchell, E. Pujade-Lauraine, Bevacizumab combined with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan in platinum-resistant recurrent ovarian cancer: analysis by chemotherapy cohort of the randomized phase III AURELIA, Trial. J Clin Oncol. 33 (32) (2015 Nov 10) 3836–3838.

[37] B.J. Monk, E. Pujade-Lauraine, R.A. Burger, Integrating bevacizumab into the management of epithelial ovarian cancer: the controversy of front-line versus recurrent disease, Ann. Oncol. (2013 Dec) (24 Suppl 10:x53–x58).

[38] J.S. Ferriss, J.J. Java, M.A. Bookman, G.F. Fleming, B.J. Monk, J.L. Walker, H.D. Homesley, J. Fowler, B.E. Greer, M.P. Boente, R.A. Burger, Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian,

fallopian tube and peritoneal cancers: an NRG Oncology/GOG study, Gynecol. Oncol. 139 (1) (2015 Oct) 17–22.

[39] B.J. Monk, A. Poveda, I. Vergote, F. Raspagliesi, K. Fujiwara, D. Bae, A. Oaknin, I. ay-Coquard, D.M. Provencher, B.K. Karlan, C. Lhommé, G. Richardson, D. Gallardo-Rincon, R.L. Coleman, A. Brize, K. Zhang, F.D. Vogl, B.A. Bach, A.M. Oza, Impact of trebananib plus weekly paclitaxel on overall survival (OS) in patients (pts) with recurrent ovarian cancer and ascites: results from the phase III TRINOVA-1 study, J. Clin. Oncol. 33 (2015) (suppl; abstr 5503).

[40] J. Pfisterer, M. Plante, I. Vergote, A. du Bois, H. Hirte, A.J. Lacave, U. Wagner, A. Stähle, G. Stuart, R. Kimmig, S. Olbricht, T. Le, J. Emerich, W. Kuhn, J. Bentley, C. Jackisch, H.J. Lück, J. Rochon, A.H. Zimmermann, E. Eisenhauer, Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. AGO-OVAR; NCIC CTG; EORTC GCG, J. Clin. Oncol. 24 (29) (2006 Oct 10) 4699–4707.

[41] Special Protocol Assessment (SPA) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf.

[42] L. Zhang, J.R. Conejo-Garcia, D. Katsaros, P.A. Gimotty, M. Massobrio, G. Regnani, A. Makrigiannakis, H. Gray, K. Schlienger, M.N. Liebman, S.C. Rubin, G. Coukos, Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer, N. Engl. J. Med. 348 (3) (2003 Jan 16) 203–213.

[43] M.L. Disis, Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with previously treated, recurrent or refractory ovarian cancer: a phase IB, open-label expansion trial, J. Clin. Oncol. (2015) 5509 2015 ASCO Annual Meeting, Vol 33, No 15_suppl (May 20 Supplement).

[44] A. Varga, Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: interim results from a phase IB study, J. Clin. Oncol. 33 (2015) (suppl; abstr 5510).

[45] R. Siegel, D. Naishadham, A. Jemal, Cancer statistics, 2013, CA Cancer J. Clin. 63 (2013 Jan-Feb) 11–30.

[46] L.E. Minion, R.L. Coleman, R.D. Alvarez, T.J. Herzog, Endpoints in clinical trials: what do our patients consider important? A survey of the Ovarian Cancer National Alliance, Gynecol. Oncol. 140 (2) (2016 Feb) 193–198, http://dx.doi.org/10.1016/j.ygyno.2015.11.030.

[47] M.K. Frey, et al., A qualitative study of ovarian cancer survivors' perceptions of endpoints and goals of care, Gynecol. Oncol. 135 (2) (2014 Nov) 261–265, http://dx.doi.org/10.1016/j.ygyno.2014.09.008.

[48] T. Herzog, et al., Ovarian cancer clinical trial endpoints: society of Gynecologic Oncology white paper, Gynecol. Oncol. 132 (1) (2014 Jan) 8–17, http://dx.doi.org/10.1016/j.ygyno.2013.11.008.

[49] A.E. Ellis, M.K. Frey, et al., Survivors' Acceptance of Treatment Side Effects Evolves as Goals of Care Change Over the Cancer Continuum. Paper Presented at: Living Better: Living Longer? Annual Meeting of the Society of Gynecologic Oncology, 2016 March 18–22 (San Diego, CA).

[50] A.C. Dueck, et al., Validity and reliability of the US National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE), JAMA Oncol. 1 (8) (2015 Nov) 1051–1059, http://dx.doi.org/10.1001/jamaoncol.2015.2639.