Gynaecological Cancer Research Review™

Making Education Easy

Issue 13 - 2023

In this issue:

- Dostarlimab for primary advanced endometrial cancer
- Pembrolizumab + chemotherapy endometrial cancer
- Cost-effectiveness of AI cytology screening
- Patient prognosis with SCC of the cervix
- Adjuvant chemotherapy as primary treatment for cervical cancer
- Lenvatinib + pembrolizumab for endometrial cancer
- Trastuzumab deruxtecan for HER2 uterine carcinosarcoma
- Paclitaxel and carboplatin use for persistent cervical carcinoma
- BMI change on recurrence risk in endometrial cancer
- Eribulin monotherapy in advanced cervical cancer

Abbreviations used in this issue:

AI = artificial intelligence; **HPV** = human papillomavirus; **dMMR** = defective DNA mismatch repair; **HER2** = human epidermal growth factor receptor-2; **HPV** = human papillomavirus; **IO** = immunotherapy; **MSI-H** = microsatellite instability-high; **SCC** = small cell carcinoma; **SOC** = standard-of-care; **ORR** = overall response rate; **PFS** = progression-free survival; **pMMR** = proficient mismatch repair gene expression.

RACP MyCPD participants can claim **the time spent reading and evaluating research reviews** as CPD in the online **MyCPD program**.

Please contact MyCPD@racp.edu.au for any assistance.

Welcome to this issue of Gynaecological Cancer Research Review.

We open this issue with a phase 3 global, double-blind, randomised, placebo-controlled trial from the NEMJ on patients treated with dostarlimab for advanced stage III or IV recurrent endometrial cancer. Another study included in this issue on advanced endometrial cancer uses pembrolizumab plus chemotherapy for stage IVB disease. A Lancet study proposes whether artificial intelligence (AI) assisted cytology testing is cost-effective in China. An interesting analysis from the BMJ used paclitaxel and carboplatin with or without bevacizumab for cervical carcinoma. We conclude this issue with a two-staged phase II clinical trial of Eribulin monotherapy for advanced or recurrent cervical cancer.

We hope that you enjoy this month's issue of Gynaecological Research Review and look forward to hearing your feedback.

Kind Regards,

Dr Geraldine Goss
geraldine.goss@researchreview.com.au

Dostarlimab for primary advanced or recurrent endometrial cancer

Authors: Mirza MR et al.

Summary: This phase 3, global, double-blind, randomised, placebo-controlled trial included 494 patients who underwent radiation for advanced stage III or IV endometrial cancer. The study found that in those in the dMMR-MSI-H population, progression-free survival (PFS) at 24 months was 61.4% in the dostarlimab group and 15.7% in the placebo group. In the overall population, the PFS was 36.1% in the dostarlimab group and 18.1% in the placebo. The most frequent adverse events (AE) were nausea, alopecia, and fatigue. The researchers found more frequent and serious AEs in the dostarlimab group than in the placebo group. The study concluded a significant increase in PFS for those with primary advanced or recurrent endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel compared to placebo.

Comment: Chemotherapy remains the standard treatment for stage IV endometrial cancer, however, results are emerging from multiple studies which have examined the addition of immunotherapy (IO), avelumab (MITO-END-3), pembrolizumab (GY018 trial), dostarlimab (RUBY), durvalumab (DUO-E), and atezolizumab (AtTEnd). In addition, phase II data has demonstrated robust response rates and disease control of dMMR disease. While this has become standard-of-care (SOC) in many parts of the world, it remains an issue of inequity that IO is not available to this cohort of women in Australia. Although a minority of women in this study had dMMR disease, the benefit in this subgroup was substantial and consistent with previously published data. While the overall response rate (ORR) was not greatly improved with dostarlimab versus chemotherapy alone, the duration of response was notably prolonged, and the median was not reached for the dMMR/MSI-H subset. The trend to overall survival improvement in the total population suggests that the benefit in pMMR disease is much smaller. Careful patient selection will properly illustrate the benefit of IO as a single agent or with chemotherapy and spare undue toxicity to those unlikely to respond.

Reference: N Engl J Med. 2023;388:2145-58

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.

Pembrolizumab plus chemotherapy in advanced endometrial cancer

Authors: Eskander RN et al.

Summary: This double-blind, placebo-controlled, randomised phase 3 trial included 816 patients with measurable disease or stage IVB recurrent endometrial cancer. In the 12-month analysis, the PFS was 74% for the treatment group and 38% for the placebo group in the dMMR cohort. In the pMMR cohort, the median PFS was 13.1 months for pembrolizumab and 8.7 months with placebo. The researchers found that the AEs were as expected for the pembrolizumab and combination chemotherapy. The study concluded that for patients with advanced or recurrent endometrial cancer, the additional use of pembrolizumab to standard therapy had a significantly longer PFS than standard therapy alone.

Comment: Similarly to the RUBY trial, a minority of women (30% had dMMR disease). Among this group, 74% of women treated with pembrolizumab remained disease free at 12 months compared with 38% of those receiving the placebo group: for those with the pMMR disease group, PFS at 12 months was 50% (pembro) and 30% (placebo). A consistent benefit for pembrolizumab in combination with chemotherapy was observed despite prior treatment or histology. Thus, unlike phase II studies, this trial suggested a benefit for pembrolizumab in pMMR disease. Given the substantial toxicity of lenvatinib, this raises the possibility that a trial of IO may be an alternative to combination therapy in pMMR disease. In both the RUBY and NRG-GY018 trials, most toxicity was attributable to chemotherapy, with no unexpected toxicity from combination therapy. Further trials will inform the optimal sequencing of chemotherapy and immunotherapy and address the role of immunotherapy alone as first-line treatment.

Reference: N Engl J Med. 2023;388:2159-70
Abstract

Cost-effectiveness of artificial intelligence-assisted liquid-based cytology testing for cervical cancer screening in China

Authors: Shen M et al.

Summary: This study included a cohort of 100,000 women aged over 30 years. Using a Markov model, the researchers were able to simulate the natural history of cervical cancer progression. Compared to no screening, all 18 screening strategies were cost-effective. For human papillomavirus (HPV) testing, screening every five years using the AI-assisted liquid-based cytology was the most cost-effective strategy compared to lower—cost, non-dominated strategies. AI-assisted liquid-based cytology testing, once every three years, was found to reduce cost by ≥10%.

Comment: Cervical cancer is both preventable and curable in its early stages, yet it remains the 4th most common cancer among women worldwide. Most cases of cervical cancer are associated with HPV. The World Health Assembly Global Strategy for cervical cancer elimination includes the pillars of vaccination against HPV and screening, yet a major key to success will be cost-effectiveness. AI models are rapidly becoming part of everyday working life, and this intriguing study offers AI-assisted liquid-based cytology as a cost-effective screening strategy. Such initiatives will hopefully pave a pathway forward to cost-effective disease prevention. It will be fascinating to observe the integration of AI into medical algorithms.

Reference: Lancet Reg Health West Pac. 2023;34:100726
Abstract

The prognosis of patients with small cell carcinoma of the cervix

Authors: Chu T et al.

Summary: This retrospective study of the SEER database included a Chinese multicentre registry of 1288 participants; 610 in the SEER cohort and 678 in the Chinese cohort. The study conducted a univariable and multivariable Cox regression analysis which showed that surgery was the better option for prognosis. The further subgroup analyses showed that surgery remained a protective factor for patients with locally advanced disease. In the SEER cohort, the protective effects of surgery was observed in those with locally advanced disease, compared to the Chinese registry, where surgery was associated with better outcomes. The researchers concluded that, although recommended non-surgical methods remain a first-line treatment, patients may benefit from early surgeries.

Comment: Patients with small cell neuroendocrine cervical cancer have a poor prognosis, with frequent nodal and haematogenous spread. In all stages of the disease, the outcome is worse than seen with squamous histology. Optimal management of early-stage disease is unclear, and prospective studies are difficult given the rarity of the disease. This retrospective study suggests that surgery may be associated with better survival, however, it is difficult to exclude selection bias, and the rationale for surgery is not defined. Given the propensity for early dissemination, primary chemotherapy/radiotherapy should likely remain the first-line treatment of choice. Comprehensive staging, including PET scanning, will assist in optimal decision-making, and the additional value of surgery should be considered in individual cases.

Reference: Lancet Oncol. 2023;24:701-8
Abstract

Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK)

Authors: Mileshkin LR et al.

Summary: This international, open-label, randomised phase 3 trial included 157 hospitals in Australia, China, Canada, New Zealand, Saudi Arabia, Singapore, and the USA. This OUTBACK trial included 926 patients randomly assigned to chemoradiotherapy or adjuvant chemotherapy. The median follow-up of these groups was 60 months, and the overall survival was 72% in the adjuvant and 71% in the chemoradiation therapy group. Of those in the safety population, the most common AEs grade 3-4 were neutrophils and anaemia. Serious AEs occurred in 107 patients in the adjuvant chemotherapy group and 98 in the chemoradiation group, the most common due to infectious complications. The study had no treatment-related deaths.

Comment: The improvement in cure rates for common cancers such as breast or colon cancer by eradicating micro-metastatic disease has led to applying the same principles to fewer common cancers. However, in addition to maximising cure rates, it remains equally important to spare patients from unnecessary toxicity without gain. Only rigorously conducted clinical trials can answer this question in individual cancer types. In this way, the OUTBACK study illustrates the importance of negative as well as positive trials. OUTBACK provides clear evidence that adjuvant chemotherapy does not extend survival over standard chemo-radiotherapy, and although negative, the trial is practice-changing.

Reference: Lancet Oncol. 2023;24:468-82
Abstract

Lenvatinib plus pembrolizumab in previously treated advanced endometrial cancer

Authors: Makker V et al.

Summary: This update to the safety and efficacy randomised study 209/KEYNOTE-755 reported on the final analysis of overall survival and PFS. This study is the final prespecified analysis of overall survival, PFS, and ORR. This study included 827 patients with advanced, recurrent or metastatic endometrial cancer. The study found that lenvatinib plus pembrolizumab showed benefits in overall survival, PFS, and ORR, versus chemotherapy. This combination was favoured in all subgroups and showed improved efficacy compared to chemotherapy and manageable safety in patients with previously treated endometrial cancer.

Comment: Treatment of advanced cancer is palliative, and quality-of-life must be assessed with efficacy assessments. In the phase Ib/II study of lenvatinib and pembrolizumab, nearly 100% of women experienced an AE, with majority requiring dose reduction or interruption of lenvatinib. In KEYNOTE 775, all patients experienced at least one AE related to therapy; 66.5% required a dose reduction after AEs, 33.0% discontinued the treatment, and 69.2% had a transient interruption to manage toxicities. Grade ≥ 3 treatment-emergent AEs occurred in 90.1% of patients receiving lenvatinib plus pembrolizumab, with grade 5 treatment-emergent AEs in 6.4%. The median dose delivered was 14mg, suggesting perhaps a role for starting therapy at a lower dose. The most frequent AEs were hypertension, an on-target effect, hypothyroidism, diarrhea, nausea, vomiting, loss of appetite, fatigue, and weight loss. Keynote 775 demonstrated significantly longer PFS, and the overall survival median in all comers was seen across different histology subtypes and in women with dMMR and pMMR disease. However, the additional benefit of lenvatinib on dMMR disease requires clarification since a similar response rate is seen with single-agent immunotherapy across a number of phase II trials. A comparison study of pembrolizumab with or without lenvatinib would define optimal therapy in all cohorts.

Reference: J Clin Oncol. 2023;41:2904-10
Abstract

Trastuzumab deruxtecan for human epidermal growth factor receptor 2–expressing advanced or recurrent uterine carcinosarcoma (NCCH1615)

Authors: Nishikawa T et al.

Summary: The STATICE trial aimed to investigate the efficacy and safety of trastuzumab deruxtecan in patients with uterine carcinosarcoma (UCS) in HER2-high and HER2-low groups. The ORR by central review was 54.5% in the HER2-high group and 70.0% in the HER2-low group. The PFS and OS in the HER2-high group were 6.2 and 13.3 months, respectively. For the HER2-high group, the PFS and OS were 6.7 months and not reached, respectively. Sixty-one per cent of patients experienced grade ≥ 3 AEs. The most common AEs were pneumonitis and interstitial lung disease. The study concluded that trastuzumab derutecan had efficacy in patients with UCS, regardless of HER2 status.

Comment: UCS is rare but highly aggressive. While originally considered a mixed tumour, it is now recognised as a metaplastic carcinoma with a sarcoma component arising from the dedifferentiation of the carcinoma component. While paclitaxel-carboplatin is considered the SOC, there is little evidence for effective second-line therapies. Antibody-drug conjugates have dominated the treatment landscape for many cancers. Trastuzumab deruxtecan (drug-to-antibody ratio, 8:1) can target tumour cells expressing low levels of HER2 and deliver its cytotoxic payload through the bystander effect to neighbouring tumour cells. It has been shown to be effective in HER2 low breast cancer. Although the sample size is small, this early-phase study suggests potential activity in UCS, although the incidence of pulmonary toxicity (27%) is higher than seen in previous studies with this drug.

Reference: J Clin Oncol. 2023;41:2789-99
Abstract

Final analysis of a randomized phase II/III trial of conventional paclitaxel and carboplatin with or without bevacizumab versus dose-dense paclitaxel and carboplatin with or without bevacizumab, in stage IVB, recurrent, or persistent cervical carcinoma (JCOG1311)

Authors: Ishikawa M et al.

Summary: This study randomly assigned 122 patients with persistent cervical carcinoma to conventional bevacizumab or dose-dense paclitaxel and carboplatin, with or without bevacizumab. The median follow-up of surviving patients was 34.8 months. In terms of overall survival, for those in the conventional group, it was 17.7 and 7.9 for those in the dose-dense group. The median PFS was 7.9 and 7.2 months for the conventional and dose-dense groups, respectively. Grade 3 to 4 non-haematological toxicity occurred in 46.7% of patients in the conventional regimen and 43.3% in the dose-dense regimen. AEs noted in this study were fistulas or gastrointestinal perforations in 82 patients.

Comment: As a cell cycle phase-specific agent, it would appear intuitive that more frequent administration of paclitaxel would improve efficacy. Paclitaxel has various properties, including the destabilisation of microtubules by disassembly and blockage of the cell cycle, causing cell death and inducing apoptosis, autophagy, and antiangiogenetic. In ovarian cancer, the JGOG3016 study showed a benefit in PFS and OS associated with weekly administration of paclitaxel in first-line therapy. However, four further studies were negative, with a meta-analysis concluding that, while weekly therapy is safe and effective, three weekly chemotherapy remains the SOC. This study has shown similar conclusions and similar rates of toxicity. Three weekly carboplatin/paclitaxel and/or bevacizumab is SOC in metastatic carcinoma of the cervix, although the toxicity of bevacizumab is not insignificant in this population.

Reference: Gynecol Oncol. 2021;162:292-98
Abstract

Effect of BMI change on recurrence risk in patients with endometrial cancer

Authors: Laskov I et al.

Summary: This study compared the effect of BMI and change in cancer recurrence risk for those with endometrial cancer. The study enrolled 211 patients, most with early-stage disease and endometroid histology. Endometroid histology and BMI increase were the most pronounced, with a BMI of 31.6kg/m^2 at surgery compared to 33.5kg/m^2 at follow-up. In the multivariate analysis, the only predictors associated with the risk of recurrence were age and BMI, ORR 1.07 and 1.37, respectively. The study concluded that patients with endometroid endometrial cancer were at increased risk for cancer recurrence if they had an increased BMI compared to patients that did not change or had a decreased BMI.

Comment: The association of obesity with endometrial cancer is well known, and public health measures to reduce obesity rates will be essential to halt the rapidly rising incidence of this disease. More than half of endometrial cancers are currently attributable to obesity, and additionally, obesity also has a negative impact on all-cause mortality. Increased adiposity increases aromatase activity, which leads to the conversion of androgens to estrogens, which directly promotes endometrial proliferation and transcription of pro-proliferative genes. Lifestyle factors really do affect the incidence of this disease, and this should not be undersold when talking to patients. Importantly, this study identifies an increase in BMI as a risk for recurrence, data that could and should be disseminated to patients after a diagnosis of endometrial cancer. In an increasingly medicalised world, such data respects patient autonomy and provides a genuine intervention that will reduce their risk for recurrence.

Reference: Int J Gynecol Cancer. 2023;33:713-8
Abstract

Two staged phase II clinical trial of Eribulin monotherapy in advanced or recurrent cervical cancer

Authors: Garcia-Sayre J et al.

Summary: This study included women with advanced/recurrent cervical cancer after more than one prior chemotherapy regimen. Thirty-two patients were enrolled in this study; 14 received prior paclitaxel; the others were treated with combination cisplatin/paclitaxel/bevacizumab or cisplatin/gemcitabine. One patient had a complete response, 5 had a partial response, and 13 had stable disease. Patients who previously weren't exposed to paclitaxel had a higher ORR of 29%. For the patients who were previously exposed to paclitaxel, they experienced a shorter PFS and overall survival. The study noted the most common grade 3/4 AEs were anaemia, neutropenia, and leukopenia.

Comment: There are few options for women with metastatic cervix cancer following progression after first-line carboplatin/paclitaxel and/or bevacizumab. Few chemotherapy agents offer a significant chance of response, as illustrated again in this study. Like paclitaxel, eribulin is a microtubule poison, likely explaining the reduced efficacy among women pretreated with paclitaxel. Myelosuppression was significant and health-related quality-of-life is lacking; such data are essential to properly inform treatment decisions where treatment is palliative and quality of life paramount. Attempts to identify appropriate biomarkers will be applauded, especially if such data spares toxicity. We await novel and effective options for this disease.

Reference: Gynecol Oncol. 2023;173:49-57
Abstract