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REVIEW

Fifth Ovarian Cancer Consensus Conference: individualized therapy and patient factors

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This manuscript reports the consensus statements regarding the design and conduct of clinical trials in patients with newly diagnosed and recurrent epithelial ovarian cancer (EOC), following deliberation at the Fifth Ovarian Cancer Consensus Conference (OCCC), held in Tokyo in November 2015. Three important questions were identified for discussion prior to the meeting and achieved consensus during the meeting: (i) What are the most important factors to be evaluated prior to initial therapy? (ii) What are the most important factors to be evaluated specifically in recurrent disease? (iii) Are there specific considerations for special patient subpopulations? In addition, we report a list of important unmet needs compiled during the consensus process, which is intended to guide future research initiatives.

Key words: ovarian cancer, consensus conference, GCIG, individualized therapy, recommendations

Introduction

At the 5th Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup (GCIG) held in Tokyo, Japan, in November 2015, representatives of 29 cooperative research groups studying gynaecologic cancers gathered to establish international consensus on issues critical to the conduct of large randomized trials. The process focused on a series of predetermined questions. Group A addressed six questions regarding clinical and biologic factors in patients with newly diagnosed and recurrent EOC.

The consensus statements for group A are presented in Tables 1–3; all statements achieved unanimous consensus. While achieving complete consensus, a list of important unmet needs was also compiled, presented in Table 4. The statements are recommendations for development of clinical trials, to be adapted, as appropriate, to the clinical setting (including local circumstances), specific agents under investigation, and study objectives.

What are the most important factors to be evaluated prior to initial therapy?

Clinical markers

Clinical trials addressing primary therapy of EOC require consideration of prognostic or predictive factors potentially confounding the interpretation of study results (Table 1).

FIGO (International Federation of Gynecology and Obstetrics) surgical stage provides a standardized basis for comparing EOC patients. The third OCCC stated that 'surgical staging should be mandatory and performed by a gynaecologic oncologist', again affirmed at the 4th OCCC [1]. In 2014, FIGO staging was updated, reflecting that EOC comprises at least five distinct types: High Grade Serous Carcinoma (HGSC), Ovarian Endometrioid Adenocarcinoma (OEA), Clear Cell Carcinoma, Ovarian Mucinous Carcinoma (OMC) and Low Grade Serous Carcinoma (LGSC) [2]. The majority (70%) of EOC are HGSC, however, site

Table 1. What are the most important factors to be evaluated prior to initial therapy?

Prognostic factors
- FIGO stage, surgical pathologic (applies to Ov, FT and P)
- Cytoreduction status (primary complete resection versus other)
- Primary treatment modality (surgery versus NACT)
- Performance status and associated variables
- Tumour markers (e.g. CA-125) documented prior to therapy
- Country or geographic region of treatment

Pathology
- Histopathology remains the gold standard for the classification of epithelial ovarian (FIGO: Ov, FT, P) cancer subgroups
- In NACT, tumour grading (and typing) should be based on the pre-chemotherapy biopsy
- Binary grading of serous carcinoma (low-grade and high-grade), with distinction of micropapillary carcinoma
- Binary grading is favoured for endometrioid carcinoma (with assignment of FIGO grade 1 to low-grade, and 2–3 to high-grade)
- Carcinosarcomas are regarded as carcinomas
- Carcinosarcoma, clear cell carcinoma and undifferentiated carcinoma should not be graded
- Mucinous carcinoma should be graded
- Access to archival tumour specimens should be documented and maintained

Biomarkers
- Germline mutation testing to include BRCA1/2 is recommended for all patients enrolled on clinical trials
- Stratification (if possible) should be performed and knowledge of mutation status should be incorporated into primary endpoint analysis
- Somatic mutation analysis for BRCA 1/2 is recommended
- Predictive biomarkers for targeted agents to be included as companion diagnostics

Table 2. What are the most important factors to be evaluated specifically in recurrent disease?

Clinical-pathologic markers
- Treatment-free interval following primary chemotherapy
  - With reference to last dose of primary platinum agent (PFI)
  - Report as a continuous variable
  - Less robust markers include acquired resistance following platinum-based therapy for recurrent disease
  - Report last dose of non-platinum therapy, maintenance therapy (particularly anti-angiogenic agents or PARPi)
- Outcome following most recent cytoreductive surgery
- Presence of non-measurable versus RECIST-measurable disease
- Additional recommendations
- Separate clinical trials, if available, should be utilized for different histological subtypes, although trials can include multiple subtypes
- Collection of tumour specimens at relapse is encouraged

Table 3. Are there specific considerations for special patient subpopulations?

Race/ethnicity
- Collection, reporting and analysis of race/ethnicity categories should be incorporated in future trials
- Emerging data support differences in clinical outcomes in relationship to race/ethnicity, however, pharmacogenomics markers have not been defined, and these population-based data are not sufficient to recommend stratification
- As data are validated within specific populations, race/ethnicity could become a stratification factor within individual studies

Frail and elderly
- Older age should not be an exclusion criterion in ovarian cancer trials
- Any limitations to eligibility criteria based on performance status, comorbidities, and prior malignancies should be justified by the trial design
- Clinical trials in ovarian cancer should include measures from the geriatric assessment domains

of origin was acknowledged to include the fallopian tube, and possibly the peritoneal surface, in the latest FIGO update [2]. The OCCC recognizes that surgical pathologic stage, with both primary cytoreductive surgery (PCS) and interval cytoreductive surgery (ICS) following neoadjuvant chemotherapy (NACT), might serve for stratification in study design.

After surgical stage, the extent of residual disease (RD) following PCS surgery is the next most important prognostic factor to

Table 4. Unmet needs to support future clinical research

- Potential role of intra-operative scoring and/or post-operative imaging to document residual disease
- Universal staging criteria in the context of NACT
- Chemotherapy response scores that can be incorporated in the primary endpoint analysis
- Standards for immunologic assessment, including lymphocyte infiltration scores, T cell subsets, PD-1/PD-L1, etc.
- There are important issues regarding the definition and categorization of race/ethnicity that would benefit from international harmonization
- Since older patients and/or those with compromised functional status are underrepresented in clinical trials, there is a need to define this population and perform trials to evaluate standards for this subgroup

be considered for stratification. Several aspects beyond surgical skill and effort influence RD status, including patient medical comorbidities, tumour biology and local institutional resources. Those patients who achieve optimal cytoreduction, without macroscopic residual disease (MRD) have been shown to achieve better overall survival (OS) relative to patients with macroscopic RD [3, 4]. Stage for stage, the absence of macroscopic RD has been shown to confer a large OS benefit compared to those patients with RD [5–7]. MRD at PCS is predictive of shorter time to first (Hazard Ratio (HR) 1.50 [1.31–1.72]) and second (HR 1.48 [1.22–1.80]) recurrence [8]. When stratifying by RD, the OCCC agreed that cytoreduction status be reported as primary complete resection (PCR) of all visible disease versus other, moving away from tumour measurements of <1 cm versus >1 cm. While groups might choose to report the extent of residual disease and outcomes according to previous definitions, the presence of RD, irrespective of size, confers a poorer survival benefit relative to complete cytoreduction. Need for accuracy and standardization in reporting the extent of RD was recognized as an unmet goal. Various measurement tools have been reported; scoring of RD has largely been subjective, without objective verification [9–12]. When disease status is assessed by postoperative computed tomography (CT), it can be discordant from surgical reports and potentially of independent prognostic value, however, there are currently insufficient data mandating postoperative imaging [11, 12].

Primary treatment modality has also become an important factor to consider for stratification. Two randomized controlled trials have shown that ICS is not inferior to PCS among patients with advanced disease. Criticism of these studies has centred on poor overall survival and low levels of complete and optimal (<1 cm) cytoreduction achieved with PCS, raising questions about surgical effort and institutional expertise. The higher optimal cytoreduction rates achieved following NACT compared with PCS (CHORUS 73% versus 41%, EORTC 80.6% versus 41.6%) did not translate into a survival benefit [11, 12]. Neither the assessment of pathologic response following NACT nor the minimum surgical requirements for ICS have been standardized. The clinical impact of complete cytoreduction post-NACT is likely to be less robust than complete cytoreduction with PCS.

Retrospective series have suggested that improved survival is possible with PCS, particularly when incorporating radical surgical techniques [5–7, 13–16]. It remains difficult to control for selection bias in retrospective data. Other studies have suggested that tumour biology and initial tumour burden remain important, even with maximum surgical effort [17, 18]. These studies also highlight the need to develop better criteria to guide the selection of patients for NACT or PCS.

Performance status (PS) and associated variables should be utilized as stratification points (SP), depending on the trial design. In the CHORUS study, designed for co-analysis with EORTC 55971, anticipated OS at 3 years in the primary surgery arm was 50%, but actual median OS was only 22–24 months. Explanations for this discrepancy included a relatively poor PS among study participants (19% PS grade 2 or 3) and an older patient population (median age 65 years). PS and other variables associated with comorbidities (e.g. nutritional status) aid interpretation of study results and should be considered in future trial design [19, 20].

Prior to instituting therapy, the importance of documenting tumour markers was affirmed. Traditional tumour markers have included CA-125 and carcinoembryonic antigen (CEA), the latter to exclude gastrointestinal primary. While acknowledging that CA-125 is not truly 'tumour-specific', an analysis of seven GOG studies found that pre-treatment CA-125 level was an independent predictor of progression-free survival (PFS), especially in patients with serous or endometrioid histology and microscopic residual disease [21].

Another promising tumour marker is Human Epididymis Protein 4 (HE4), shown to have good sensitivity and specificity in EOC, both at initial diagnosis (differentiating EOC from benign) and in documentation of recurrence [22–24]. A failure of HE4 to normalize at completion of treatment is an indicator of poor prognosis [24, 25]. Documentation of appropriate pre-treatment tumour markers should be incorporated in future trials of primary therapy.

Country/region of treatment was determined to be an important potential stratification factor, recognizing differences in race, ethnicity, local resources and clinical practice. The EORTC 55971 study showed widespread variations in optimal PCS rates by country [26]. In the same study, however, regional OS did not correlate with cytoreduction rates, with patients from regions with the lowest rates of optimal cytoreduction achieving the best survival [27]. In the SCOTROC-1 study, patients from the UK with no MRD had less favourable PFS relative to non-UK patients [28]. Nuances in care and patient selection will impact outcomes from apparent standardized treatments. Consider country or region of treatment as a stratification factor where appropriate.

Pathologic markers

Consistent with the fourth OCCC, histopathology remains the gold standard for the classification of EOC cancer subgroups [1].

Where required, diagnostic accuracy of histopathology can be improved with standardized application of immunohistochemistry (IHC) [29]. For pathological reporting within randomized clinical trials (RCT), histological subtype and grade should not be reported separately. Following NACT, morphological features of the tumour at ICS could differ greatly from the original tumour, including necrosis, inflammation, fibrosis and altered differentiation status [30]. The OCCC determined that tumour grading (and typing) should be based on the pre-chemotherapy tissue biopsy. For serous carcinoma, there was consensus recommending a binary grading system, limited to HGSC and LGSC (incorporating micropapillary carcinoma). Discrimination between LGSC and HGSC follows the degree of nuclear atypia in combination with mitotic activity [31]. LGSC is characterized by frequent mutations in KRAS, BRAF and ERBB2 genes and infrequent TP53 mutations [32]. Whereas TP53 mutations are rare in LGSC, they are ubiquitous in HGSC. Absence of a loss-of-function molecular alteration in TP53 is inconsistent with a diagnosis of HGSC [33, 34].

The OCCC recommends that in HGSC, the fallopian tubes be intensively sampled using a Sectioning and Extensively Examining of the Fimbriated End (SEE-FIM) protocol [35]. With serous tubal intraepithelial carcinoma (STIC) and widespread peritoneal involvement, where ovarian surface involvement or parenchymal involvement is <5 mm, these tumours should be classified as tubal primaries.

When categorizing ovarian endometrioid adenocarcinoma (OEA), adoption of a binary grading system was also recommended. This differs from the 2014 WHO classification of female reproductive organs and reporting standards endorsed by the International Collaboration on Cancer Reporting (ICCR), where OEA are graded identically to uterine endometrioid carcinomas – grade 1, 2 or 3 [36, 37]. FIGO grading of endometrioid endometrial carcinoma reflects not only the presence of high-grade cytological features but also the actual percentage of high-grade solid tumour, which is less relevant in the setting of a non-endometrial primary site. High-grade endometrioid tumours demonstrate mutational profiles similar to HGSC harbouring TP53 mutations, while the low-grade tumours showed distinct mutations in CTNNB1, PTEN and/or PIK3CA [38]. Mutations in the Wnt/Beta-cat signalling pathways present in low-grade tumours were absent in high-grade endometrioid carcinoma. The consensus recommends classifying FIGO grade 1 tumours to low-grade, and grades 2 and 3 to high-grade.

Clear cell carcinoma, carcinosarcoma and undifferentiated carcinoma should be classified as high-grade epithelial malignancies [37]. Carcinosarcomas are included, despite having mixed epithelial and mesenchymal components, attributed to epithelial–mesenchymal transition [39]. Most OMC are of intestinal type, arising through a continuum from benign to borderline to malignant [31]. These are usually well to moderately differentiated (grade 1 or 2) and can exhibit expansile (non-destructive) or infiltrative (destructive) invasion, although controversy exists about the ability to prognosticate based on pattern of invasion [37]. According to WHO (2014), Mullerian and endocervical type tumours, previously classified as mucinous, and now classified as seromucinous, are thought to be more closely related to endometrioid tumours than to mucinous intestinal types [36]. Grading of OMC is recommended.

The importance of access to archival tumour specimens for future molecular studies was affirmed. Study protocols should account for the documentation and maintenance of archival specimens. One method endorsed by the ICCR is to record the origin and designation of tissue blocks in the final pathology report [37]. Collected specimens allow for extended correlative studies, where bio-specimens are linked to clinical data.

Genomic biomarkers

For patients enrolled in clinical trials, germline mutation testing to include BRCA1/2 was recommended, with stratification and incorporation of mutation status into endpoint analysis. Many series have shown that BRCA 1/2 mutation is associated with improved outcomes [40]. One large aggregated analysis has suggested that the advantage associated with BRCA1 mutations may become less favourable over time [41]. The power of a long-term retrospective analysis could be impacted by non-germline (somatic) mutations and other molecular factors within the BRCA "wild-type" cohort. There was debate whether germline testing should be limited to non-mucinous histologies; in view of the risk of misclassification, as well as concordance with published guidelines, it was recommended that within a trial, patients with EOC should undergo germline testing [40].

The consensus recommends somatic mutation analysis of tumour samples. Loss of BRCA function secondary to somatic mutations in OC accounts for 7%–13% of BRCA mutations in HGSC [42–44]. Somatic analysis from The Cancer Genome Atlas (TCGA) project demonstrated that approximately 50% of HGSC have associated homologous recombination deficiency (HRD), potentially targetable with poly (ADP-ribose) polymerase (PARP) inhibitors [45]. Extending BRCA1/2 testing to include somatic mutation analysis was recommended.

As validated predictive biomarkers become available, these should be included as companion diagnostics. Several potential biomarkers were discussed. The creation of an HRD score based on loss of heterozygosity (LOH) correlates with mutations in BRCA1/2 and other genes, while accurately predicting both OS and PFS [46]. Regardless of histology, HRD defects are associated with both platinum sensitivity and improved OS [44]. Another HRD signature based on LOH correlates with response to PARP inhibitor [45, 47].

A potentially targetable biomarker is the overexpression of Cyclin E1 (CCNE-1) seen in OC [48]. CCNE-1 amplification correlates with shorter PFS when PCS is followed by platinum/taxane chemotherapy, and it correlates with platinum resistance in HGSC [49, 50]. A third potential biomarker is represented by intratumoural T-cells in EOC tissue. In patients with stage III/IV EOC, the presence of intratumoural T cells correlates with improved PFS and OS [51]. This illustrates another area of unmet need, where immunologic functional scoring might guide the development of immunologic interventions.

What are the most important factors to be evaluated specifically in recurrent disease?

The OCCC addressed factors to consider in the design of phase III trials in the recurrent setting. Treatment-free interval (TFI)

following primary chemotherapy was identified as the most important clinical factor. As treatment with a platinum-based regimen remains standard of care in the primary setting, the platinum free interval (PFI) should be documented and utilized to determine eligibility or serve as a stratification factor (Table 2).

Several studies have shown a differential impact of subsequent treatments based on the PFI. AGO-OVAR 2.5 comparing gemcitabine/carboplatin versus carboplatinum showed differential PFS (7.9 versus 9.7 months) based on initial PFI, between partially platinum sensitive patients (6–12 months) and those who were platinum sensitive (>12 months) [52]. Penultimate platinum treatment should be considered at randomization. The analysis by Hanker et al. [8], addressing effectiveness of chemotherapy at recurrence, included patients on trials in the primary setting to characterize PFS/OS from the second to the sixth lines of therapy. PFI following first-line treatment was strongly prognostic for PFS up to the third recurrence (OR 0.56 [0.5–0.63] at first recurrence; OR 0.76 [0.64–0.9] at second recurrence). In the CALYPSO trial, a subset of patients with a prolonged TFI >24 months was analysed separately, reflecting their different tumour biology [53].

Considering the linear relationship between extended PFI and platinum sensitivity, we recommend reporting PFI following primary chemotherapy as a continuous variable, rather than adopting an arbitrary definition of 'platinum-sensitive' or 'platinum-resistant' disease based on a single fixed time point (such as 6 months). Future trials could define eligibility or patient cohorts according to any appropriate PFI, depending on the nature of the study, and may, therefore, not be limited to a fixed 6-month window.

Platinum-based therapy (PBT) remains the most active agent in the management of EOC, and primary PFI clearly provides important prognostic and predictive information. Many patients receive multiple lines of PBT, and the time interval following the most recent PBT can also provide prognostic information, due to acquired resistance and clonal evolution associated with intervening non-platinum treatments.

A variety of non-platinum agents have been integrated with conventional therapy, and other prognostic/predictive markers are needed to guide treatment decisions in the management of recurrence. Several trials have affirmed that targeting the vascular endothelial growth factor (VEGF) improves clinical outcomes as maintenance post-chemotherapy or in combination with chemotherapy for recurrence [54–60]. PARP inhibitors have demonstrated improved PFS as single agents in the management of recurrence and as maintenance following chemotherapy [60]. Recognizing emerging treatment strategies, the OCCC also recommended that the last dose of non-platinum agents, including maintenance therapy, be recorded.

Secondary (or subsequent) cytoreductive surgery has been increasingly utilized in selected patients with recurrent ovarian cancer, and the OCCC recommends stratification based on the outcome of the most recent cytoreductive surgery. Complete resection was associated with prolonged survival in the recurrent setting in the exploratory DESKTOP OVAR trial (45.2 versus 19.7 months, HR 3.71, $P < 0.0001$), also confirmed elsewhere [61, 62].

With recurrence, the presence of non-measurable versus RECIST (response evaluation criteria in solid tumours)-measurable disease should be documented, including small solid/cystic lesions and fluid collections as well as diffuse tumour implantation on vital organs without measurable solid components, depending on study eligibility. Solid tumour response was defined in RECIST version 1.1 [63], and RECIST guidelines for progression of disease can be applied to patients with non-measurable disease at enrolment. GCIG guidelines to determine tumour response and progression using CA-125 exist, and although these have not been accepted as primary endpoints by regulatory authorities, they can be utilized to provide supporting data [64].

Histological subtype remains an important factor to guide enrolment in sub-type specific trials, or as a SP. In light of different genetic risk factors, molecular abnormalities and precursor lesions, as well as variable response to chemotherapy and targeted agents across histologies, histotype must be considered [65]. Collection of tumour specimens at relapse is encouraged, with an emphasis on paired samples collected at the outset and at recurrence, enhancing the study of molecular targeting and acquired resistance.

Are there specific considerations for special patient subpopulations?

Race and ethnicity

Differences in outcome of cancer treatments attributable to race/ethnicity are becoming recognized, the result of both biological and environmental interactions [66] (Table 3). When comparing treatment and survival between Asian and white women with EOC in the US, age, stage of presentation, as well as histological subtype/grade differed between the groups [67]. Dividing Asians into immigrant versus US-born, 5-year disease-specific survival favoured immigrant Asians compared with US-born Asians and whites (55%, 52%, and 48%, respectively, $P < 0.001$). Increases in 5-year OS over the past 30 years seen in whites (36%–45%) have been met with a decrease in blacks (43%–39%) over the same time period [68]. A positive first line maintenance trial investigating pazopanib has shown inferior outcome in Asian patients compared with placebo, meaning a drug could harm specific patient subgroups, even in a positive trial [69]. A separate study examining potential racial disparities between blacks and whites enrolled in GOG clinical trials found equivalent PFS between the two groups (37.9 and 39.7, respectively, $P > 0.05$) [70].

The collection, reporting and analysis of race/ethnicity categories should be incorporated in future trials. Predefined and prospective data collection minimizes confounding and strengthens associations found in post hoc analysis of trial data. Race and ethnicity are differentially categorized by country and region; development of universal standards was recognized as an unmet need, limiting international data harmonization.

In a meta-analysis of RCTs treating advanced stage non-small cell lung cancer, a difference in the overall response rate between Asians and Caucasians was observed (65% versus 31%, $P = 0.01$), where ethnicity was identified as the only independent predictor of response to treatment by multivariable analysis [71]. Several studies have shown associations or putative effects between polymorphisms and outcome/toxicity. Attempts to validate

a previously defined set of polymorphisms from the Scottish Randomized Trial in Ovarian Cancer, no pharmacogenetics markers for outcome or toxicity were identified [72]. Until more data emerge, existing studies do not support stratification; as data are validated within specific populations, race/ethnicity could become a stratification factor within individual studies.

Frail and elderly patients

In the conduct of phase III trials in EOC, frail and elderly patients have been underrepresented. Comorbidities and physiologic factors are predictive of outcomes and toxicity, compared to age; older age should not be an exclusion criterion in EOC trials.

The improvements in cancer survival over the past decades generally seen in younger patients have not translated to elderly cohorts, with a widening gap of OS rates between younger and more elderly cohorts [73, 74]. In Germany between 1979 and 2003, age-specific OC survival remained stable for women age 75 and over, yet OS steadily increased for women aged 15–54. Women aged 55–74 experienced an increase from 1994 onwards, representing the highest age gradient seen across all tumours [75].

Outcomes for elderly patients may relate directly to the care they receive, particularly when that care deviates from the standard. Surveillance, Epidemiology and End Results Program (SEER) data investigating risk factors for early death show that the largest risk factor for death at one year was receiving non-standard treatment [76]. This is echoed by the German experience, where differential treatment in women over 70 was associated with differences in survival. Analysing patients enrolled in phase III RCTs addressing first-line treatment, women >70 (10.7% of patients) were more likely to experience discontinuation of their treatment and receive 4 or fewer cycles [77, 78]. Multivariate analysis of PFS in women 70 or older receiving 4 or fewer cycles of chemotherapy was 2.3 ($P < 0.001$), translating into a difference in PFS of 18.4 ($P < 0.001$) months and OS of 33.8 months ($P < 0.001$) [79].

Patients enrolled in clinical trials tend to have better outcomes based on the need to meet eligibility requirements, with healthier patients more likely to achieve enrolment. The results of some trials then become poorly generalizable, as they are not addressing the realities of patients seen in the real-world clinical domain [80, 81]. Apart from advanced age, OC patients may present with comorbidities or poor PS, which will impact OS [20, 82]. While prior cancer diagnosis is often an exclusion criterion from an RCT out of concern that it might interfere with the current study, no data exist which support this practice [83]. To improve generalizability of trial results, with the goal to make trials available to the broadest population possible, any limitations to eligibility criteria based on PS/comorbidities/prior malignancies must be justified by the trial design.

Adequately comparing patients for trial inclusion requires validated measures to minimize confounding. While elderly patients must be considered for inclusion as trials are developed, inclusion based on the age alone is insufficient. In conjunction with age and geriatric conditions, comorbidities, disability and physical reserve must be considered in consort. The goal is to differentiate elderly patients who could receive standard treatment from frail patients – those with low physiologic reserve – who are not candidates for standard therapy and could benefit from a comprehensive geriatric assessment (CGA) to help guide therapy [84]. To date, measures of frailty have failed to achieve both the high sensitivity and specificity required to ensure that patients deemed fit enough for standard treatment truly are, and to differentiate these patients from those who will benefit from a CGA [84]. The consensus recommends that clinical trials in EOC should include measures from geriatric assessment domains.

Unmet needs to support future clinical research

In the process of assigning important SP throughout the consensus process, unmet needs were identified as areas with potential to enhance clinical research but which lack direction. In regards to the issue of assessing residual disease at the time of debulking surgery, the group sees a potential role for intra-operative scoring [85] and/or post-operative imaging (see Clinical markers section) to document RD (Table 4).

Universal staging criteria in the context of NACT are needed. In CHORUS and EORTC 55971, women in the NACT arms were staged clinically using imaging [3, 4]. No validated process exists for documenting the extent of disease outside of surgery.

Treating patients with NACT will result in morphological changes to the tumour. While attempts at quantifying the chemotherapy effect on tumour morphology have been undertaken, none have proven to be prognostic. The International Collaboration on Cancer Reporting has recently published a validated chemotherapy response score (CRS) with prognostic significance for PFS [86]. There is a need for creation of a CRS that can be incorporated in primary endpoint analysis and pathological reporting.

Immunotherapy in OC represents a rapidly evolving treatment domain, with an urgent need for the standardization of immunologic assessment. Programmed cell death ligands (PD-1 and PD-L1) and CD8+ T cells are prognostic in OC, the former allowing for immune evasion of tumour cells [87]. T cell infiltration into OC tumour samples is associated with improved OS [51]. Standards for immunologic assessment, including lymphocyte infiltration scores, T cell subsets and PD-1/PD-L1, are required for comparison among studies and in order to allow for incorporation as SP in future studies.

There are important issues regarding definition and categorization of race/ethnicity that would benefit from international harmonization (see Race and ethnicity section). Older patients and/or those with compromised functional status are underrepresented in clinical trials. There is a need to define this population and perform trials to evaluate standards for this subgroup (see Frail and elderly patients section).

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