Gynaecological Cancer Research Review™

Making Education Easy

Issue 16 - 2024

In this issue:

Abbreviations used in this issue:

EC = endometrial cancer; **ICI** = immune checkpoint inhibitor; **ORR** = overall response rate; **OS** = overall survival; **TRAE** = treatment-related adverse event.

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Welcome to issue 16 of Gynaecological Cancer Research Review.

We open this month's issue with a *Nat Med study* on nivolumab for dMMR or hypermutated gynecologic cancers. This phase 2 trial included biomarker analysis of nivolumab in 35 patients with dMMR uterine or ovarian cancers. This was followed by a study on the detection of endometrial cancer in cervico-vaginal fluid and blood plasma. We also include a dual analysis of HPV vaccination on lifetime projections of cervical cancer and the effect of the HPV vaccination programme on the incidence of cervical cancer in England. These two studies focus on three key pillars: vaccination, screening, and the treatment of pre-cancer and advanced diseases. Finally, we conclude this month's issue with a long-term follow-up of the efficacy and safety of selinexor maintenance treatment in advanced or recurrent *TP53*wt endometrial cancer.

We hope that you enjoy this month's issue, and we look forward to receiving your feedback.

Kind Regards,

Dr Geraldine Goss
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Nivolumab for mismatch-repair-deficient or hypermutated gynecologic cancers

Authors: Friedman CF et al.

Summary: This study evaluated nivolumab, a PD-1 inhibitor, in 35 patients with dMMR uterine or ovarian cancers. The primary endpoints, objective response rate (ORR) and progression-free survival at 24 weeks (PFS24) were met with an ORR of 58.8% and a PFS24 rate of 64.7%. The disease control rate (DCR) was 73.5%, and the median overall survival (OS) was not reached, with a one-year OS rate of 79%. Treatment-related adverse events (TRAEs) were common, affecting 91% of patients, with 29% experiencing grade 3 or 4 TRAEs. No grade 5 events occurred. Exploratory analyses indicated that dysfunctional T cells and certain somatic mutations (MEGF8 or SETD1B) were associated with PFS24.

Comment: Trials of different immune checkpoint inhibitors (ICIs) have shown consistent response rates in dMMR endometrial cancer, and dMMR/MSI-H is an effective biomarker for PD-1 blockade, more so than PD-L1 expression. Significantly, durable responses and even some cures are seen in this population. Although this trial included uterine carcinosarcoma and ovarian endometroid or clear cell carcinomas in addition to endometroid endometrial cancer, the ORR here is similar to previously reported in EC: this suggests that dMMR/MSI-H is a broad predictor of response despite histology or organ of origin. Although a small study, the identification of further somatic mutations and tumour microenvironment parameters highlights further the importance of translational research in influencing optimal treatment selections. The next advance is the identification of treatment for those who do not respond to ICI.

Reference: Nat Med. 2024;30:1330-8
Abstract

Gynaecological Cancer Research Review™

Independent commentary by Dr Geraldine Goss

Dr Geraldine Goss a medical oncologist at Eastern Health and Epworth Healthcare in Melbourne is a specialist in treating and caring for women with breast and gynaecological cancers. After completing her postgraduate training in medical oncology, she undertook laboratory-based research as a Breast Cancer Fellow. She completed her MD thesis then travelled to Boston, USA, completing fellowships at St Elizabeth's Medical Centre and the Dana Farber Cancer Institute. Here she developed her interest in gynaecological cancers. She holds a master's degree in Women's Health from the University of Melbourne, and more recently undertook a graduate diploma in Health and Medical Law, with a focus on Ethics and Human Rights Law. She maintains an interest in clinical research and is the Secretary of the Ovarian Cancer Research Foundation.

Detection of endometrial cancer in cervico-vaginal fluid and blood plasma

Authors: Njoku K et al.

Summary: This study compared blood plasma and cervicovaginal fluid samples from symptomatic post-menopausal women with and without endometrial cancer to identify diagnostic protein biomarkers. Using SWATH-MS and machine learning, researchers found that cervicovaginal fluid was a better discriminator of cancer presence than plasma. A five-biomarker panel from cervicovaginal fluid (HPT, LG3BP, FGA, LY6D, and IGHM) achieved an AUC of 0.95, with 91% sensitivity and 86% specificity. In contrast, a three-marker plasma protein panel (APOD, PSMA7, and HPT) had an AUC of 0.87, with 75% sensitivity and 84% specificity. For detecting stage I endometrial cancer, the cervicovaginal fluid model had an AUC of 0.92, while the plasma model had an AUC of 0.88.

Comment: Currently, there is no consensus on the early detection strategies for endometrial cancer (EC), and diagnostic practices such as transvaginal ultrasound, hysteroscopy, and endometrial biopsy are invasive, costly and low in specificity. However, it is unlikely that a single biomarker will serve as an accurate screening or diagnostic test for EC. Notably, this study utilises machine learning to generate optimal proteomic signatures. A diagnostic test is applied to symptomatic women and requires a high specificity to avoid false positive results. This differs from a screening test, which is applied to asymptomatic women and requires a high sensitivity to avoid false negative tests. In this diagnostic setting, the three marker plasma panel was not sufficiently sensitive or specific, and, although more accurate, the five marker C-V fluid panel would still likely yield high numbers of false positive results. The search for a minimally invasive but maximally accurate detection test is ongoing.

Reference: EBioMedicine. 2024;102:105064
Abstract

Equity impact of HPV vaccination on lifetime projections of cervical cancer burden among cohorts in 84 countries by global, regional, and income levels, 2010–22

Authors: Abbas K et al.

Summary: This study analysed the equity impact of HPV vaccination on cervical cancer burden among cohorts vaccinated from 2010 to 2022 in 84 countries. Using WHO and UNICEF immunisation data and the PRIME model, researchers estimated the lifetime health impact of HPV vaccination in terms of deaths, cases, and disability-adjusted life years (DALYs) averted. The results showed substantial variation in health impact, ranging from 2 to 34 deaths, 4 to 47 cases, and 40 to 735 DALYs averted per 1000 vaccinated girls. The concentration index of 0.33 indicated significant inequities in HPV vaccine coverage, with higher cervical cancer burden countries having lower vaccination rates. Inequities were noted across regions and income levels, favouring countries with lower vaccine impact, suggesting a need for improved equity in HPV vaccination efforts.

Reference: EClinicalMedicine. 2024;70:102524
Abstract

Effect of the HPV vaccination programme on incidence of cervical cancer and grade 3 cervical intraepithelial neoplasia by socioeconomic deprivation in England

Authors: Falcaro M et al.

Summary: This study analysed the impact of HPV vaccination on cervical cancer and CIN3 incidence among women aged 20-64 in England between January 2006 and June 2020. HPV vaccination was introduced nationally in 2008 for girls aged 12-13, with catch-up campaigns for older teenagers. The study found that among women routinely vaccinated at ages 12-13, the incidence of cervical cancer and CIN3 dropped by 83.9% and 94.3%, respectively, compared to unvaccinated women. By mid-2020, the vaccination prevented an estimated 687 cervical cancers and 23,192 CIN3 cases. While the highest rates remained in the most deprived areas, significant reductions were observed across all deprivation levels. Women who were offered catch-up vaccination showed more significant decreases in CIN3 rates in less deprived areas. The strong correlation between higher cervical cancer incidence and higher deprivation seen in unvaccinated groups disappeared among vaccinated women, indicating the vaccine's substantial impact across different socioeconomic groups.

Reference: BMJ. 2024;385:e077341
Abstract

Comment: Cervical cancer is both preventable and curable in its early stages, yet few diseases reflect global inequities in healthcare more. It remains the 4th most common cancer among women worldwide, which is truly shameful. In addition, in 2018, nearly 90% of the deaths occurred in low- and middle-income countries. Both of these studies confirm the efficacy of HPV vaccination in reducing CIN3 and cervical cancer: the first in a broad range of high- and low-income countries, while the second looked at different levels of socioeconomic deprivation in a single country. Worse outcomes among lower socioeconomic groups may reflect poor implementation of vaccination and screening programs, poor health literacy and poor access to medical care. However, improved outcomes resulting from vaccination are seen across all groups. In August 2020, the World Health Assembly adopted the Global Strategy for cervical cancer elimination, requiring all countries to reach and maintain an incidence rate of below 4 per 100,000 women. The strategy is focussed on the three key pillars of vaccination (goal of 90% by age 15), screening (goal of 70% by age 35 and again at age 45) and treatment of pre-cancer and advanced disease (goal of treating 90% of women in each group).

Prognostic impact and causality of age on oncological outcomes in women with endometrial cancer

Authors: Wakkerman FC et al.

Summary: This study used data from 1801 women in the PORTEC-1, PORTEC-2, and PORTEC-3 trials to analyse the impact of age on endometrial cancer outcomes. The cohort included patients with intermediate, high-intermediate, and high-risk endometrial cancer. With median follow-ups of 12.3, 10.5, and 6.1 years for the respective trials, findings showed that both overall recurrence and endometrial cancer-specific death significantly increased with age. Older women also exhibited higher frequencies of deep myometrial invasion, serous tumour histology, and p53-abnormal tumours. Age was found to be an independent risk factor for overall recurrence (HR 1.02 per year) and endometrial cancer-specific death (HR 1.03 per year) and was identified as a significant causal variable in prognosis.

Comment: EC typically affects postmenopausal women, with a mean age at diagnosis of 65 years, although the incidence in young women is rising. Worse oncologic outcomes in older women (typically defined as 75-80) may relate to comorbidities and a lower performance status, which may increase surgical risk. Age and health status may influence management, including the extent of surgical staging and adjuvant treatment, which may result in undertreatment. This study was comprised of clinical trial participants who were likely to have relatively good performance status. Independent of these considerations are pathologic features of cancer: previous studies report that among older women, there are higher rates of deep myometrial invasion, lymphovascular involvement, serous tumour histology, and p53-abnormal tumours. However, age alone is not universally identified to be a specific independent predictor of recurrence or disease-specific survival. Thus, age alone should not be the sole decision factor in prescribing treatment for older women with EC: arguably, this study supports the notion of a person-centred model of care that places emphasis on the patient as a whole rather than a purely biomedical approach.

Reference: Lancet Oncol. 2024;25:779-89
Abstract

Primary results and characterisation of patients with exceptional outcomes in a phase 1b study combining PARP and MEK inhibition, with or without anti–PD-L1, for *BRCA* wild-type, platinum-sensitive, recurrent ovarian cancer

Authors: Mutch D et al.

Summary: This phase 1b study evaluated the combination of PARP and MEK inhibitors, with or without PD-L1 inhibition, for BRCA wild-type, platinum-sensitive, recurrent ovarian cancer (PSROC). Patients were treated with cobimetinib and niraparib, with or without atezolizumab. The ORR was 35% with the doublet regimen and 27% with the triplet regimen, with median progression-free survival of 6.0 and 7.4 months, respectively. Post-hoc analyses revealed better ORR and PFS in homologous recombination-deficiency-signature (HRDsig)-positive subgroups. Tolerability matched the known profiles of the individual agents. NF1 and MKNK1 mutations correlated with sustained benefit from the respective regimens. Overall, the chemotherapy-free doublet and triplet therapies showed promising activity in patients with BRCA wild-type PSROC, especially in HRDsig-positive or NF1/MKNK1 mutation cases.

Comment: Phase 3 results for PD-L1 inhibitors and chemotherapy (with or without bevacizumab) for ovarian cancer have been disappointing. PARP inhibitors are active where defects in the homologous DNA recombination (HRD) system are present, irrespective of BRCA status. The postulated synergy between PARPis and ICIs led to a phase 3 evaluation in ovarian cancer. In contrast, early trials of MEK inhibitors (MEKis) blocking the mitogen-activated protein kinase (MAPK) pathway previously focused on low-grade serous ovarian tumours. In preclinical studies, PARPi and MEKi combinations demonstrated synergy *in vitro* and *in vivo* in *RAS*-mutant tumour models, independent of BRCA mutation status. While safety was the primary objective in this study, the response rate was robust. Unsurprisingly, efficacy was better in the positive group, but the association of NF1 or *MKNK1* mutations with sustained benefit is intriguing.

Reference: Cancer. 2024;130:1940-51
Abstract

Diagnosing and staging epithelial ovarian cancer by serum glycoproteomic profiling

Authors: Dhar C et al.

Summary: This study explored the use of glycoproteomic for diagnosing and staging epithelial ovarian cancer. Researchers analysed serum from individuals with EOC, benign pelvic masses, and healthy controls, quantifying 653 analytes. A biomarker panel was identified, distinguishing benign lesions from epithelial ovarian cancer with 83.5% sensitivity and 90.1% specificity in the training set and 86.7% sensitivity and specificity in the test set. ROC analysis confirmed the strong performance of this panel. Higher levels of fucosylated multi-antennary glycopeptide markers were found in late-stage compared to early-stage epithelial ovarian cancer, a pattern also seen in tissue samples. These findings suggest that blood glycopeptide biomarkers could effectively differentiate between benign and malignant pelvic masses and distinguish early- from late-stage epithelial ovarian cancer, warranting further clinical evaluation.

Comment: Early detection of ovarian cancer remains an elusive goal, and it is unlikely that a single biomarker will fulfil this goal. To achieve a positive predictive value of 10% in the general population, a given test must exhibit a sensitivity of at least 75% and a specificity greater than 99.7%. A positive predictive value of 10% still means nine false positive results and potentially invasive follow-up tests per one case of ovarian cancer identified. This study utilises a diagnostic test (not a screening test) done in women with a pelvic mass. In this setting, a biomarker test must outperform the ROCA: a triage goal would involve referral to a gynecologic oncologist. In the presence of a pelvic mass, it is unlikely that serum biomarkers alone will identify women for whom surgery would be avoided altogether.

Reference: Br J Cancer. 2024;130:1716-24
Abstract

DEAR model in overweight endometrial cancer patients undergoing fertility-sparing treatment

Authors: Chen Y et al.

Summary: This study evaluated the DEAR weight management program for overweight patients undergoing fertility-sparing treatment for endometrial cancer or atypical hyperplasia. Seventy-two women with a BMI over 25 kg/m² were randomly assigned to either the DEAR program or a self-management control group. Body morphology, composition, glycolipid metabolism, and tumour outcomes were measured before and after 3 and 6 months. The DEAR group showed significant reductions in median body weight (69.45 vs. 78.05), BMI (26.19 vs. 29.15), lipid accumulation index (29.21 vs. 57.86), body fat mass (24.00 vs. 29.30), visceral fat area (112.5 vs. 133.3), and glycolipid metabolic indices compared to the control group (all $P < 0.05$). Additionally, the DEAR group achieved a higher complete remission rate (88.46% vs. 57.14%, $P < 0.05$), though the time to complete remission did not differ significantly between groups. These results suggest that DEAR weight management effectively improves metabolic health and remission rates in this population.

Comment: Rising obesity rates are associated with increases in both incidence and mortality from gynecologic malignancies, although data are lacking regarding the effect of weight loss on prognosis. Up to 90% of women with type 1 endometrial cancer are overweight or obese. The relative risk of death is higher for women with a BMI of 35–39 and even higher if BMI is > 40 in cohorts with both early and advanced-stage disease. Group and monitored interventions are universally more successful than individual attempts at weight management, but the optimal method for sustained weight loss is not defined. Evidence suggests that weight management and physical activity improve overall health and well-being. If lifestyle factors could be confirmed as important in cancer prognosis, they may provide additional options for cancer survivors to maximise health and well-being as well as cancer-specific outcomes.

Reference: Gynecol Oncol. 2024;148-55
Abstract

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Phase 1b study of mirvetuximab soravtansine, a folate receptor alpha (FRα)–targeting antibody-drug conjugate, in combination with carboplatin and bevacizumab in patients with platinum-sensitive ovarian cancer

Authors: Richardson DL et al.

Summary: This study assessed the efficacy and safety of a triplet regimen combining mirvetuximab soravtansine, carboplatin, and bevacizumab in patients with recurrent, platinum-sensitive ovarian cancer. Forty-one participants received the combination therapy, with a median of 6 cycles of carboplatin, 12 cycles of MIRV, and 13 cycles of bevacizumab. The regimen achieved a confirmed objective response rate of 83%, including nine complete and 25 partial responses. The median duration of response was 10.9 months, and the median progression-free survival was 13.5 months. Common adverse events included diarrhoea (83%), nausea (76%), fatigue (73%), thrombocytopenia (71%), and blurred vision (68%), mostly mild to moderate. Thrombocytopenia was the main reason for dose modifications. Overall, the triplet therapy demonstrated high activity and a manageable safety profile compared to historical regimens.

Comment: The frequent overexpression of surface protein folate receptor α (FRα), encoded by the FOLR1 gene in ovarian cancer, has made the α (FRα) an attractive therapeutic target. Notably, FRα is normally expressed in the fallopian tube but not the ovary, consistent with the notion that EOC originates from the fallopian tube fimbriae rather than from the ovary. One therapeutic approach is based on monoclonal antibodies that target the FRα protein, such as farletuzumab; however, in clinical trials, the addition of farletuzumab to chemotherapy did not improve PFS in women with recurrent ovarian cancer. A second approach is to use antibody-drug conjugates, where a drug payload is delivered by targeting antigen-expressing tumour cells. Mirvetuximab soravtansine comprises a humanised anti-folate receptor alpha (FRα) monoclonal antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent. This study was primarily a feasibility study, and this ADC will certainly be developed further.

Reference:
Abstract

Long-term follow-up of efficacy and safety of selinexor maintenance treatment in patients with TP53wt advanced or recurrent endometrial cancer

Authors: Makker V et al.

Summary: This study reports on the long-term efficacy and safety of selinexor maintenance therapy in adults with TP53 wild-type (TP53wt) stage IV or recurrent EC who achieved partial or complete remission after chemotherapy. Analysing data from the phase 3 SIENDO study, researchers found that median progression-free survival for TP53wt patients receiving selinexor was 28.4 months, compared to 5.2 months for placebo (HR 0.44). The benefit was observed regardless of mismatch repair status, with median progression-free survival for TP53wt/pMMR EC at 39.5 months versus 4.9 months and TP53wt/dMMR EC at 13.1 months versus 3.7 months. Selinexor was generally manageable, with no new safety concerns. These findings suggest that selinexor offers promising efficacy and manageable safety for TP53wt EC patients' post-chemotherapy, warranting further evaluation in ongoing trials.

Comment: Selinexor is a selective inhibitor of nuclear transport (SINE) compound, blocking exportin-1 mediated protein transport from the cell nucleus to cytoplasm. It is approved for the treatment of multiple myeloma. In this study, the improvement in progression-free survival among the cohort of women with wtp53/pMMR was outstanding, although the small number of women in this subgroup (n=70) is insufficiently powered for firm conclusions. However, this cohort has limited therapeutic options. Of concern is the very high number of adverse events in an essentially palliative situation. However, there were 'no new safety signals', half of the patients required a dose reduction or interruption, and 10.5% discontinued therapy. The incidence of nausea (83%) and vomiting (51%) was high. No improvement in progression-free survival was seen in serous histology. This drug is being further evaluated in larger trials to define its role further, especially in wtp53 endometrial cancer.

Reference: Gynecol Oncol. 2024;185:202-11
Abstract

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