Outcomes and endpoints of relevance in gynecologic cancer clinical trials

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ABSTRACT

Drug development is paramount to improve outcomes in patients with gynecologic cancers. A randomized clinical trial should measure whether a clinically relevant improvement is detected with the new intervention compared with the standard of care, using reproductible and appropriate endpoints. Clinically meaningful improvements in overall survival and/or quality of life (QoL) are the gold standards to measure benefit of new therapeutic strategies. Alternative endpoints, such as progression-free survival, provide an earlier measure of the effect of the new therapeutic drug, and are not confounded by the effect of subsequent lines of therapy. Yet, its surrogacy with improved overall survival or QoL is unclear in gynecologic malignancies. Of relevance to studies assessing maintenance strategies are other time-to-event endpoints, such as progression-free survival two and time to second subsequent treatment, which provide valuable information on the disease control in the longer term. Translational and biomarker studies are increasingly being incorporated into gynecologic oncology clinical trials, as they may allow understanding of the biology of the disease, resistance mechanisms, and enable a better selection of patients who might benefit from the new therapeutic strategy. Globally, the endpoint selection of a clinical trial will differ according to the type of study, population, disease setting, and type of therapeutic strategy. This review provides an overview of primary and secondary endpoint selection of relevance for gynecologic oncology clinical trials.

INTRODUCTION

Gynecologic cancers are a major cause of morbidity and mortality despite recent advances in oncology drug development, and clinical trials are paramount to improve patient outcomes.[1] A clinical trial is defined as a prospective experiment or research aimed at testing one or more interventions (systemic therapy, radiation, surgery) in specific populations of patients using appropriate statistical design and clinically meaningful endpoints.[2] A clinical endpoint will reflect how a patient feels, functions, or survives.[2] The National Cancer Institute (NCI) defines an endpoint as an event or outcome that can be measured objectively to determine if the intervention being studied is beneficial, whereas the outcome is the consequence of interest.[3]

The primary endpoint of a trial is the most important data point being evaluated.[2] The primary endpoint will be selected according to the phase of the trial, setting and frequency of the disease, type of intervention, and expected treatment effect, among others, and will determine the power, sample size, and trial duration.

The priorities of novel therapeutic strategies for patients with gynecologic cancers are to live longer or better (ideally both), compared with outcomes without the new intervention,[4] and current gold standards for assessing efficacy of novel therapeutics remain overall survival and quality of life (QoL). Yet, progression-free survival is often used for drug approval by regulatory agencies.[4] Certain tools, such as the European Society of Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) and the American Society of Clinical Oncology (ASCO) value framework, provide a rational and structured methodology to rank the magnitude of clinically meaningful benefit of anti-cancer treatments.[5 6] These tools will consider elements of clinical benefit, toxicity, and symptom palliation. Globally, treatments with an improved survival and/or QoL will receive a higher rank, distinguishing them from interventions that demonstrate a limited or marginal benefit.

Endpoints in Gynecologic Oncology Clinical trials

Clinical trials should include reproducible, valid, and appropriate endpoints that measure clinical benefit.[7] Overall survival is undoubtedly one of the most relevant markers of clinical benefit of cancer therapeutics in clinical trials (Table 1). However, it requires prolonged follow-up, has higher costs, and it can be confounded by cross-over and subsequent therapies.[7] Contemporary phase III clinical trials have become larger, and more resource intensive in order to detect modest differences in overall survival.[7]

Here, we will review benefit and limitations of endpoint selection in phase II and III studies in gynecologic oncology in the novel therapeutic landscape, including an overview of the recommendations provided in the Gynecologic Cancer Inter-Group (GCIG) ovarian cancer consensus conferences.[8 9] Given that the focus of phase I trials is the assessment of dosing and safety of a new agent or combination, these are out of the scope of the current manuscript.

Table 1 Summary of pros and cons for endpoint selection in clinical trials

Endpoint	Pros	Cons
Overall survival	► Highly relevant ► Measured objectively ► Diminished risk of lived-time bias	► Long time to assess the results ► Confounded by subsequent therapy ► Confounded by other causes of death unrelated to cancer ► Higher cost of the trial
Quality of life (QoL)	► Highly relevant ► Provides patients' perspective ► May allow future cost-utility analysis	► Less established as primary endpoint in early-phase therapeutic studies ► May encounter challenge in selection of relevant questionnaires. Disease-specific measurements may be less comprehensive ► Lengthy questionnaires can be time-consuming for the patients to complete ► Many studies lack per protocol minimally important difference and plan for missing data handling
Disease-free survival or progression-free survival	► Early disease assessment ► Shorter follow-up time ► Smaller sample size than with overall survival ► No confounding by subsequent lines of therapy	► Absence of progressive disease does not necessarily mean clinical benefit if toxicity is high and there is no impact on overall survival ► Time-dependent biases (lead-time bias, informative censoring) ► Late toxicities (secondary malignancies, other) are not captured ► No clear correlation with overall survival benefit
Overall response rate	► Early disease assessment ► Small sample size ► Relatively easy to evaluate	► Limited clinical relevance ► Inter- and intra-observer variability ► Selection bias in exceptional responders or indolent disease, makes measurable disease mandatory ► Difficult to measure benefit from agents that stabilize the tumor ► No clear correlation with overall survival benefit

Progression-free Survival and Disease-free Survival

A relevant benefit of using progression-free survival as primary endpoint is the lack of confounding by subsequent lines of treatment (Table 1).[4] Progression-free survival provides an earlier assessment of anti-tumor activity, and requires smaller sample sizes. Yet, the association of progression-free survival with overall survival in the contemporary oncology landscape must be done with caution, given that most published literature do not support the surrogacy.[4] Similarly, an improvement in progression-free survival does not always correlate with a QoL benefit, given that the toxicity associated with therapy and increased number of hospital visits must be accounted for, among other factors.[10]

Ovarian Carcinoma

Buyse assessed the surrogacy of progression-free survival to overall survival in ovarian cancer in a meta-analysis.[11] The study was limited to four trials assessing chemotherapy (non-taxane containing, cisplatin-based regimens), and progression was defined using a prior World Health Organization (WHO) definition. A correlation between progression-free survival and overall survival benefit was detected at the individual level (Kendall τ of 0.84; 95% CI 0.83 to 0.85) and at group level (Pearson correlation 0.95; 95% CI 0.82 to 1.00).[11] However, the regimens used in the clinical trials do not represent current standard of care. More recently, a GCIG meta-analysis assessed the role of progression-free survival and combined GCIG criteria (CA-125 levels) as surrogate of overall survival in randomized controlled trials including patients receiving front-line therapy for ovarian cancer that had been published between 2001 and 2016.[12] The study used individual data from 11 029 patients out of 17 clinical trials, including five maintenance studies. None of the trials included poly-(ADP-ribose)-polymerase (PARP) or immune checkpoint inhibitors. Although a strong correlation between progression-free survival and overall survival was detected at the individual level (Kendall τ=0.724; 95% CI 0.72 to 0.73), there was a low correlation between the overall treatment effects on progression-free survival and overall survival (R^2=0.24; 95% CI 0 to 0.59; threshold for surrogacy criteria $R^2 \geq 0.8$).[12] Similarly, on subgroup analysis, the treatment effect on progression-free survival did not predict overall survival on maintenance and non-maintenance trials. It is important to note that surgical studies were not included in these meta-analyses. Recent landmark trials assessing the role of secondary cytoreduction in recurrent ovarian carcinoma,[13 14] and systematic lymphadenectomy in newly diagnosed ovarian cancer,[15] selected overall survival as their primary endpoint. In these studies, the benefit or lack of it, was observed for both progression-free survival and overall survival. Yet, the surrogacy between these is not established in surgical trials for ovarian cancer and selecting overall survival as primary outcome may be more prudent.

To our knowledge, the surrogacy of progression-free survival and overall survival has not been properly assessed in the contemporary

therapeutic landscape of maintenance with PARP inhibitors in ovarian cancer, both in first line and in the recurrence setting.[16–30] The surrogacy of progression-free survival and overall survival may be different in first line and in recurrence. In addition, the genomic biomarker probably has a relevant role, and populations with different status of *BRCA* or homologous recombination deficiency may have different correlation between progression-free survival and overall survival. In this regard, maintenance with olaparib in the front line (SOLO1) and the platinum sensitive setting (SOLO2) in patients with ovarian cancer harboring *BRCA1/2* mutations, improved the disease-free survival or progression-free survival with a clinically relevant improvement in overall survival, although not statistically significant, despite cross-over in subsequent lines of therapy (Table 2).[16–30] The PAOLA-1/ENGOT-ov25 trial demonstrated that the benefit of adding olaparib to bevacizumab in the maintenance setting improved both progression-free survival and overall survival, but only for patients with homologous recombination deficiency tumors.[19] However, the primary and secondary endpoints were progression-free survival and overall survival, respectively, in the intention-to treat population, and between-group differences in overall survival were not statistically or clinically significant. Overall survival results of PRIMA/ENGOT-ov26/GOG-3012, and ATHENA-MONO/GOG-3020/ENGOT-ov45, are awaited to assess the correlation between the benefit in progression-free survival and overall survival with PARP inhibitor maintenance as monotherapy in the first-line setting.

The recurrence setting has provided intriguing results. In a phase III trial assessing rucaparib versus chemotherapy in recurrent ovarian carcinoma harboring *BRCA1/2* mutations (ARIEL4), although a clear progression-free survival benefit was observed with rucaparib as treatment, overall survival favored the chemotherapy arm.[31] In addition, two studies assessing PARP inhibitor maintenance in the platinum-sensitive setting, following response to platinum, NOVA/ENGOT-ov16 and ARIEL3, have shown a benefit in progression-free survival with niraparib and rucaparib, respectively, in the non-*BRCA* mutation carrier cohort of patients.[21–23 29 30] Yet, there was a non-statistically significant trend in overall survival in favor of the control arm. The interpretation of these results is limited due to the lack of potency of the trials to assess the overall survival properly in the different biomarker subgroups, and the impossibility of having control over subsequent interventions, including the cross-over. Additionally, both studies showed that progression-free survival two (progression on the second-line therapy, see Figure 1), which is a solid post-progression outcome, were superior for niraparib or rucaparib than for the control arm, making even more intriguing the overall survival interpretation.[21–23 29 30] Nevertheless, these findings raise the need to rethink the selection of endpoints in the recurrent setting and place overall survival as a co-primary or key secondary endpoint properly assessed.

The fifth GCIG Ovarian Cancer Consensus on recurrent ovarian cancer held in 2015 reached an important recommendation on primary endpoints of clinical trials. The choice of the primary endpoint was recommended based on the expected median overall survival.[32] The consensus recommended that studies including patient cohorts with expected overall survival of ≤12 months, should include overall survival as primary endpoint. Progression-free survival could be an alternative when the expected median overall survival was >12 months, when supported by additional endpoints, including predefined patient-reported outcomes, time to second subsequent therapy, or time until definitive deterioration of quality of life.[32] For front-line therapy trials, the consensus recommended overall survival as the preferred primary endpoint.[33] Progression-free survival was also proposed as an alternative primary endpoint, when overall survival is measured as a secondary endpoint. They recommended that progression-free survival must have support of additional endpoints, including predefined patient-reported outcomes and time to first or second subsequent therapy.[33] The fifth Ovarian Cancer Consensus reached a different recommendation for rare ovarian cancers.[8] It was suggested that overall survival may be unrealistic in slow-growing tumors such as sex-cord stromal tumors and low-grade serous cancer, where both patient numbers as well as trial duration will undermine feasibility.[8] But a recommendation on the optimal primary endpoint selection was not made.

In the sixth GCIG Ovarian Cancer Consensus Conference held in 2021 recommendations of primary endpoint choice were made according to the type of study. The consensus recommended that in randomized phase II trials that include a combination of agents, progression-free survival should be considered as the primary endpoint.[9] In phase III trials, progression-free survival assessed by an investigator and overall survival are the preferred primary endpoints (not necessarily dual). The consensus highlighted that when progression-free survival is chosen as primary endpoint this should be assessed by investigators (not centrally), irrespective of the blinding and placebo control.[9] Secondary endpoints may include the sample-based or full blinded independent central review, and when a central analysis is performed, both results should be reported.[9]

Cervical and Endometrial Carcinoma

The assessment of surrogacy between progression-free survival and overall survival in endometrial and cervical cancer studies remains an important unmet need; globally overall survival and/or QoL should be considered as primary outcome measure. We should note that if progression-free survival is chosen as primary endpoint, overall survival should be measured as a secondary outcome, as well as predefined patient-reported outcomes.

The incorporation of immune checkpoint inhibition has changed the treatment landscape in advanced endometrial and cervical carcinoma.[34 35] Clinical trials including immune checkpoint inhibition have shown disease response patterns that may differ from classic oncology therapeutics. Survival curves in randomized clinical trials involving immune checkpoint inhibition may show a delayed separation of survival curves, with maintained and profound duration of benefit in responders.[34–36] Ye et al assessed the relationship between progression-free survival, overall response rate, and overall survival with immune checkpoint inhibition across multiple malignancies (cervical or endometrial carcinomas not included) in a meta-analysis.[36] The study showed that improvements in progression-free survival and overall response rate were likely to translate into increased overall survival. Yet, little or no progression-free survival or overall response rate improvement did not translate to absence of overall survival benefit.[36] These observations will need confirmation in gynecologic malignancies in future studies.

For individual clinical trial data, the landmark randomized phase III clinical trials exploring the role of immune checkpoint

Table 2 Results from landmark phase III randomized clinical trials assessing switch maintenance PARP inhibition in advanced front-line or recurrent epithelial ovarian cancer[16–31]

Clinical trial	Population	PFS HR (95% CI)	PFS2 HR (95% CI)	TSST HR (95% CI)	OS HR (95% CI)
Front-line					
SOLO1 (NCT01844986) Olaparib vs PCB	*BRCA*m	HR 0.33 (0.25 to 0.43)	HR 0.46 (0.34 to 0.65)	HR 0.46 (0.34 to 0.63)	HR 0.55 (0.40 to 0.76) Not final analysis. p=0.0004, with p<0.0001 required for statistical significance
PRIMA (NCT02655016) Niraparib vs P	ITT	HR 0.62 (0.50 to 0.76)	HR 0.81 (0.58 to 1.14) Immature (20% maturity in ITT)	NA	Immature
	HRd	HR 0.43 (0.31 to 0.59)	HR 0.84 (0.49 to 1.45) Immature (20% maturity in ITT)	NA	Immature
PRIME (NCT03709316) Niraparib vs P	ITT	HR 0.45 (0.34 to 0.60)	NA	NA	Immature
	HRd	HR 0.48 (0.34 to 0.68)	NA	NA	Immature
ATHENA-MONO (NCT03522246) Rucaparib vs P	ITT	HR 0.52 (0.40 to 0.68)	NA	NA	Immature
	HRd	HR 0.47 (0.31 to 0.72)	NA	NA	Immature
PAOLA-1 (NCT02477644) Olaparib+B vs P+B	ITT	HR 0.59 (0.49 to 0.72)	HR 0.78 (0.64 to 0.95)	HR 0.78 (0.64 to 0.95)	HR 0.92 (0.76 to 1.12)
	HRd	HR 0.33 (0.25 to 0.45)	HR 0.56 (0.41 to 0.77)	HR 0.48 (0.35 to 0.66)	HR 0.62 (0.45 to 0.85)
Platinum-sensitive recurrence					
SOLO2 (NCT01874353) Olaparib vs P	*BRCA*m	HR 0.30 (0.22 to 0.41)	HR 0.50 (0.34 to 0.72)	HR 0.51 (0.39 to 0.68)	HR 0.74 (0.54 to 1.00)
NOVA (NCT01847274) Niraparib vs P	g*BRCA*m	HR 0.27 (0.17 to 0.41)	HR, 0.67 (0.48 to 0.94)	NA	HR, 0.85 (0.61 to 1.2)
	Non-g*BRCA*m	HR 0.45 (0.34 to 0.61)	HR, 0.81 (0.62 to 1.05)	NA	HR 1.06 (0.81 to 1.37)
ARIEL3 (NCT01968213) Rucaparib vs P	*BRCA*m	HR 0.23 (0.16 to 0.34)	HR 0.67 (0.48 to 0.94)	HR 0.53 (CI 0.36 to 0.80)	HR 0.83 (0.58 to 1.19) 73% maturity
	HRd	HR 0.32 (0.24 to 0.42)	HR 0.72 (0.56 to 0.92)	HR 0.67 (0.50 to 0.91)	HR 1 (0.76 to 1.32)
	ITT	HR 0.36 (0.30 to 0.45)	HR 0.7 (0.58 to 0.85)	HR 0.68 (0.54 to 0.85)	HR 0.99 (0.81 to 1.22)

The primary endpoint of all the studies was PFS.[11–25]
B, bevacizumab; *BRCA*m, *BRCA* mutation carrier; CI confidence interval; g*BRCA*m, germline *BRCA* mutation carrier; HRd, homologous recombination deficiency; ITT, Intention to treat; NA, not available; OS, overall survival; P, placebo; PFS2, progression on the second-line therapy; PFS, progression-free survival; TSST, time to second subsequent treatment.

inhibition in cervical and endometrial cancer have used overall survival as primary endpoint. In cervical cancer, these include the KEYNOTE-826 clinical trial (NCT03635567) assessing the role of pembrolizumab versus placebo in combination with standard front-line therapy,[35] and the EMPOWER-Cervical 1 clinical trial (NCT03257267) assessing the role of cemiplimab versus chemotherapy in the recurrent setting,[37] where overall survival and progression-free survival (dual endpoints) and overall survival, were chosen as the primary outcomes, respectively. In endometrial cancer, the KEYNOTE-775 (NCT03517449) study assessing pembrolizumab and lenvatinib versus single-agent chemotherapy also used progression-free survival and overall survival

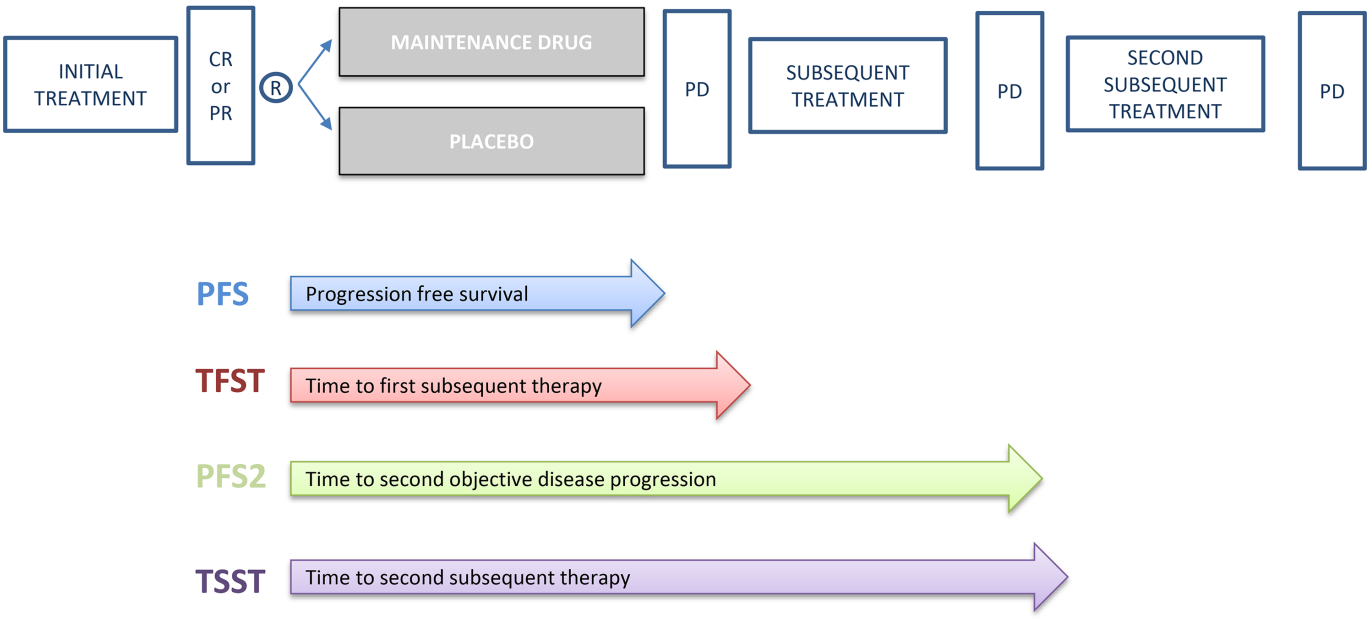

Figure 1 Time to event endpoints incorporated in maintenance clinical trials in ovarian cancer. CR, complete response; PD, progressive disease; PR, partial response; R, randomization.

as dual primary endpoints.[34] These three studies demonstrated an improvement in both progression-free survival and overall survival. Whether a lack of, or little, progression-free survival benefit translates in absence of overall survival benefit in cervical and endometrial malignancies has not been addressed. Thus, it may be prudent to continue considering overall survival at least as co-primary endpoint in phase III clinical trials assessing treatment with immune checkpoint inhibition.

Recent landmark trials assessing the role of adjuvant radiotherapy in endometrial cancer have used variable primary endpoints. The primary outcome in the GOG-0258 (NCT00942357) trial comparing chemotherapy with chemoradiotherapy in stage III–IVA endometrial cancer,[38] and the GOG-0249 (NCT00807768) study comparing brachytherapy and chemotherapy with pelvic radiotherapy in intermediate and high-risk, early-stage disease,[39] was relapse-free survival. In both trials, the arms that received less radiation therapy had a higher rate of local recurrence. It is important to note that in studies assessing economization in local therapy, whether recurrences are local and distant need to be accounted.

In contrast, external beam pelvic radiotherapy was administered in both arms of the PORTEC-3 (NCT00411138) trial, which compared the role of adjuvant chemoradiation with pelvis radiotherapy in high-risk endometrial cancer.[40] The primary endpoints of this trial were failure-free survival (absence of relapse, non-relapse mortality, or addition of another systemic therapy) and overall survival. A secondary endpoint was the assessment of vaginal, pelvic, or distant recurrences. In the overall population, the 5-year failure-free survival rate was significantly higher in the chemoradiotherapy arm (75.5% vs 68.6%; HR=0.71, p=0.022).[40] Patterns of relapse reflected the effect of combining systemic therapy with external beam pelvic radiotherapy (5-year probability of distant metastases 22% for chemoradiation versus 28% for radiotherapy, respectively, with the same 5-year probability of isolated local recurrence).

Other Time to Event Endpoints

Other time to event endpoints, including time from randomization to progression on the second-line therapy or death (progression-free survival two) and time to second subsequent therapy, can be used as secondary outcomes in phase III clinical trials (Figure 1).[41] These measures are important to support the hypothesis that the benefit provided by the increase in progression-free survival is maintained over time, and the disease remains controlled at a longer term.[41] In cases where it is not feasible to ensure regular disease reassessment until the time of second progression, time to second subsequent therapy should be used instead of progression-free survival two.

Regulatory agencies recommend that maintenance trials should report the impact in the subsequent line of therapy. Both progression-free survival two and time to second subsequent therapy have an important role in studies assessing maintenance strategies.[41] Prolonged administration of a treatment as maintenance may reduce the ability of patients to benefit from the same or similar agents; patients could develop cross-resistances and treatment-related toxicity that might decrease tolerance to subsequent therapy. Analysis of the benefit in time to second subsequent therapy could help to elucidate whether a statistically non-significant difference in overall survival might be real.[41]

Table 2 illustrates time to event endpoints of landmark clinical trials assessing switch maintenance strategies in advanced or recurrent ovarian cancer. Progression-free survival two and time to second subsequent therapy have been reported as secondary or as part of a post hoc analysis in most clinical trials assessing PARP inhibition maintenance in ovarian cancer. The importance of reporting these time-to-event endpoints is highlighted by a significant overlap between mechanisms of resistance to platinum chemotherapy and PARP inhibition.[42] For example, in a post hoc analysis from the SOLO2 trial (NCT01874353) a potential decreased efficacy to subsequent platinum therapy following

olaparib maintenance has been reported in the recurrent setting in *BRCA* mutation carriers, but both progression-free survival two and time to second subsequent therapy benefited the olaparib arm (Table 2), supporting the use of PARP inhibition in this setting.[43]

Tumor Response Rate

The overall response rate is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum period.[44] It is generally calculated as the sum of complete and partial responses using unidimensional radiographic measures, according to the Response Evaluation Criteria in Solid Tumors (RECIST),[44] and may be used as primary endpoint in phase II clinical trials.

One of the limitations of overall response rate is that it is not clear whether tumor measures can be reliably obtained by different readers, or by the same reader at different times (Table 1). In non-small cell lung cancer, it has been reported that an intra-observer and inter-observer misclassification of stable lesions led to the incorrect diagnosis of progressive disease in 9.5% and 29.8% of cases, respectively.[45] A retrospective study by Krasovitsky et al assessed inter-observer and intra-observer variability of RECIST assessment in ovarian carcinoma.[46] The study concluded that although selection of target lesions and measurement concordance were generally high, peritoneal lesions had marginal reproducibility, and lymph node lesions had moderate concordance. Another challenge of using overall response rate as primary endpoint is its limitation to measure the benefit from agents that mostly stabilize, but do not decrease the disease size, such as certain hormonal therapies.[47]

The clinical benefit rate or disease control rate are defined as the percentage of patients with complete response, partial response, and stable disease.[48] It has occasionally been used in phase II studies in gynecologic malignancies.[49 50] Yet, this measure has not been clearly defined or validated as a primary endpoint.[9] It is unclear if there is a benefit with stabilization of the disease in slow-growing tumors, such as low-grade serous ovarian carcinoma, where the absence of progression may reflect disease evolution. Therefore, when clinical benefit rate or disease control rate are used, the duration of the 'clinical benefit' or 'disease control' that are appropriate for the specific patient population and type of drug should be reported.

The sixth GCIG ovarian cancer consensus conference recommended that overall response rate should be the primary endpoint for single-arm phase II studies and could be used in randomized trials.[9] The consensus recommended not to use disease control rate as primary endpoint given the lack of clear definition of duration of stable disease needed to qualify for disease control. If used as an exploratory endpoint, the duration of stabilization must be predefined, with a recommended duration of at least 6 months.[9] These recommendations should also be considered for clinical trials assessing other gynecologic malignancies.

Patient-Reported Outcomes and Quality of life

A patient-reported outcome is a broad term, defined as a measurement that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the response (health-related QoL, symptoms, functions, experience).[51] Health-related QoL is defined as a multidomain concept that represents the patients' general perception of the effect of illness and treatment on physical, psychological, and social aspects of life (EORTC QLQ-C30, FACT-G).[51] The assessment of patient-reported outcomes, including health-related QoL, is increasingly being recognized by clinicians and regulatory agencies as critical determinants of treatment benefit and they are able to provide a thorough understanding of the risks and benefits of a therapeutic strategy (Table 1).

At the time of designing a trial and interpreting the QoL measures several factors, including disease site, type of therapy, and patient aspects, need to be considered.[52] Globally, worsening of QoL should be considered as an adverse outcome, but failure to improve QoL requires special consideration in risk–benefit decisions.[10] A higher level of toxicity may be acceptable in the front-line therapy where cure or prolonged disease control are the goal, compared with the recurrent setting where the focus is symptom-control improvement.[52] The association between QoL and progression-free survival or overall survival was assessed in a retrospective cohort study including 45 randomized phase III trials and 24 806 participants.[10] Among included trials, 13% of the studies included patients with ovarian cancer, but endometrial or cervical cancer studies were not included. The experimental therapy showed an improvement in QoL in 24% of the trials. An association between improved QoL and overall survival was detected, but not with progression-free survival benefit.

Quality of life has usually been incorporated as a secondary endpoint in randomized clinical trials for gynecologic cancers. In a systematic review, Wilson et al assessed the adequacy of reporting of QoL in randomized phase III trials assessing systemic therapy in ovarian cancer in front-line and recurrent setting.[53] The study included 35 trials with 24 664 patients, which were published between 1980 and 2014. The adequacy of reporting QoL was evaluated according to the adherence to established reporting guidelines and the recommendations on the inclusion of patient-reported outcomes in clinical trials from the Fifth Ovarian Cancer Consensus Conference (refer to section 1.1 progression-free survival in ovarian cancer).[32 53] The systematic review showed that patient-reported outcome assessments increased from 2% (1980s) to 62% (2010 or later). However, QoL was only a co-primary endpoint in one clinical trial, and most trials did not include a definition of minimally clinical important differences and missing data. Wilson et al highlighted the importance of adopting standardized approaches and checklists for patient-reported outcomes and QoL reporting, including thorough follow-up of published guidelines (ISOQOL, CONSORT-PRO) and reporting and accounting for missing data.[9]

The impact on QoL of maintenance strategies is of especial relevance. It has been suggested that when a maintenance therapy improves progression-free survival without overall survival improvements, in some cases it may provide patients a QoL improvement by delaying the administration of more toxic subsequent therapies.[41] Yet, even in this setting, the symptomatic benefit due to delayed progression and its magnitude, would need to be considered with the impact on QoL that the toxicity of the maintenance agent may cause. Therefore, to collectively assess the impact of the maintenance strategy, it is paramount to collect QoL data over the subsequent line of treatment and minimize missing data.[41]

Clinical trials assessing switch maintenance with PARP inhibitors in ovarian cancer have not shown any clinically significant

differences in the primary QoL measures between the PARP inhibitor and control arms.[28 54] It must be noted that in this setting, an active agent is being administered during a time when patients do not have active disease or have low symptom burden (all enrolled patients were at a stage of complete or partial response following platinum chemotherapy). Exploratory patient-reported outcomes, such as time without significant symptoms of toxicity and quality-adjusted progression-free survival, have shown improvements favoring the PARP inhibitor arms.[55–59] These measures provide an overview of time without significant treatment toxicity and disease-related symptoms over time.

Clinical trials assessing immune checkpoint inhibition in cervical carcinoma have yielded interesting data on the impact of therapy on QoL. The KEYNOTE-826 study (NCT03635567) assessing the addition of pembrolizumab or placebo to front-line therapy for persistent, recurrent, or metastatic cervical carcinoma included patient-reported outcomes as an exploratory endpoint.[35] The study assessed both time to deterioration in the five-level EQ-5D Visual Analog Scale score and the proportion of patients with stable or improved scores, with deterioration, or improvement predefined as ≥10 point change from baseline. Results showed that both measures significantly favored the pembrolizumab arm.[35] This highlights the potential to improve both overall survival and QoL in this population.

In the recurrent setting, the EMPOWER Cervical 1 (NCT03257267) clinical trial assessed the role of cemiplimab versus single-agent chemotherapy in cervical carcinoma.[37] Patient-reported outcomes were included as a secondary objective of the study, aiming to assess the change in EORTC-QLQC-30 scores at each post-baseline time point. In the primary publication, the threshold for a clinically meaningful difference was stablished as an increase by ≥10 points from baseline to cycle 8. The study showed that the mean between-arm difference in the global health status and QoL score was 7.8 points favoring the cemiplimab arm.[37]

Patient-reported outcomes may also be helpful as secondary outcomes to assess whether common disease-related symptoms improve with a new therapy. These may include ascites disappearance, and selected patient-reported outcomes version of Common Terminology Criteria for Adverse Events (PRO-CTCAE) items measuring severity, frequency and/or interference of abdominal pain, bloating, and nausea, among others.[60] Selection of additional patient-reported outcomes from the PRO-CTCAE or EORTC library may also be used to provide an overview of patient-self reported treatment tolerability.[61 62]

The sixth ovarian cancer consensus recommended that incorporation of patient self-reported tolerability measures (PRO-CTCAE) should be considered.[9] Additionally, patient-reported outcome endpoints should be included as part of the statistical analysis plan in randomized clinical trials, and when possible, these should be measured until the initiation of the next therapy. Importantly, the consensus also suggested that when progression-free survival is the primary endpoint, it could be considered to include patient-reported outcomes as an additional primary endpoint. These considerations remain prudent for clinical trials involving other gynecologic malignancies.

Biomarker-based and Translational Endpoints

The incorporation of a biomarker in a clinical trial may have an integral role, an integrated role, or an exploratory role.[63] Integral role means that the biomarker is inherent in the design of the trial and it is used to determine eligibility or to stratify to different arms of the trial—for instance, the presence of *BRCA* mutations in the SOLO-1 trial.[17] A biomarker has an integrated role when it is included in the design with the aim to identify or validate assays or markers that are planned for use in the future, as, for example, homologous recombination deficiency status in the PAOLA-1 study.[27] Finally, an exploratory role refers to retrospective biomarker assays that are useful only for hypothesis-generating analyses or the design of new trials. As an example, the SIENDO trial (NCT03555422) showed that selinexor as maintenance after first-line platinum-based chemotherapy for advanced endometrial cancer derived benefit in patients with p53 wild-type tumors, and not in the overall population.[64] This finding led to the design of a confirmatory trial in which p53 had an integral role, and will only allow inclusion pf patients with p53 wild-type tumors (NCT05611931).

The use of biomarker assessments can be included as secondary or exploratory endpoints in clinical trials. Although clinically useful for treatment monitoring and patient selection, biomarkers should not be concealed as surrogates of clinical endpoints.

In addition to its role as a diagnostic marker for ovarian cancer, the measurement of CA-125 has been proposed as part of the tumor evaluation criteria in clinical trials. The definitions based on a 50% or 75% decrease of CA-125 levels have demonstrated to accurately predict which drugs in phase II trials for relapsed ovarian cancer were active and justified further investigation.[65] In the CALYPSO trial, investigators incorporated CA-125 (GCIG criteria) and symptomatic deterioration in addition to RECIST criteria to determine progression.[66] This phase III trial randomized 976 patients with platinum-sensitive relapsed ovarian cancer to carboplatin–paclitaxel or carboplatin–pegylated liposomal doxorubicin. Radiological and serological (CA-125) assessments were performed every 3 months until progression. The benefit of either arm of treatment in progression-free survival was not influenced by type of first progression (RECIST or CA-125), and both tests performed similarly in determining disease progression. In patients treated with bevacizumab this correlation might be slightly different, and approximately 10% of patients might demonstrate progression earlier by CA-125.[67]

To standardize the measurement dynamics of CA-125, other approaches such as the KELIM score (elimination rate constant K) have been explored in patients with high-grade ovarian cancer treated with first-line bevacizumab. Both ICON-7 and GOG-0218 validation studies showed an association between unfavorable KELIM score and benefit from bevacizumab for progression-free survival and overall survival.[68] In clinical trials with PARP inhibitors, a favorable KELIM score may be associated with higher PARP inhibitor efficacy. In the VELIA trial, veliparib combined with carboplatin–paclitaxel, followed by maintenance veliparib was associated with improved progression-free survival compared with chemotherapy alone.[69] As exploratory analyses, investigators found that increasing KELIM values were associated with higher benefit from veliparib in homologous recombination deficiencient tumors. The highest progression-free survival benefit was observed in patients

with both favorable KELIM and *BRCA* mutation or *BRCA* wild-type homologous recombination deficiencient tumors.[69]

Other tumor markers commonly used in daily practice in other gynecological malignancies (CEA, SCC, CYFRA, HE4) do not have sufficient evidence to be incorporated as endpoints in clinical trials.

One of the premises of circulating tumor DNA (ctDNA) is the ability to detect driver and, eventually druggable, mutations. Charo et al recently studied 105 patients with gynecologic cancer who had ctDNA testing, and 78 (74.3%) of them had accompanying tissue tumor sequencing.[70] The majority of gynecologic cancers were ovarian (47.6%), uterine (35.2%), and cervical (12.4%). On ctDNA analysis, 75.2% of patients with gynecologic cancer had one genomic alteration. TP53 mutations were found in more than half of the patients, and PIK3CA mutations were found in nearly a quarter of the patients. These findings suggest that eventually druggable alterations can be identified using ctDNA analysis, emphasizing the possibility of individualized therapy. Currently, contemporary biomarkers such as ctDNA clearance are being incorporated as endpoints in clinical trials in ovarian cancer (EudraCT:2021-005458-27).

The use of translational studies in clinical trials has substantially increased their costs, but they provide the possibility of improving outcomes in future studies with a better selection of recruited patients. Frequently, translational studies are performed once the clinical trial has been completed, and sometimes as exploratory endpoints not included in the original design of the study. This fact is commonly associated with a suboptimal collection of biological samples, given its retrospective nature. When tissue samples are collected at the end of the study, it might diminish the odds of including all the intention-to-treat population in the translational track, and by this, the analyses may be biased. The prospective incorporation of pre-designed translational endpoints in clinical trials may improve the performance of the studies and minimize the impact of potential bias.[71]

The identification of molecular markers associated with DNA damage repair pathways (homologous recombination deficiency, *RAD51*, *ARID1A*) have driven new drug development, and better patient selection. In endometrial cancer, translational studies derived from the PORTEC trial biobank, incorporating comprehensive analysis of molecular factors, led to improved risk assessment of uterine carcinoma.[72]

There are some potential roadblocks to completing translational endpoints that could be overcome by predefining them in the protocol, assuring an adequate and efficient sample management, even by central collection of pathologically reviewed samples, considering cost–benefit impact analyses, improving data sharing between different international research consortiums and, finally, increasing the involvement of patient advocates in the design of clinical trials.

Patients' Perspective on Clinical Trials and Endpoint Relevance

The Ovarian Cancer National Alliance conducted a survey of patients with the aim of identifying meaningful surrogate study endpoints and the impact of treatment-related toxicity and quality of life.[73] The study recorded 1413 responders with gynecologic cancers (95% ovarian cancer). When patients were asked about the most important outcome of a trial, the more frequent response was 'cure', followed by 'live longer even though not cured'.[73] Participants reported that they would accept greater toxicity in front-line therapy when cure is possible ($p<0.0001$). The study also showed that the desired minimum extension of progression-free survival and overall survival with new therapeutics was ≥5 months in 77% (95% CI 75% to 79%) and 85% (95% CI 83% to 87%) of cases, respectively.[73] Up to 55% (95% CI 52% to 58%) of responders would also be interested in a therapy that produced disease stability without improvements in overall survival.

An under-reported aspect is the impact that clinical trial procedures may have in patients, including repeated blood draws, research biopsies, and frequent radiological reassessments. Contemporary clinical trials may require mandatory research biopsies for biomarker discovery, which may even be sequential. A prospective study in patients with gynecologic malignancies showed that research biopsies were generally well accepted in research study participants, and most patients would accept serial biopsies (83%).[74] In a recent phase I study of patients with multimetastatic solid tumors (including three with ovarian cancer) who were treated with a combination of radiation and immunotherapy, mandatory biopsies were performed without major complications and allowed for the detection of efficacy surrogate markers.[75] Yet, psychosocial factors may be important determinants in patients' and physicians' experience and willingness to undergo research biopsies.[74]

CONCLUSION

Clinical trials in gynecologic oncology should provide an objective assessment of a meaningful benefit for a patient, which may need to be tailored according to the disease site, type of intervention, and patient characteristics. Well-designed randomized phase III trials using overall survival as the primary endpoint provide valuable information to address the impact that the new therapeutic strategy may have in the patient population, being a highly relevant endpoint for patients, clinicians, and regulatory agencies. Efforts should be made to standardize and increase the use and quality of patient-reported outcomes in the studies. Finally, the adequate incorporation of biomarker research to clinical trials will allow a better identification of the intervention benefit and the patient selection for new therapies in the clinic.

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