Clinical research in endometrial cancer: consensus recommendations from the Gynecologic Cancer InterGroup

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The Gynecologic Cancer InterGroup (GCIG) Endometrial Cancer Consensus Conference on Clinical Research (ECCC) was held in Incheon, South Korea, Nov 2–3, 2023. The aims were to develop consensus statements for future trials in endometrial cancer to achieve harmonisation on design elements, select important questions, and identify unmet needs. All 33 GCIG member groups participated in the development, refinement, and finalisation of 18 statements within four topic groups, addressing adjuvant treatment in high-risk disease; treatment for metastatic and recurrent disease; trial designs for rare endometrial cancer subgroups and special circumstances; and specific methodology and adaptation for trials in low-resource settings. In addition, eight areas of unmet need were identified. This was the first GCIG Consensus Conference to include patient advocates and an expert on inclusion, diversity, equity, and access to take part in all aspects of the process and output. Four early-career investigators were also selected for participation, ensuring that they represented different GCIG member groups and regions. Unanimous consensus was obtained for 16 of the 18 statements, with 97% concordance for the remaining two. Using the described methodology from previous Ovarian Cancer Consensus Conferences, this conference did not require even one minority statement. The high acceptance rate following active involvement in the preparation, discussion, and refinement of the statements by all representatives confirmed the consensus progress within a global academic setting, and the expectation that the ECCC will lead to greater harmonisation, actualisation, inclusion, and resolution of unmet needs in clinical research for individuals living with and beyond endometrial cancer worldwide.

Introduction

The Gynecologic Cancer InterGroup (GCIG) is a collaborative body comprising 33 clinical research groups worldwide (appendix p 2), and has organised two previous endometrial cancer meetings including a State of Science Meeting (Manchester, UK, 2006) and a Clinical Trials Planning Meeting (Leiden, Netherlands, 2012). This first GCIG Endometrial Cancer Consensus Conference on Clinical Research (ECCC) included four patient advocates[1] and an expert on inclusion, diversity, equity, and access. The ECCC was held according to GCIG methodology which was developed and refined in previous ovarian cancer consensus conferences.[2–4] Planning was initiated in May, 2022, and the meeting was hosted by the Korean Gynaecologic Oncology Group (KGOG).

Consensus process

The Scientific Committee for the preparation and organisation of the ECCC was organised according to the GCIG methodology (appendix p 3), including representation from the host group KGOG. Additionally, each of the 33 GCIG member groups appointed two delegates who were members of the topic groups and participated in all aspects of the ECCC. Care was taken to provide multidisciplinary representation, including gynaecological oncologists and surgeons, medical and clinical oncologists, radiation oncologists, pathologists, translational scientists, and statisticians. Additionally, pathology representatives from the International Society of Gynaecological Pathology, four patient representatives from different global regions, one expert on inclusion, diversity, equity, and access, two additional radiation oncology representatives, one expert on rare tumours, four GCIG harmonisation group members, and four early career investigators were invited. A list of speakers and discussants is presented in the appendix (pp 7–8) and an overview of all 96 participants of the ECCC by GCIG group and/or GCIG role is shown in the appendix (pp 9–12).

20 key topics were identified, and organised within four topic groups to focus initial discussions. During the planning process and the consensus meeting, some topics were integrated, resulting in 18 final consensus statements and tabulation of unmet needs for future clinical research (panels 1–5). First drafts of the consensus statements were developed in monthly virtual meetings of the topic groups, with designation of a presenter and a discussant for each statement and sub-statement (appendix pp 7–8). To optimise preparation and participation across time zones and languages, 10-min lectures of each presenter and discussant were pre-recorded and available in video format before the meeting for review by all delegates. Due to local restrictions and unforeseen circumstances, seven representatives were not able to participate onsite, but five participated in their topic group sessions and plenary discussions by video conference.

The ECCC started with plenary lectures presented by a patient advocate and the expert on inclusion, diversity, equity, and access. All four topic groups then presented

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‡All delegates are listed in the appendix (pp 9–12)

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their draft statements, with plenary discussions and suggestions for refinement, followed by topic group meetings to discuss and implement revisions. During the second day, revised statements were presented, followed by discussion and finalisation of each statement and voting. Each of the 33 GCIG member groups had a single vote and voted on the 18 statements. The consensus statements, voting records, and areas of unmet need for future research were collected (as shown in panels 1–5).

Summary of plenary presentations

Patient advocate involvement

It is increasingly recognised that the meaningful input of people with lived experience of cancer can help to shape research that is relevant and impactful.[5] In recognition of this, four patient advocates were invited to participate as ECCC partners; one each from Canada, India, New Zealand, and the UK. One participated onsite, and virtual attendance was arranged as needed. Messaging between the advocates and the early career investigators in their topic group facilitated active participation.

The patient advocates were involved throughout all stages of the ECCC, from pre-conference topic group meetings to contributing during the conference, resulting in patient-focused input into the draft consensus statements, and delivery of a plenary presentation setting out advocates' perspectives on clinical trials and improvement of outcomes for patients, which are summarised as follows: first, trials should focus on less frequently studied areas, including prevention, early detection, biomarker monitoring, supportive care, and long-term quality of life. Prevention was perceived by advocates as the area with the most substantial opportunity to effect change. Second, trials need to be accessible to a more diverse patient population so that results are truly representative of all those affected, removing social, cultural, and racial barriers to improve recruitment and retention. This includes providing accessible and inclusive patient information, education, and ongoing support. Third, trials that find more affordable, precise, and effective treatments are needed, especially for rare cancers and those with poor prognoses. Affordability of treatments is especially important with respect to low-income and middle-income countries (LMICs) and marginalised socioeconomically deprived communities. Fourth, trial endpoints that capture the real-life experiences of patients should be incorporated more often into trial design, including accessible patient-reported outcome (PRO) measures of treatment burden, long-term quality of life, and adverse effects. More meaningful endpoints will help future patients weigh the risks against the benefits when making treatment decisions. Fifth, meaningful involvement of people with relevant lived experience, advocates, and relevant communities should be embedded throughout the trial lifecycle to make trials more patient-centric, community-led, or both, to increase trial success. These themes framed the patient advocates' collective input to the ECCC, contributing to the refinement of the statements and helping to identify areas of unmet need for future research.

Inclusion, diversity, equity, and access to endometrial cancer clinical trials

Countries worldwide are becoming more diverse. For example, Europe and Asia were home to the most international migrants in 2020 compared with other regions; with an international migrant population of 86·7 million in Europe and 85·6 million in Asia.[6]

New drug approvals rely on the generalisability of evidence from clinical trials to represent the population expected to receive treatment; however, patients from minority backgrounds are consistently under-represented. Black patients represent 13·4% of people with cancer in the US, but account for only 4–6% of trial participants.[7] Similarly, in the UK only 26% of studies from 2007 to 2022 reported on race or ethnicity, and of those that did, 49% reported no Asian participation and 43% reported no Black participation. Additionally, LMICs are vastly under-represented in trials, with only 8% of phase 3 trials initiated and conducted in LMICs even though 75% of cancer deaths will be in LMICs by 2030.[8] Of note, precision management of endometrial cancer relies on genomic testing, and molecular differences between races have emerged, including a higher proportion of *CCNE* alteration and *TP53* mutation in Black patients, and lower rates of microsatellite instable (MSI) or mismatch repair deficient (MMRd) cancers.[9,10]

There are many potential barriers to achieving inclusion, diversity, equity, and access, including clinician (eg, implicit bias and limited time), patient (eg, distrust, low health literacy, financial, and language), institutional (eg, access to trials and diversity of staff), and trial specific (eg, restrictive eligibility criteria and numerous study visits) barriers.[11]

An American Society of Clinical Oncology and Association of Community Cancer Centers joint research statement (2022) outlines recommendations to increase racial and ethnic diversity in clinical trials. These include ensuring all patients have opportunities to participate, designing trials with a focus on inclusion, diversity, equity, and access, forming long-standing partnerships with communities; ongoing training in anti-bias and cultural competencies, building a diverse workforce, support with clinical trial navigators, and collecting and reporting race and ethnicity data.[7] Worldwide efforts to address diversity in clinical trials include the US Food and Drug Administration guidance on diversity plans, WHO guidance on under-represented populations in clinical trials, Australian Clinical Trials Alliance recommendations, and Health Canada draft guidance.[12–15] There is a clear need for inclusive research that is representative of the population expected to use the medicine to help understand potential differences in

efficacy and safety between different individuals and groups within the population, and to help mitigate health disparities.

Pathology: standardisation and minimal requirements for pathological evaluations

There are two types of tissue samples, diagnostic biopsies and surgical resection specimens. Appropriate tissue handling is important, since delayed or prolonged fixation could interfere with optimal pathological and biomarker assessment. Histopathological assessment, primarily using hematoxylin and eosin stain and immunohistochemical stains, is essential for proper histological subtyping and staging. Biomarker assessment is critical in endometrial cancer to establish The Cancer Genome Atlas molecular subtype. The Cancer Genome Atlas classification requires testing for pathogenic *POLE* mutation, assessment of MSI or MMR protein expression, and *TP53* mutational status or p53 immunohistochemical expression pattern according to published guidelines for interpretation.[16–20]

To assign a molecular subtype to an endometrial carcinoma, *POLE* testing must be performed in addition to MSI or MMR and p53 testing. It is only in the absence of a pathogenic *POLE* mutation that a tumour can be assigned to MSI or p53 abnormal molecular subgroup. Some endometrial tumours have double classifiers, where both pathogenic *POLE* mutation and p53-abnormal expression are present.[21] In the case of multiple classifiers, *POLE* status is considered first, followed by MSI or MMR status.[22] The WHO algorithm for determining molecular status is in the appendix (p 4).

It should be noted that there are emerging techniques of determining *POLE* status without next generation sequencing, which is expensive and not available in some centres and countries. Examples are *POLE* multiplex tests[23,24] and deep learning techniques,[25] which have been shown in first studies to accurately identify *POLE* status. In addition, costs can be saved when omitting intensive and costly adjuvant therapies in patients with apparently high-grade or high-risk cancers, among whom about 8–10% *POLE*-mutated cancers are found. These women will have a completely different prognosis and outlook when the *POLE*-mutated status is identified. This was also emphasised in a study of a decision algorithm on *POLE* testing, which led to a reduction in the number of *POLE* sequencing tests by 67% without affecting the risk classification.[26]

The International Collaboration on Cancer Reporting has updated a standardised dataset for pathology reporting of resection specimens of endometrial cancers,[27] with the following two types of elements: core elements that are essential for diagnosis, clinical management, staging or prognosis, such as lymphovascular space invasion (both presence and extent),[28,29] and non-core elements that are clinically important and recommended as good practice and should ideally be included in the dataset (appendix p 4).

Consensus statements

Two statements were not topic group-confined but more general, and are listed in panel 1.

The statement that patients should be eligible for clinical trials by default, with patient advocates and those with lived experience being partners in the design and development of clinical trials, was strongly endorsed. Efforts should be made to collect data in each trial on patients who were not included as they did not meet all eligibility criteria of a trial (so-called screen failures), and to report their characteristics in the publication as supplementary data. Information on excluded patients and non-participation might help to broaden inclusion and exclusion criteria and increase inclusivity and diversity, leading to a trial population more representative of the real world. Frail patients (separating calender age from biological age and resilience), not amenable to inclusion in pivotal trials, should be included in dedicated trials. Efforts should also be made to collect pharmacokinetics data in frail patients, and adapted treatment dosing and schedules should be investigated from early phase drug development.

***Panel 1*: General consensus statements (inclusivity of clinical trials and biomarkers)**

Statement 1

Patients should be eligible for a clinical trial by default. Any exclusion criteria are tailored to the scientific objectives of the study and substantial patient safety concerns (33 [100%] of 33 groups approved)

- a Patient advocates and persons with lived experience should be partners in designing clinical trials and development/validation of reliable frailty scoring tools
- b Patient participation should be optimised by use of stratification factors that address comorbidities and lifestyle elements that could affect compliance, completion of treatment, or breadth of accrual diversity
- c Broader eligibility with stratification will create a more real-world inclusivity and applicability of the outcome of the clinical trial
- d Separate studies, using validated organ dysfunction or frailty discriminants, should be considered where such patients cannot be enrolled safely in primary studies

Statement 2

Existing and potential biomarkers of response, relapse, toxicity, and resistance should be integrated into trials (33 [100%] of 33 groups approved)

- a Longitudinal biospecimen collection for serial biomarker assessment should be integrated in clinical trials.
- b When biological samples are collected within a trial with appropriate patient informed consent, investigators need to have access to the specimens and the annotated data

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See **Online** for appendix

Given the critical impact of biomarkers in prognostication, therapy, and outcomes, the potential use of biospecimens in other future unspecified research should be clearly requested in the informed consent for each trial. Biospecimen collection should be repeated at predefined endpoints, starting from diagnosis or trial inclusion. Beyond efficacy outcomes, biomarkers should also be correlated with toxicity. Access to biological specimens and annotated data by trial investigators is essential, regardless of whether the trial is academic or industry supported.

Adjuvant treatment in high-risk endometrial cancer

Consensus statements on trials in adjuvant therapy for high-risk disease are summarised in panel 2. The consensus definition of high-risk is given in the appendix (pp 5–6). There has been a substantial transformation in the treatment paradigm for endometrial cancer through molecular classification and its incorporation in risk stratification.[30] This is likely to continue in the coming years, and will play a major role in clinical trials. Complete risk stratification generally follows surgical staging but pre-operative information could categorise patients as high-risk (eg, through presence of p53-abnormal endometrial cancer).

By definition, patients with high-risk disease are at high risk of recurrence and metastatic spread beyond the uterus. It is therefore recommended that cross-sectional imaging of the chest, abdomen, and pelvis is performed to rule out nodal or distant disease. This can be done pre-operatively if high-risk features are identified, or post-operatively before adjuvant therapy. No evidence exists to guide which imaging modality is most effective. It is important to recognise imaging limitations in detecting micro-metastases, especially in lymph nodes. We therefore recommend adopting surgical-pathological staging as the primary standard approach for detecting microscopic disease beyond the uterus. However, the role of surgical staging in patients already identified as high risk is less clear, as it would not necessarily change clinical management. Sentinel lymph node assessment is the preferred method as it adds less morbidity and should be applied as the standard of care where possible.[31] Similarly, minimally invasive surgery is also accepted as the standard of care where available.[32] In women with presumed early-stage high-risk disease, the routine practice of a minimally invasive sentinel lymph node approach where feasible avoids the toxicity of systematic lymphadenectomy. Ultrastaging is essential when using sentinel lymph node.[33] However, pathologists report variation in the methods used to identify micrometastases which could lead to variation in reporting. It is therefore mandated that minimum requirements of pathological assessment are defined clearly within trial protocols, and protocols ensuring centralised review are considered.[34]

Four molecular subtypes of endometrial cancer have been identified[16] that relate to prognosis as well as response to therapeutic options.[17,35] Moving forward, it is therefore recommended that clinical trials are targeted to these specific molecular subtypes where relevant. Dedicated clinical trials are recommended for patients with p53-abnormal subtypes of endometrial cancer, as their prognosis is especially poor. De-escalation trials within the *POLE*-mutated subtype are also encouraged. Presence of substantial lymphovascular space invasion is important in risk definition and as an independent prognostic marker.[29,36] This could contribute to clinical management decisions, particularly regarding external beam radiotherapy, and should therefore be clearly reported according to WHO criteria.[28]

Trials involving multiple molecular subtypes should include the subtype as a stratification factor due to the disparate prognoses. This will guide future understanding of treatment options and disease behaviour. This is especially important in rare endometrial cancer subgroups as they might respond

***Panel 2:* Consensus statements on adjuvant therapy for high-risk endometrial cancer**

For the consensus definition of high-risk disease, see the appendix (pp 5–6).

Statement 3

Contribution of imaging and lymph node evaluation for the definition of high-risk disease (33 [100%] of 33 groups approved)

- a Patients with high-risk disease should have cross sectional imaging of chest, abdomen, and pelvis before enrolment in a clinical trial
- b Primary surgical-pathological staging including lymph node assessment, preferably by minimally invasive surgery and sentinel lymph node algorithm, is the recommended standard approach to identify high-risk disease
- c Definition of minimal requirements of pathological assessment, including ultrastaging of sentinel lymph nodes, is mandatory within clinical trials

Statement 4

Molecular classification and histological subtypes in selection and stratification; other key prognostic factors (33 [100%] of 33 groups approved)

- a In patients with high-risk disease, tailored treatment approaches in distinct molecular subtypes and biomarker defined groups are recommended, including trials of rare endometrial cancer subgroups
- b Stratification by molecular subtypes is recommended in clinical trials with broader inclusion criteria
- c Pathologists should be engaged in the design of clinical trials expected to develop or investigate a biomarker test
- d The prognostic value of additional pathological or molecular features in rare endometrial cancer subgroups should be interpreted in the context of molecular subtypes requiring further validation before being used to modify clinical management

Statement 5

Standard arms/reference groups in clinical trials (33 [100%] of 33 groups approved)

- a In the adjuvant treatment of patients with endometrial cancer with high-risk disease the control arm is represented by platinum–paclitaxel chemotherapy and radiotherapy (concomitant chemoradiotherapy followed by chemotherapy or sequential chemotherapy and radiotherapy) or platinum–paclitaxel chemotherapy alone
- b When the control arm is chemotherapy with or without radiotherapy, radiotherapy should be a stratification factor

***Panel* 3: Consensus statements on trials for advanced primary, recurrent, and metastatic endometrial cancer**

Statement 6

Randomised phase 3 trials are the optimal design to change practice in advanced primary, recurrent, or metastatic endometrial cancer. Trials should include relevant stratification factors and be powered to detect clinically meaningful improvements for patients (32 [97%] of 33 groups approved*)

a The standard arm for first-line trials in patients with metastatic mismatch repair deficient endometrial cancer planned for chemotherapy treatment should be carboplatin plus paclitaxel and an immune checkpoint inhibitor. For other patients, the standard arm should be carboplatin and paclitaxel with or without an immune checkpoint inhibitor

b Patients with stage 3 disease and residual disease that is measurable or evaluable by Response Evaluation Criteria in Solid Tumours post-hysterectomy can be included, with stage being a stratification factor

c Patients who received adjuvant chemotherapy with platinum and paclitaxel are allowed to be included if completed more than 6 months before relapse

d In first-line trials, stratification factors could include a selection of: mismatch repair status, p53 status, no specific molecular profile/copy-number low molecular type, oestrogen receptor and progesterone receptor status, receipt of previous adjuvant chemotherapy, performance status, race or ethnicity, region, and advanced or recurrent disease. The stratification factors chosen, including other clinical factors or biomarkers, will depend on the agent being tested and the size of the trial

e The primary endpoints for first-line trials should be progression-free survival, overall survival, or both. For multiple primary endpoints, the type I error must be strongly controlled. Secondary endpoints could include response rate, duration of response, adverse events, overall survival (if not a primary endpoint), and relevant PRO measures

f The duration of maintenance therapy, if used in trials, should be justified based on the agent being tested, and trials should be designed in order to determine the specific contribution of maintenance therapy. It is essential to assess the impact of any maintenance therapy on health-related quality of life

Statement 7

The trial design and study endpoints for first-line trials of hormonal therapy for oestrogen receptor or progesterone receptor-positive tumours should be similar to those for other first-line trials (32 [97%] of 33 groups approved†)

a First-line trials of hormonal therapy should ideally be randomised

b To be eligible for hormonal trials, the recommended cutoff for oestrogen receptor and/or progesterone receptor expression is ≥10%. The study should be powered for this cohort. However, enrolment in a separate cohort with at least 1% oestrogen receptor and/or progesterone receptor expression is an option. Retesting of a site of metastatic disease is recommended whenever feasible

c The specific level of oestrogen receptor and/or progesterone receptor expression should be recorded for all patients. Stratification for the level of oestrogen receptor and/or progesterone receptor expression should be considered

d The endocrine therapy in the standard arm will depend on the agent being tested. This should enable the relative contribution in terms of efficacy and toxicity of each individual agent and any combination treatment to be determined

e The primary endpoint should be progression-free survival for randomised trials. Overall survival, clinical benefit rate, response rate, and PRO measures should also be assessed as secondary endpoints

Statement 8

Second-line and beyond systemic therapy trials in recurrent or metastatic endometrial cancer should be biomarker-driven (33 [100%] of 33 groups approved)

a Second-line trials should ideally be randomised. Signal-seeking single-arm studies or other novel designs might be needed for rare biomarker subtypes

b The standard arm for second-line randomised trials will vary depending on previous therapy. It should include a checkpoint inhibitor in immunotherapy-naive patients. The standard arm in immunotherapy-pretreated patients could include platinum-based or non-platinum-based chemotherapy, depending on the platinum-free interval, or hormonal therapy

c Stratification factors should include the molecular classification as well as previous therapy and other important prognostic or predictive factors relevant to the treatment being studied

d Patient selection for targeted therapy trials should be based on a relevant, validated biomarker assay. Biospecimens should be collected where feasible for translational analysis with appropriate patient consent

e The primary endpoint for randomised second-line trials could be progression-free survival, overall survival, or both. Secondary endpoints should include response rate, duration of response, adverse events, and PRO measures

Statement 9

Clinical trials in endometrial cancer should include PRO measures dedicated to assessing the impact of therapies and their acute and late toxicities on all patients (33 [100%] of 33 groups approved)

a Validated endometrial cancer-specific PRO measures should be used in endometrial cancer trials

(Continues on next page)

(Panel 3 continued from previous page)

- b Validated PRO measures specific to immunotherapy should be used to assess the impact of immunotherapy on patients
- c Longitudinal self-reported acute and late toxicity should be collected using PRO-CTCAE
- d Other novel PRO measures should be incorporated into endometrial clinical trials, such as measures of quality-adjusted survival depending on the agent being tested
- e Multiple ways to complete PRO measures should be made available to capture the experience of all patients
- f The optimal schedule of PRO assessments depends on the trial design and should be based on pre-specified hypothesis questions to test using PRO measures
- g The design, analysis, and reporting of PROs should follow international guidelines.The primary PROs should be reported in the primary publication or in a timely fashion

PRO=patient-reported outcome. CTCAE=Common Terminology Criteria for Adverse Events. *Disagreement regarding item c, the duration of 6 months. †Disagreement regarding item b, cutoff for oestrogen receptor and/or progesterone receptor expression.

well to certain targeted therapies and should not be excluded from clinical trials.

Adjuvant chemotherapy with platinum–paclitaxel combined with radiotherapy provides an overall survival benefit compared with radiotherapy alone for high-risk disease, at the increased risk of manageable toxicity. In the PORTEC-3 trial a 5-year overall survival benefit of 9% for stage III endometrial cancer and 13·5% for serous or p53-abnormal endometrial cancer was found.[37] Chemotherapy and radiotherapy were not associated with a longer relapse-free survival compared with chemotherapy alone in the GOG258 trial for stage III–IVA disease, but radiotherapy did reduce pelvic and para-aortic nodal recurrences.[38–40] Based on evidence of numerous well designed trials it is recommended that the standard group for clinical trials in this setting should include platinum–paclitaxel chemotherapy and radiotherapy (chemoradiation followed by chemotherapy or sequential chemotherapy and radiotherapy) or chemotherapy alone. No evidence exists regarding the optimum sequencing. A substantial proportion of patients in these studies received full pelvic with or without para-aortic lymphadenectomy, which might have contributed to nodal control, and this is not the modern standard of care. For patients with high-risk disease who have not undergone surgical lymph node staging, external beam radiotherapy should be included as standard of care to minimise nodal relapse risk. Due to the positive impact radiotherapy has on disease control, unbalanced delivery of radiotherapy between clinical trial groups should be avoided. Therefore, in a scenario where radiotherapy is not required as standard but is optional, it should be a stratification factor.

Treatment of advanced primary, metastatic, and recurrent endometrial cancer

Based on two randomised controlled trials[41,42] with first-line carboplatin–paclitaxel chemotherapy and an immune checkpoint inhibitor, combination chemotherapy with immune checkpoint inhibitor is recommended as standard first-line therapy for MMRd metastatic endometrial cancer, and should therefore be the control group of clinical trials in this setting (panel 3). The improvement in outcomes when adding an immune checkpoint inhibitor was smaller in the MMR-proficient cohort in both trials, hence the standard group for MMR-proficient cancers was recommended to be carboplatin–paclitaxel with or without an immune checkpoint inhibitor. There is a need to identify biomarkers for MMR-proficient subgroups who could benefit from immune checkpoint inhibitors. The findings from subgroup analysis of the RUBY trial[41] suggest that p53-mutant MMR-proficient tumours are the only type that benefit from immune checkpoint inhibitors.

For individuals with recurrent disease who received previous adjuvant chemotherapy with platinum–paclitaxel, the platinum-free interval should be more than 6 months to be rechallenged with platinum-based chemotherapy, based on a retrospective study[43] which reported a statistically significant overall survival benefit when second-line treatment with platinum was started 6 months or more since the last platinum treatment compared with an earlier start.

It is a priority to include patients with frailty or Eastern Cooperative Oncology Group performance status 2 in clinical trials. There is a need to develop a concise, validated, easy-to-use frailty index to ensure these patient groups are well defined and included. As race and ethnicity contribute to the prognosis of advanced endometrial cancer, these were recommended as stratification factors in future clinical trials. The primary endpoint for first-line trials is recommended to be progression-free survival, overall survival, or both given that effective second-line therapies are now available. If multiple primary endpoints are used, the type 1 error must be strongly controlled, and a statistician involved in trial design.

How to optimally select patients for first-line hormonal therapy trials requires further research. For hormonal therapy trials, a 10% or greater cutoff is recommended for oestrogen receptor or progesterone receptor expression, as this cutoff is based on most research in endometrial cancer.[44,45] Additionally, we suggest enrolling in each trial a separate small cohort of patients with tumours with 1% to 10% oestrogen receptor or progesterone receptor expression, to determine whether low expression results in treatment efficacy, and to assess the relationship between the level of oestrogen receptor

and progesterone receptor expression and the therapeutic effects. The exact expression level and intensity should be recorded for all patients, and stratification should be considered. Since oestrogen receptor and progesterone receptor expression in metastatic disease can be different from the primary tumour, retesting oestrogen receptor and progesterone receptor expression in a biopsy of metastatic disease is recommended whenever feasible.

The standard group in hormonal therapy trials will vary depending on the agents being tested. It is important to think of molecular cancer drivers in the development of endocrine therapies. The primary endpoint for first-line trials of hormonal therapy is recommended to be progression-free survival, as overall survival usually takes a long time to assess in oestrogen-receptor-positive and progesterone-receptor-positive disease.

Defining the optimal second-line systemic treatment is challenging given the rapid developments. For immune checkpoint inhibitor-naive patients, standard groups in trials should include an immune checkpoint inhibitor (alone or in combination) on the basis of previous randomised trials.[46–48] For patients previously treated with immune checkpoint inhibitors, the standard group might include platinum or non-platinum-based chemotherapy, depending on the platinum-free interval, or hormonal therapy. Further studies are needed to determine the optimal therapy for immune checkpoint inhibitor-treated patients.

Molecular classification is an important stratification factor,[30] along with other prognostic or predictive factors relevant to the treatment being studied. In trials involving targeted therapies, patient selection should be based on a relevant, validated biomarker assay. Targeting HER2 (also known as ERBB2) is promising, as 25–35% of p53-abnormal endometrial carcinomas overexpress HER2. However, no validation of the cutoff for endometrial cancer is yet available. For those with lower HER2 expression, antibody–drug conjugates are being explored based on promising data in breast cancer.

Assessment of PROs should have a more prominent role to assess the impact of therapies and their acute and late toxicities, and endometrial cancer trials should include validated PRO measures. EuroQol-5D (EQ-5D), EORTC QLQ-C30,[49] and its endometrial cancer module EN24,[50] are commonly used tools in the pivotal endometrial cancer trials, as well as the five-level version of EQ-5D (EQ-5D-5L) and the neurotoxicity subscale of Functional Assessment of Cancer Therapy/GOG (FACT/GOG-Ntx). To assess the impact of immunotherapy, validated PRO measures specific for immunotherapy should be used, such as the recently developed FACT-Immune Checkpoint Modulator.[51] Self-reported acute and late toxicities should be collected longitudinally using the Patient-Reported-Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).[52] Other novel PRO measures should be incorporated into endometrial cancer trials to assess quality-adjusted survival,[53] particularly if maintenance therapy is being tested.

PRO measures should be available in multiple languages, and be able to be completed using paper questionnaires as well as electronically. The schedule of PRO assessments should be based on prespecified hypotheses. The design of PRO assessment, analysis, and reporting should follow international guidelines. The primary PRO should be reported in the main publication or in a timely fashion.

Panel 4: Consensus statements on trial designs for rare endometrial cancer subgroups and special circumstances

Statement 10

Clinical trials should be inclusive of rare endometrial cancer subgroups, defined histologically and by molecular classification (33 [100%] of 33 groups approved)

- a Molecular classification can aid in clinical trial stratification, providing both prognostic and predictive information.
- b For endometrial cancer of no specific molecular profile, oestrogen receptor status and tumour grade provide prognostic stratification and should be included in future clinical trials.
- c Broad molecular testing in rare endometrial cancer can identify patients who have been proven to benefit from, or might benefit from targeted therapy strategies

Statement 11

Reference arms for trials in rare endometrial cancer should be molecularly-driven, as for other endometrial cancer, for both initial and recurrent disease management (33 [100%] of 33 groups approved)

- a In relapse after immunotherapy, options include chemotherapy and/or endocrine therapy according to patient factors and molecular subtype under investigation.
- b When there is no dedicated clinical trial, individuals with rare histological or molecular subgroups should be included in clinical trials with the appropriate molecular subtype stratification.

Statement 12

Hysterectomy is the standard treatment for early-stage disease. Uterine-sparing management can be an option for specific conditions and should be assessed in prospective studies for selected patients (33 [100%] of 33 groups approved)

- a Those desirous of uterus preservation for fertility.
- b Those who are not fit for hysterectomy.

Statement 13

Individuals with cancers involving the endometrium and ovary are most likely to have an endometrial primary cancer with spread to the ovary; FIGO2023 IA3 and IIIA1 (33 [100%] of 33 groups approved)

- a Those with FIGO stage IA3 have an excellent prognosis from retrospective analysis and should be considered for inclusion in future clinical trials to assess the value of treatment.
- b Those with FIGO stage IIIA1 have a worse prognosis and should be included in clinical trials for advanced stage.

Statement 14

Patients with an endometrial cancer which is FIGO2023 stage IA1 or IA2 (endometrioid type, grade 1 or 2, no or <50% myometrial invasion, no or focal LVSI and p53 wild type[19]), who have a second primary cancer, can be included in clinical trials appropriate for their second cancer (33 [100%] of 33 groups approved)

FIGO=The International Federation of Gynecology and Obstetrics. LVSI=lymphovascular space invasion.

Rare endometrial cancer subgroups and special circumstances

Endometrial cancer is defined as rare if it occurs with an incidence lower than 6/100 000 per year. Rarity can refer to either histological subgroups or to molecular alterations and includes carcinosarcomas, clear-cell carcinomas, oestrogen receptor-negative endometrial cancer of no specific molecular profile, and *POLE*-mutated tumours. Endometrial cancer with no specific molecular profile is a heterogeneous subgroup defined by default. Oestrogen receptor-negative tumours have an unfavourable prognosis. Beyond molecular classification, broad testing with immunohistochemistry or DNA and RNA sequencing can help to identify actionable alterations, including HER2 overexpression (or *ERBB2* amplification), activating mutations in *FGFR2*, *KRAS* (especially G12C), *PIK3CA*, *PIK3R1*, or *ARID1A;* amplification in *CCNE1;* or homologous recombination deficiency or genomic instability.[54] In relapse after PD-(L)1 inhibitor treatment, the reference group in trials should be chosen depending on the molecular subtype (panel 4): hormonal therapy is acceptable in low-grade tumours with high oestrogen receptor or progesterone receptor expression, whereas chemotherapy is more appropriate in high-grade p53-abnormal serous tumours. The design of trials in the post immunotherapy setting is challenging and necessitates a uniform definition of resistance to immunotherapy, as described by the Society for Immunotherapy of Cancer.[55] Hence, therapeutic options will be different in patients with primary and secondary rsistance to immunotherapy, and those who did not develop progressive disease during immune checkpoint inhibitor therapy.

Uterine-sparing strategies should be addressed in dedicated trials. This is of particular interest to young patients who want to maintain fertility, and seems especially relevant to those with MSI-high or mismatch repair-deficient and *POLE*-mutant cancers, where single agent immunotherapy can achieve complete pathological response.[56] Some patients are not fit for hysterectomy, either due to frailty or comorbidities (eg, recent pulmonary embolism or severe obesity) and could also benefit from trials investigating non-surgical options. Importantly, neoadjuvant trials could provide an opportunity to understand new therapies' mechanism of action, but require specific designs and biosample collection.[57]

Another circumstance to consider is the co-existence of endometrial and ovarian cancer. Immunohistochemistry for p53 (according to published recommendations for interpretation[19]), MMR proteins, oestrogen and progesterone receptors, and *POLE*-testing will assist with the diagnosis of metastatic spread from one primary cancer to another site versus two independent primary co-existent cancers. Molecular profiling has demonstrated that the overwhelming majority are clonally related and one is a metastasis from another.[58,59] Therefore, these tumours should no longer routinely be regarded as synchronous primaries.

Trial designs and specific methodology for rare and small subgroups and low-resource settings

Rare subgroups of endometrial cancer, defined histologically or by molecular alterations (eg, carcinosarcomas, or stage III *POLE*-mutated cancers), are

Panel 5: **Consensus statements on trial designs and specific methodology for rare and small subgroups and low-resource settings**

Statement 15

Clinical trial designs should be innovative to advance patient care, particularly in rare endometrial cancer patient cohorts (33 [100%] of 33 groups approved)

- a Rare cohorts must be defined in context of the clinical trial
  - These could include, but not be limited to, histological subtype, molecular classification, tumor biomarkers, and clinical scenarios
- b Clinical trials must be designed to evaluate relevant outcomes in rare cancer cohorts and molecular subgroups
- c All rare tumors should ideally have centralised pathology review
- d Single-arm trials might be appropriate

Statement 16

Clinical trials must be representative and inclusive of the diversity seen in the endometrial cancer population, including but not limited to geographical, ethnic, and racial diversity (33 [100%] of 33 groups approved)

- a Self-reported data on race and ethnicity should be reported in all clinical trials and results should be disaggregated with respect to the subcategories of race and ethnicity when feasible
- b Enrolment goals for appropriate representation of race and ethnicity should be defined a priori
- c Clinical trial design and implementation should avoid systemic barriers to inclusion.
- d Clinical trial design and implementation should reflect more inclusive criteria, through feasible schedule of assessments, novel trial designs, site selection, translated materials, community engagement, and support for social and cultural determinants of health factors to enable participation

Statement 17

Low-cost pragmatic trials are relevant to all resource settings, treatment modalities, and stages of the patient journey (33 [100%] of 33 groups approved)

- a Real-world data serve as complementary evidence to answer questions on the effectiveness, safety, impact on health-care resource utilisation, physician practice, and how the disease and treatment impacts on patients' quality of life
- b De-escalation clinical trials should specify the selected primary endpoint(s) based on quality of life, toxicity, efficacy, and/or cost
- c Pragmatic trials should allow patient-centred and stakeholder-centred endpoints

Statement 18

Clinical trial design must facilitate broad and rapid collaboration, with standardised diagnostic workup, common data-elements, and flexibility for local standards of care (33 [100%] of 33 groups approved)

- a International collaborations should advocate for harmonisation of approval regulations and indemnification of academic clinical trials
- b Allow for decentralisation of clinical trials, including those that reflect local standards of care.
- c There should be the possibility to share protocols and share or merge different databases, enabling regional differences to be allowed for in the trial protocols

frequently under-represented in randomised clinical trials.[60] They can require tailored designs and need to be recognised as priorities for clinical trials (panel 5). Furthermore, the potentially challenging histological and molecular features of rare tumours require expert confirmation of the diagnosis of these tumours,[61] and so it is crucial that all rare tumour studies incorporate centralised expert pathology review.

Rare tumours and molecular subgroups lend themselves to novel and innovative clinical trial designs, as a phase 3 randomised trial design in these cohorts could be hampered by numbers required for randomised trials with survival endpoints, and by the potential absence of a defined standard of care group.[62] These trials need clinically relevant inclusion criteria and endpoints, with pragmatic trial designs such as adaptive, basket, or umbrella designs, and use of Bayesian analyses to reduce uncertainty around the magnitude of treatment effects in rare cohorts.[62]

Defined enrolment goals of all included populations and cohorts should be documented a priori with justification of feasibility. The trial site selection process must allow for diverse inclusion, and the ongoing monitoring of predefined enrolment goals should form a transparent part of all trials.[63] People from racial and ethnic minority groups are under-represented in clinical trials, including early phase 1 trials, and have a greater burden of mortality with the same tumours. Addressing systemic barriers and considering the social and cultural determinants of health is crucial in achieving inclusivity by ensuring that inclusion criteria encompass and report self-reported race and ethnicity data.[64] Additionally, equity based on gender identity, in all its forms, must be a focus of inclusivity in clinical trials, along with lifestyle, BMI, and age.[65] Health equity in endometrial cancer clinical trials cannot exist without universal and equitable access to biomarkers and molecular testing.[66] Principal investigators, GCIG and other representative groups, and pharmaceutical companies involved in endometrial cancer research must continue to advocate for this.

Although the incidence of endometrial cancer is increasing in developing countries, the burden of mortality compared with incidence is greatest in LMICs.[67] Pragmatic trial design is needed to allow broad participation, and allow the evaluation of effectiveness of interventions in real-life settings. Pragmatic trials with locally relevant standards of care are even more essential in LMIC settings. Appropriate investigation of therapeutic de-escalation, such as necessity for adjuvant therapy for *POLE*-mutated tumours,[68] and selection of meaningful endpoints in these populations such as PROs or quality of life outcomes[69] are relevant approaches that promote patient-centred clinical trials. There should also be a provision added for sharing and combining protocols, facilitating the incorporation of regional variations. Clinical trial designs including rare tumour cohorts benefit from international decentralised research and cross-regional collaboration, which must particularly prioritise and commit to research advancement in LMICs, thereby facilitating broad collaboration.[70]

***Panel 6*: Unmet needs and unanswered questions needing further study**

- Pathology
  - Definition of oestrogen receptor and progesterone receptor positivity and how to best assess oestrogen receptor and progesterone receptor status
  - Definition of methodology of ultrastaging
  - Method of defining LVSI-WHO criteria and methodology
  - Method of defining of HER2 positivity
  - Role of digital pathology
- Studies on screening, risk reduction, and early detection are needed
- Surgery and initial management
  - Role of surgical staging in the molecular era
  - Role of surgery in the management of (oligo)metastatic or recurrent disease
  - Neoadjuvant therapy is an important strategy to investigate in advanced stage disease
- Radiotherapy
  - Role of radiotherapy according to molecular subtypes
  - Role of radiotherapy in the treatment of oligometastatic disease
- Second-line therapies
  - More research is needed to determine the best subsequent therapy for patients treated first-line with immunotherapy
  - The duration of immune checkpoint inhibitor treatment should be investigated in future trials, and long-term outcome data on toxicity, morbidity, and quality of life with immune checkpoint inhibitors are needed
- Molecular classification and biomarkers
  - Pre-operative risk stratification according to molecular biomarkers
  - Molecular classification and biomarkers to appropriately test strategies for uterine sparing management
  - Role of circulating tumour-DNA (ctDNA) as a predictive or prognostic biomarker in high-risk optimally resected disease
  - The development of molecularly or biomarker-driven clinical trials in all endometrial cancers, including rare sub-types, along with the longitudinal collection of biological samples
- Quality of life
  - Better instruments to capture quality of life and specific aspects of quality of life should be developed with involvement of patient advocates and those with lived experience
  - Instruments should better capture the burden of treatment, to help future patients weigh the benefit of treatment (survival) against the harm (impact of adverse events and treatment burden on ability to live a meaningful life)
  - A symptom–benefit questionnaire for endometrial cancer and more endometrial cancer-specific PRO measures should be developed
- Frailty—priorities are:
  - To broaden clinical trial participation to include people who are frail or have WHO/ECOG performance status 2
  - To determine a pragmatic tool to assess frailty
  - To develop clinical trials on different treatment modalities, prehabilitation, and supportive care specifically dedicated to frail patients, with quality of life assessment and patient reported outcomes as predefined or primary endpoints
  - To determine best treatment for frail individuals with metastatic disease

ECOG=Eastern Cooperative Oncology Group. LVSI=lymphovascular space invasion. PRO=patient-reported outcome.

Search strategy and selection criteria

Primary references for the development of consensus statements were identified within the topic group discussions and presentations, with a focus on most recent developments, and selected by topic group presenters and discussants. All references were disclosed and reviewed during the consensus conference, with active moderation by the topic group co-chairs. PubMed searches were conducted using the terms "endometrial", "uterine", "cancer", "neoplasms", and "studies" for articles published from Jan 1, 2020, to Oct 1, 2023, to ensure consideration of all relevant new studies. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the consensus statements.

Conclusion

Extensive molecular characterisation of endometrial cancer has profoundly changed the landscape of endometrial cancer diagnosis, prognosis, translational research, treatment schedules, agents for targeted treatments, and clinical trials. New molecular characteristics have continued to emerge and have been used in first clinical studies. The emergence of evidence of effective new agents for each molecular group and specific subgroups of endometrial cancer have accelerated substantially over the past decade, prompting the GCIG Endometrial Cancer Committee to plan updates of the statements annually during the GCIG meetings. Patient advocates and people with lived experience of endometrial cancer should be key partners in designing clinical trials and in the development and validation of PROs and reliable frailty scoring tools, to ensure wider availability of trials across global regions, broader applicability to diverse racial and ethnic groups, health settings, and sociocultural regions to attain real world inclusion and applicability of results. Implementation of the principles and research guidelines summarised within these consensus statements will help to improve clinical trial design to address the unmet needs (panel 6) of people with endometrial cancer worldwide.

Contributors

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