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Evidence-Based Series 4-8 Version 4 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy for Advanced or Recurrent Endometrial Cancer, and Advanced or Recurrent Uterine Papillary Serous Carcinoma

Members of the Expert Panel on Endometrial Cancer or Uterine Papillary Serous Carcinoma

An assessment conducted in November 2020 indicated that Guideline 4-8 Version 4 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 4-8 Version 4 is comprised of 2 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/501

Section 1: Clinical Practice Guideline (ENDORSED)
Section 2: Document Assessment and Review

July 23, 2019

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/
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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original version 2004	1966-2004	Full Report	Web publication	NA
Reviewed Version 2 March 2014	2004 to December 2013	New data found in Appendix A	Updated web publication	2004 recommendations are **ENDORSED**
Reviewed Version 3 June 6 2017	December 2013 to March 2017	New data found in Appendix B	Updated web publication	2004 recommendations are **ENDORSED**
Current Version 4 July 2019	March 2017 to March 2019	New data found in Section 2: Document Assessment and Review	Updated web publication	2004 recommendations are **ENDORSED**

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Evidence-based Series 4-8 Version 4: Section 1

Systemic Therapy for Advanced or Recurrent Endometrial Cancer, and Advanced or Recurrent Uterine Papillary Serous Carcinoma

Practice Guideline Report #4-8

C. Gawlik, M. Carey, W. Faught, M. Fung Kee Fung, A. Chambers, and members of the Gynecology Cancer Disease Site Group

Report Date: August 17, 2004

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 2: Document Assessment and Review for a summary of updated evidence published between 2017 and 2019, and for details on how this Clinical Practice Guideline was ENDORSED.

SUMMARY

Guideline Questions

1. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?
2. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma?

Target Population

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Recommendations

For women with advanced or recurrent endometrial cancer:

- Combination chemotherapy is favoured over single agent chemotherapy because of higher response rates.
- Paclitaxel in combination with cisplatin/doxorubicin chemotherapy improves both response rate and median survival; however, the use of this three-drug combination is associated with increased toxicity.
- Hormonal therapy may be a therapeutic option for those patients with minimal symptoms or non-life threatening advanced or recurrent endometrial cancer.

For women with uterine papillary serous carcinoma:

- Evidence supporting or refuting various chemotherapy regimens for uterine papillary serous carcinoma is limited.
- Patients should be encouraged to participate in randomized trials.

Qualifying Statements:

- The decision to use the three-drug combination, consisting of cisplatin/doxorubicin/paclitaxel, should be made with consideration of both the greater toxicity and the three-month increase in median survival time in comparison with the two-drug doxorubicin/cisplatin regimen. However, recent data suggest no benefit to the three-drug combination in terms of recurrence-free survival and was associated with increased toxicity.
- For uterine papillary serous carcinoma treatment, the most studied regimen is a paclitaxel/platinum combination. The addition of paclitaxel in small, non-comparative studies is associated with improved response rates and survival compared to non-platinum containing regimens.

Added to Endorsement in June 2017:

- As mentioned in the Qualifying Statements above, there are data suggesting that a taxane-platinum drug combination has similar efficacy with better toxicity when compared with the three-drug paclitaxel/cisplatin/doxorubicin combination. The Expert Panel recognizes that this evidence comes from an abstract of an interim analysis of a phase III RCT with no full publication and does not meet the criteria for inclusion in this review. However, practice has changed in light of this evidence with preference for a taxane-platinum drug combination although the three-drug combination is still an option.

Added to Endorsement in July 2019:

- There has been one small randomized phase II study showing a benefit of adding trastuzumab to carboplatin/paclitaxel in patients with overexpression of Her2/Neu in advanced (stage III or IV) or recurrent uterine serous carcinoma. Please see Section 2 for further details.

Methods

Entries to MEDLINE (1966 to April 2004), CANCERLIT (1975 to October 2002), and Cochrane Library (2004, Issue 1) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997 to 2003) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by four members of the Practice Guidelines Initiative's Gynecology Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gynecology Cancer Disease Site Group, which comprises gynecologic oncologists, medical oncologists, radiation oncologists, an oncology nurse, a pathologist, and patient representatives.

External review by Ontario practitioners is obtained for all practice guidelines through a mailed survey. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Seventeen randomized trials (including six abstracts and four phase II randomized trials) provided the evidence for systemic therapy of advanced or recurrent endometrial cancer. There were no randomized trials identified that compared systemic therapy to a control group of patients who received no treatment.
- Limitations of the evidence include: heterogeneous patient populations with respect to histology; type of previous treatment (surgery, radiation, chemotherapy, or hormonal therapy); results that are still maturing; and non-comparable outcome measurements.
- Chemotherapeutic options studied for the treatment of advanced or recurrent carcinoma of the endometrium have included single-, double-, and triple-agent therapies. There is limited information available on quality of life and meaningful survival data.
- Single-agent chemotherapy has reported response rates as follows: doxorubicin 17-27% and platinum agents 21%.
- For double-agent chemotherapy, randomized trials of doxorubicin/cisplatin reported response rates ranging from 28-45%, other agents in combination with doxorubicin reported response rates of 30% (cyclophosphamide) and 43% (paclitaxel).
- A randomized trial reported a 57% response rate in the doxorubicin/paclitaxel/cisplatin arm compared to 34% in the doxorubicin/cisplatin arm ($p < 0.01$).
- One randomized trial has compared doxorubicin/cisplatin to whole abdominal radiotherapy and preliminary reports indicate that doxorubicin/cisplatin is more beneficial than radiotherapy in patients with advanced endometrial cancer in terms of overall survival and progression-free survival ($p<0.01$). However, recurrence rates are still high (55%) in both treatment arms.
- Neuropathy, hematological, and gastrointestinal toxicities were the most common adverse effects reported; toxicity increased in incidence with the increase in the number of agents used.
- One randomized trial comparing two dosages of medroxyprogesterone acetate (hormonal therapy) for advanced or recurrent endometrial cancer detected that patients receiving a lower dosage of medroxyprogesterone acetate had significantly increased overall survival ($p=0.026$) and response rate ($p<0.05$) than patients receiving a higher dosage. Hormonal agents were well tolerated: adverse effects were reported at less than 5%.
- Four non-comparative trials (two retrospective and one abstract) provided the evidence for systemic therapy of advanced or recurrent uterine papillary serous carcinoma. Response rates in the four small non-comparative studies ranged from 50-89%

Future Research

In terms of future studies, it is important to be able to control for prognostic factors that affect outcome in these patient populations. Patients should be properly stratified with respect to their disease status (advanced versus recurrent), the amount of previous treatment, type of previous treatment (radiation or chemotherapy), and disease recurrence either in or out of the radiated field. Patients with uterine papillary serous carcinoma should be analyzed separately. Results relating to systemic therapy should be first assessed and proven in those patients with measurable disease so that an accurate assessment of any prolongation in disease-free survival can be made with reasonable assurance that these improvements are due to treatment. Treatment-related toxicity must be studied very carefully in the future in this patient population in order to ensure that the treatment itself has acceptable morbidity in relation to the patient's quality of life, as median survival is generally limited and rarely more than a year in this patient population. Survival, response and toxicity should be studied with regard to impact on quality of life. Comparing tumour responses for both chemotherapy and hormonal agents, stratified by grade, would provide valuable data for making treatment decisions.

Added to Endorsement in July 2019:

Immunotherapy is an emerging treatment, particularly in patients with tumours with high microsatellite instability, and should be addressed in future guidelines as studies become available.

For further information about this practice guideline report, please contact Dr. Michael Fung Kee Fung, the lead author, through the PEBC at:
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The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

For information about the PEBC and the most current version of all reports, please visit the CCO website at https://www.cancercareontario.ca/en/guidelines-advice or contact the PEBC office at:
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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:
[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

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FULL REPORT

I. QUESTION

1. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?
2. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma (UPSC)?

II. CHOICE OF TOPIC AND RATIONALE

Endometrial carcinoma is the most common gynecologic malignancy in Ontario, with an estimated 1,450 new cases in 2003 (1). At least 75% of cases present with early-stage (I/II) disease, and the majority of these patients are cured with surgery (2,3). Since most patients with the disease have a good prognosis, patients presenting with advanced or recurrent disease are relatively uncommon (4). Isolated pelvic recurrences are treated with radiation, whereas most other patients with advanced or recurrent disease receive systemic therapy (either chemotherapy or hormonal therapy). Response rates to systemic therapy reported in the literature vary considerably, ranging from 10-78%, due to marked differences in the studied patient populations (4). Reported median duration of survival in such patients is rarely more than one year.

Recently, newer agents such as paclitaxel have shown promising survival and response rates in phase II studies (5,6). This new evidence has generated renewed interest in systemic chemotherapy for cases of advanced or recurrent carcinoma of the endometrium.

From an historical perspective, doxorubicin with or without cisplatin is considered by most as standard chemotherapy for this disease, although some practitioners substitute carboplatin because of its more favourable side-effect profile (7). Previous studies have shown that hormonal systemic therapy, with either megestrol or progesterone, represents a good treatment option in selected patients, based on reported response rates that approach or exceed those for more toxic chemotherapy (8).

Impressive response rates with new agents like paclitaxel have also been reported in patients with adverse histological subtypes such as UPSC. Systemic chemotherapy is a subject of interest in this malignancy, with the recognition that biologic spread patterns are similar to those in patients with ovarian carcinoma (9). Unfortunately, our experience with either chemotherapy or hormonal therapy in this setting has been disappointing. UPSC patients are infrequently cured and rarely live more than a year or two from the diagnosis of advanced or recurrent disease, which has prompted investigators to look to newer agents with different mechanisms of action as promising new treatments for this disease (9).

In view of the volume of literature that has been published, the Gynecology Cancer Disease Site Group (Gynecology Cancer DSG) decided to conduct a systematic review of the available evidence. We examined the efficacy of systemic therapy, either chemotherapy or hormonal therapy, in the management of patients with advanced or recurrent carcinoma of the endometrium. We elected to review the evidence on UPSC separately as this adverse histological variant has a predilection for metastatic spread, presenting frequently in an advanced stage.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (10). Evidence was selected and reviewed by four members of the PGI's Gynecology Cancer Disease Site Group (Gynecology Cancer DSG) and

methodologists. Members of the Gynecology Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on systemic therapy for endometrial cancer, developed through systematic reviews and evidence synthesis. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

The MEDLINE (1966 to April 2004), CANCERLIT (1975 to October 2002), and Cochrane Library (2004, Issue 1) databases were searched using the medical subject headings (MeSH) endometrial neoplasms, uterine neoplasms, and antineoplastic agents, and the following text words: endometrium, endometrial, serous, uterus, uterine, cancer, carcinoma, chemotherapy, hormone(s), hormonal. Search terms related to study design or publication type included systematic review, clinical trial, meta-analysis, controlled clinical trials, clinical trials/phase II, clinical trials/phase III, multicentre studies, and randomized controlled trials (MeSH). Proceedings of the 1997 to 2003 meetings of the American Society of Clinical Oncology (ASCO) and reference lists of papers and review articles were scanned for additional citations. The Canadian Medical Association Infobase (http://www.cma.ca/cma/common/start.do?lang=2), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) Web sites were searched for existing evidence-based practice guidelines.

Inclusion Criteria

Evidence-based clinical practice guidelines or systematic reviews regarding systemic therapy for advanced disease from other guideline-development groups were eligible for inclusion.

To address the question regarding the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer, full articles or abstracts were selected for inclusion if they met the following criteria:

1. Randomized controlled trials (RCT) or meta-analyses comparing regimens of systemic chemotherapy or hormonal therapy to the standard treatment for advanced or recurrent endometrial cancer reporting at least one of the following outcomes: survival, quality of life, response rate, or toxicity.
2. RCTs that reported on heterogeneous populations (e.g., included women with a range of disease stages) were eligible if results were given separately for the group with advanced or recurrent endometrial cancer.
3. When RCTs were not available, phase II trials of chemotherapy and hormonal therapy agents were included.

To address the question regarding the chemotherapeutic options for women with advanced or recurrent UPSC, full articles or abstracts were selected for inclusion if they met the following criteria:

1. RCTs comparing systemic therapy regimens that included women with stage IIIc or IV UPSC with measurable or evaluable disease at the start of systemic therapy, and reported at least one of the following outcomes: survival, quality of life, response rate, or toxicity.
2. When RCTs were not available, phase II trials of chemotherapy agents were included.

Exclusion Criteria

1. Non-English language publications were excluded.
2. Studies evaluating the role of radiotherapy, administered with chemotherapy or hormonal therapy, were excluded.

Synthesizing the Evidence

The Gynecology Cancer DSG identified 17 RCTs that compared various chemotherapy regimens for the treatment of advanced or recurrent endometrial cancer, including abstracts and randomized phase II trials. The results of RCTs could not be pooled because of the differences among the studies in terms of:

1. The number of advanced versus recurrent cases. Advanced cases actually have a poorer prognosis with a shorter expected survival than most patients presenting with recurrence.
2. The greater proportion of patients previously treated with radiation therapy and documentation with respect to the site of recurrence (either in or out of the radiated field). Patients with disease in the radiated field are known to have lower response rates to systemic chemotherapy than patients with disease outside the field.
3. The inclusion or exclusion of adverse histologic subtypes. Trials differed with respect to the inclusion or exclusion of patients with adverse histologic subtypes. It was only within the last three to five years that the Gynecologic Oncology Group (GOG) decided to separate patients with serous carcinomas as a distinct entity in subsequent GOG studies.
4. The inclusion criteria concerning previous systemic therapy. There were marked differences among studies with respect to the number of prior chemo-hormonal regimens administered to patients.

IV. RESULTS

Literature Search Results

Practice Guidelines

No evidence-based clinical practice guidelines on systemic therapy for advanced or recurrent endometrial cancer or UPSC were identified.

Systematic reviews

No relevant systematic reviews were found. However, a recently published narrative review by two Gynecology Cancer DSG members was used to complement the literature search (4). The authors of the narrative review searched the CANCERLIT, EMBASE, MEDLINE, Investigational Drug and R&D Focus databases. Search terms included: endometrial cancer, chemotherapy, endocrine/hormonal therapies, molecular biologics, and specific drug names (personal communication). This review by Elit and Hirte (4) includes an extensive list of phase II and III studies of chemotherapy and hormonal therapy for endometrial cancer.

Clinical trials

There are 13 RCTs (7,11-22) that compare chemotherapy regimens in women with advanced or recurrent endometrial cancer (Table 1a). Two of the 13 RCTs compared different chemotherapy regimens given with hormonal therapy (20,21), while the other eleven studies compared chemotherapy regimens, without hormonal therapy. Two RCTs used an intention-to-treat approach to survival analysis (7,12), and only one described the number of patients lost to follow-up (12). Eight RCTs have been published in full reports that included detailed descriptions of eligibility criteria (7,11,16,19-22). The randomized trial by Long et al (17), reported in an abstract for ASCO 1995, was closed prematurely because of low accrual. There was one RCT (abstract) identified that compared chemotherapy to radiotherapy in women with advanced endometrial cancer (13).

There were three RCTs (8,23,24) identified that measured hormonal therapy in women with advanced or recurrent endometrial cancer (Table 1a). None of the randomized trials of hormonal therapy assessed quality of life. The RCTs appear to have used an intention-to-treat approach to survival analysis; however, only Thigpen et al (8) describe the number of patients lost to follow-up. The RCTs have been published in full reports that included detailed descriptions of eligibility criteria. There is one RCT (25) that compares chemotherapy-to-chemotherapy plus hormonal therapy in women with advanced or recurrent endometrial cancer.

In addition to the RCTs, 19 prospective phase II studies (5,6,26-42) of agents that have not been used in randomised trials were also identified: carboplatin, paclitaxel, oral etoposide, dactinomycin, topotecan, liposomal doxorubicin, vinorelbine, gonadotrophin-releasing hormone agonist, luteinizing hormone-releasing hormone agonist, aromatase inhibitors, and LY353381. This is not an exhaustive list of all prospective single-cohort studies of systemic therapy for advanced or recurrent endometrial cancer but includes the results of a systematic search for all relevant studies of specific agents that are of current interest to Gynecology Cancer DSG members (mostly agents that are currently used in Ontario). Seven phase II studies examining hormonal therapies for women with advanced endometrial cancer were also identified (43-49). The details of the chemotherapy and hormonal therapy phase II studies are described in Appendix 1, for information.

Four non-comparative studies (two retrospective) have been identified that measure systemic therapy in women with UPSC; no RCTs were found. Table 1b lists studies of chemotherapy for UPSC. Doses and schedules of administrations used in the clinical trials are listed in Appendix 2.

Table 1a. Studies on systemic therapy for advanced or recurrent endometrial cancer.

Drug or combination	Evidence	Reference number
Chemotherapy		
doxorubicin/cyclophosphamide vs doxorubicin alone	1 RCT	(7)
doxorubicin/cisplatin vs doxorubicin/cisplatin/paclitaxel	1 RCT	(11)
doxorubicin/cisplatin vs doxorubicin alone	2 RCTs: - 1 phase II/III - 1 phase III	(12) (18) [abstract]
doxorubicin/cisplatin vs radiotherapy	1 RCT	(13) [abstract]
doxorubicin/cisplatin vs carboplatin/paclitaxel	1 RCT (phase II)	(14) [abstract]
doxorubicin/cisplatin vs doxorubicin/paclitaxel	1 RCT	(15) [abstract]
ifosfamide vs cyclophosphamide	1 RCT (phase II)	(16)
methotrexate/vinblastine/doxorubicin/cisplatin vs doxorubicin/cisplatin	1 RCT	(17) [abstract]
doxorubicin/cyclophosphamide/cisplatin vs cisplatin alone	1 RCT (phase II)	(19)
cyclophosphamide/doxorubicin/5-FU vs melphalan/5-FU (+ megestrol in both groups)	1 RCT	(20)
doxorubicin/cyclophosphamide vs cyclophosphamide/doxorubicin/5-FU (+ megestrol in both groups)	1 RCT	(21)
doxorubicin vs cyclophosphamide	1 RCT	(22)
Hormonal Therapy		
oral medroxyprogesterone acetate 200mg/day vs oral medroxyprogesterone acetate 1,000mg/day	1 RCT	(8)
megestrol acetate vs megestrol acetate + tamoxifen	1 RCT (phase II)	(23)
medroxyprogesterone acetate vs tamoxifen	1 RCT	(24)
Combined chemotherapy and hormonal therapy		
cyclophosphamide/doxorubicin/5-FU vs cyclophosphamide/doxorubicin/5-FU + medroxyprogesterone + tamoxifen	1 RCT	(25)

Note: RCT, randomized controlled trial; vs, versus.

Table 1b. Studies on systemic therapy for uterine serous papillary carcinoma.

Drug or combination	Evidence	Reference number
platinum + paclitaxel	1 phase II study 1 retrospective review	(6) [abstract] (9)
paclitaxel	1 prospective cohort	(50)
cisplatin/doxorubicin/cyclophosphamide	1 retrospective review	(51)

Characteristics of Study Participants

Characteristics of the patients who participated in studies of chemotherapy or hormonal therapy for advanced or recurrent endometrial cancer are summarized in Tables 2a and 2b.

Six GOG RCTs included patients with high-risk histology (7,11,13,15,18,20). Three to five percent of participants in these studies had clear cell carcinoma and 4% to 19% had UPSC. Chemotherapy was given intravenously in all of the RCTs.

Table 2a. Description of participants in randomized trials of chemotherapy.

Study	Chemotherapy	# entered (eligible)	Recurrent disease (%)	Advanced disease (%)	Performance status	% with prior HT	% with prior CT	% with prior RT
Fleming, 2004 (11) (GOG)	dox/cisplatin vs dox/cisplatin/ paclitaxel	273 (263)	170 (65%)	93 (35%)	GOG 0-2: 100%	NR	none	51% vs 46%
Aapro, 2003 (12) (EORTC)	dox/cisplatin vs dox	177 (177)	105 (59%)	72 (41%)	WHO 0-1: 78% 2: 18%	23%	0.5%	50%
Randall, 2003 (13) (GOG)	dox/cisplatin vs radiotherapy	422 (388)	NR	NR	NR	NR	NR	NR
Weber, 2003 (14)	dox/cisplatin vs carboplatin/ paclitaxel	70	NR	NR	NR	NR	NR	NR
Fleming, 2000 (15) (GOG)	dox/cisplatin vs dox/paclitaxel	314	NR	NR	GOG 0-2: 100%	NR	none	52%
Pawinski, 1999 (16) (EORTC)	Ifosfamide vs cyclo	74 (61)	47 (77%)	14 (23%)	WHO 0-1: 79% 2: 21%	28%	51%	67%
Long, 1995 (17) (NCCTG)	methotrexate/ vinblastine/dox/ cisplatin vs dox/cisplatin	28 (28)	none	28 (100%)	NR	NR	NR	NR
Thigpen, 1994 (7) (GOG)	dox/cyclo vs dox	387 (356)	NR	NR	GOG 0-1: 69% 2-3: 31%	NR	none	70%
Thigpen, 1993 (18) (GOG)	dox/cisplatin vs dox	297 (223)	NR	NR	NR	NR	none	NR
Edmonson, 1987 (19) (NCCTG)	dox/cyclo/ cisplatin vs cisplatin	30 (30)	none	30 (100%)	ECOG 0-1: 53% 2-3: 47%	100%	NR	63%
Cohen, 1984 (20) (GOG)	cyclo/dox/5-FU/megestrol vs melphalan/5-FU/megestrol	295 (257)	115 (74%)	40 (26%)	0-1: 74% 2-3: 26%	NR	none	NR
Horton, 1982 (21)	dox/cyclo/ megestrol vs cyclo/dox/5-FU/megestrol	149 (126)	none	126 (100%)	ECOG 0-1: 70% 2-3: 30%	38%	none	74%
Horton, 1978 (22) (ECOG)	dox vs cyclo	47 (40)	none	40 (100%)	ECOG 0-1: 53% 2-3: 47%	100%	none	NR

Note: 5-FU, 5-fluorouracil; CT, chemotherapy; cyclo, cyclophosphamide; dox, doxorubicin; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GOG, Gynecologic Oncology Group; HT, hormonal therapy; NCCTG, North Central Cancer Treatment Group; NR, not reported; RT, radiotherapy; vs, versus; WHO, World Health Organization

Table 2b. Description of participants in trials of hormonal therapy.

Study	Hormonal therapy	# entered (eligible)	Performance status	Recurrent disease (%)	Advanced disease (%)	% with prior HT	% with prior CT	% with prior RT
Pandya, 2001 (23)	megestrol vs megestrol/ tamoxifen	66 (62)	ECOG 0-1: 82% 2: 18%	NR	NR	none	6%	82%
Thigpen 1999 (8)	MPA 200mg/day vs MPA 1,000mg/day	324 (299)	GOG 0-1: 77% 2: 23%	214 (72%)	85 (28%)	none	none	65%
Rendina, 1984 (24)	MPA vs tamoxifen	93 (93)	NR	0	93 (100%)	NR	NR	NR

Note: CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; GOG, Gynecologic Oncology Group; HT, hormonal therapy; MPA, medroxyprogesterone acetate; NR, not reported; RT, radiotherapy; vs, versus.

Chemotherapy for Advanced or Recurrent Endometrial Cancer

Survival

Survival data have been reported in nine randomized trials (Table 3) (7,11-15,17,19,20). Median survival ranged between 4.2 to 15 months in the nine studies. Two RCTs detected a significant difference in survival between treatment groups ($p<0.05$) (11,13). Fleming et al's RCT (11) detected a significant improvement in median survival for women receiving doxorubicin/cisplatin/paclitaxel/G-CSF compared to women receiving doxorubicin/cisplatin. The death hazard relative to the doxorubicin/cisplatin arm (stratified by performance status) was 0.75 (95% CI 0.57-0.988, p=0.037).

The other RCT that detected a survival difference between treatment arms compared doxorubicin/cisplatin to radiotherapy (13). Randall et al (13) reported the results of their GOG study (abstract) which included 388 evaluable women. They detected a progression-free survival (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.52-0.89; $p<0.01$) and overall survival (HR, 0.67; 95% CI, 0.51-0.89; $p<0.01$) advantage for the women receiving chemotherapy. Despite the advantages in survival, they reported that recurrences in both treatment arms were frequent (55% overall). They also noted that the adverse events were more common among the patients receiving chemotherapy than the patients receiving radiotherapy, but did not provide any details of the events.

The remaining seven RCTs did not detect a significant difference in median survival. Two of those trials were small, including about 30 patients each (17,19). The two oldest RCTs (19,20) compared combination chemotherapy with doxorubicin to a chemotherapy regimen that did not include doxorubicin. Two other RCTs that did not detect a significant difference in survival compared combination chemotherapy including doxorubicin with doxorubicin by itself (7) or doxorubicin in combination (15). The phase II/III RCT by Aapro et al (12) that compared doxorubicin and cisplatin with doxorubicin alone did not detect a survival difference; however, they did detect a significant difference in tumour response in favour of the combination therapy. One abstract of a phase II RCT comparing doxorubicin/cisplatin to carboplatin/paclitaxel has only presented preliminary results at this point (14). Weber et al (14) need to follow the patients in their study for a longer period before they can establish the role of carboplatin/paclitaxel in the treatment of advanced endometrial cancer. However, Weber et al report that thus far carboplatin/paclitaxel seems promising in terms of response rate and overall survival when compared to doxorubicin/cisplatin.

Table 3. Survival data of chemotherapy for advanced or recurrent endometrial cancer.

Study	Chemotherapy	# patients	Median Survival (months)	log-rank p value
Fleming, 2004 (11)	doxorubicin + cisplatin	129	12.3	0.037
	doxorubicin + cisplatin + paclitaxel	134	15.3	
Aapro, 2003 (12) (Phase II/III)	doxorubicin	87	7	NS p=0.064
	doxorubicin + cisplatin	90	9	
Randall, 2003 (13) [abstract]	doxorubicin + cisplatin	190	NR	PFS hazard ratio 0.68 (95% CI 0.52-.089) favouring chemotherapy p<0.01
	radiotherapy	198	NR	
Weber, 2003 (14) [abstract] (Phase II)	doxorubicin + cisplatin	34	6.7 (time to progression)	NR
	carboplatin + paclitaxel	36	7.7 (time to progression)	
Fleming, 2000 (15)	doxorubicin + cisplatin + GCSF	157	12.4	NS
	doxorubicin + paclitaxel + GCSF	160	13.6	
Long, 1995 (17) [abstract]	MVAC	13	15	NS
	doxorubicin + cisplatin	15	15	
Thigpen, 1994 (7)	doxorubicin	132	6.7	NS
	doxorubicin + cyclophosphamide	144	7.3	
Edmonson, 1987 (19) (Phase II)	cisplatin	14	4.2	NS
	cyclophosphamide/doxorubicin/ cisplatin	16	6.7	
Cohen, 1984 (20)	melphalan + 5-florouracil + megestrol	122	10.6	NS
	doxorubicin/cyclophosphamide/5-florouracil + megestrol	131	10.1	

Note: CI, confidence interval; MVAC, methotrexate/vinblastine/doxorubicin (Adriamycin)/cisplatin; NS, not significant; PFS, progression-free survival

Tumour Response

Tumour response data from 12 randomized trials are listed in Table 4. Three RCTs detected a statistically significant difference in response rate between treatment groups (11,12,18). Two of those RCTs detected that patients treated with doxorubicin/cisplatin had significantly improved tumour response rates compared to patients who had received doxorubicin alone (12,18). No other RCT compared doxorubicin with cisplatin to doxorubicin alone. The report by Aapro et al (12) reported a significant difference in favour of combination therapy with doxorubicin plus cisplatin over doxorubicin alone in a randomized phase II/III trial (p=0.001). The difference in the response rates reported by Thigpen et al (18) for their phase III trial of doxorubicin versus doxorubicin plus cisplatin were also significant (p<0.001, Gynecology Cancer DSG calculation), in favour of combined therapy.

The other RCT that detected a significant difference in tumour response compared doxorubicin, cisplatin and paclitaxel to doxorubicin and cisplatin (11). They found that patients receiving doxorubicin, cisplatin and paclitaxel had greater tumour response than patients receiving doxorubicin, and cisplatin (p<0.001). Another randomized phase III trial prepared for

the 2000 ASCO meeting (GOG #163) by Fleming et al (15) comparing doxorubicin with cisplatin to doxorubicin with paclitaxel did not detect a significant difference in response rates between treatment groups (no p-value reported).

The other nine RCTs failed to detect a significant difference between the treatments being compared. Four of these RCTs included less than 65 patients which suggests that these studies were not powered to detect significant differences between treatment groups (16,17,19,22). Weber et al (14) reported preliminary results and thus could not make conclusions regarding tumour response. Four of the RCTs that failed to detect a significant difference between the treatments did not compare a platinum-based agent to a non-platinum-based regimen (7,20-22). However, two of the three RCTs that did detect a significant difference between treatment groups compared a platinum-based agent (in combination) to treatment not including platinum (12,18).

Table 4. Tumour response data from clinical trials of chemotherapy for advanced or recurrent endometrial cancer.

Study	Regimen	# evaluated	# complete responses (CR)	# partial responses (PR)	Response rate (CR + PR) (%)
Fleming, 2004 (11)	- doxorubicin/cisplatin - doxorubicin/cisplatin/ paclitaxel	263	7% 22%	26% 35%	(34%)* (57%)*
Aapro, 2003, (12)	- doxorubicin - doxorubicin/cisplatin	87 90	8 13	7 26	15 (17%) * 39 (43%) *
Weber, 2003 (14) [abstract] (Phase II)	- doxorubicin/cisplatin - carboplatin/paclitaxel	63	NR	NR	(27.6%) (35.3%)
Fleming, 2000 (15) [abstract]	- doxorubicin/cisplatin - doxorubicin/paclitaxel	157 160	23 27	40 42-	63 (40%) 69 (43%)
Pawinski, 1999 (16)	- cyclophosphamide - ifosfamide	29 32	0 2	2 2	2 (7%) 4 (12%)
Long, 1995 (17) [abstract]	- MVAC - doxorubicin/cisplatin	13 15	4 2	5 2	9 (69%) 4 (26%)
Thigpen, 1994 (7)	- doxorubicin - doxorubicin/cyclophosphamide	132 144	7 18	22 25	29 (22%) 43 (30%)
Thigpen, 1993 (18) [abstract]	- doxorubicin - doxorubicin/cisplatin	122 101	10 22	23 23	33 (27%) * 45 (45%) *
Edmonson, 1987 (19)	- cisplatin - CAP	14 16	1 0	2 5	3 (21%) 5 (31%)
Cohen, 1984 (20)	- megestrol/melphalan/5-FU - MCAF	77 78	12 13	17 15	29 (38%) 28 (36%)
Horton, 1982 (21)	- MCA - MCAF	55 56	4 3	11 6	15 (27%) 9 (16%)
Horton, 1978 (22)	- doxorubicin - cyclophosphamide	21 19	1 0	3 0	4 (19%) 0 (0%)

Note: 5-FU, 5-flourouracil; CAP, cyclophosphamide/Adriamycin) cisplatin; MCA, megestrol/cyclophosphamide/doxorubicin (Adriamycin); MCAF, MCA+5-fluorouracil; MVAC, methotrexate/vinblastine/Adriamycin/cisplatin

* p value statistically significant

Quality of Life

One RCT assessed quality of life during chemotherapy (14), and one RCT was identified that assessed quality of life before, during, and after chemotherapy (52). At this point, both trials are only published in abstract form, and Weber et al (14) have only published preliminary results. Weber et al conducted a randomized phase II study comparing six cycles of doxorubicin/cisplatin to six cycles of carboplatin/paclitaxel. Every cycle tolerance was evaluated, and every two cycles of efficacy and quality of life were evaluated.

Watkins-Bruner et al (52) reported the quality-of-life data for the GOG 122 RCT, which compared whole abdominal radiation therapy to doxorubicin and cisplatin in women with advanced endometrial cancer. They used several quality-of-life measurement scales including: the Fatigue Scale (FS), Assessment of Peripheral Neuropathy (APN), Functional Alterations due to Changes in Elimination (FACE), and Functional Assessment of Cancer Therapy (FACT). FACT is a measure of overall quality of life. Watkins et al reported that after six months women treated with radiation therapy have similar FS and FACE scores as their pre-treatment scores; however, they had significantly worse FS and FACE scores than the women receiving chemotherapy ($p<0.01$). Women receiving chemotherapy had higher APN scores than the women receiving radiation therapy ($p<0.01$), and those high scores for women receiving chemotherapy were maintained beyond the six months of treatment. The results of that trial will require more investigation once the full report has been published.

One small phase II study measured performance status and pain, before and after treatment with paclitaxel plus cisplatin (29). Dimopoulos et al (29) reported that the performance status (defined by the Eastern Cooperative Oncology Group [ECOG]) improved in eight of 14 women with a pre-treatment performance status of 1 or 2. Improvement was defined as an increase of at least one point on the ECOG scale. Before starting chemotherapy, ten of 24 patients enrolled in the study were taking opioid analgesics regularly to manage pain. After chemotherapy, six of those ten women were no longer using pain medication or had substituted nonsteroidal anti-inflammatory drugs for the opioid analgesics. The remaining four women reported no change in pain after chemotherapy or a worsening of symptoms. It is important to note that the study included patients with all stages of endometrial cancer in their study, not just advanced stage as in the other studies mentioned.

Adverse Events

Data on severe adverse events (grade 3 or 4) were reported for seven randomized trials (Table 5). Thirteen deaths possibly related to treatment were reported across the seven studies: seven with doxorubicin alone or with cyclophosphamide (7), one with carboplatin (17), and five with paclitaxel/doxorubicin/cisplatin (11). In the Fleming et al RCT (11), there were five treatment-related deaths in the paclitaxel/doxorubicin/cisplatin arm (n=134) and no treatment-related deaths in the doxorubicin/cisplatin arm (n=129). The authors of the RCT report, however, that only two of the deaths were clearly treatment-related (one case of acute myeloid leukemia and one case of neutropenic sepsis). The other three patients died due to possible hemolytic uremic syndrome and disease, infection and disease, or superior mesenteric artery thrombus. Fleming et al also reported that more deaths among patients being treated cisplatin/doxorubicin have been reported in the GOG trials with identical cisplatin/doxorubicin treatment arms (53).

Table 5. Serious adverse event data (Grade 3/4) from clinical trials of chemotherapy for advanced or recurrent endometrial cancer.

Study	# of patients	Treatment	Leuko-penia	Thrombo-cytopenia	Gastro-intestinal	Neuro-logical
Fleming, 2004 (11)	263	doxorubicin/cisplatin	50%	3%	25%	1%
		doxorubicin/cisplatin/ paclitaxel	36%	22%	34%	12%
Aapro 2003 (12)	165	doxorubicin	30%	5%	12%	0
		doxorubicin/cisplatin	55%	13%	36%	0
Fleming, 2000 (15) GOG 163	314	doxorubicin/cisplatin	54%	6%	13%	8%
		doxorubicin/paclitaxel /GCSF	48%	9%	11%	9%
Pawinski, 1999 (16)	61	cyclophosphamide	52%	0	not reported	not reported
		ifosfamide	46%	4%		
Thigpen, 1993 (18) GOG 107	223	doxorubicin	39%	2%	2%	not reported
		doxorubicin/cisplatin	61%	14%	16%	
Cohen, 1984 (20)	155	megestrol/melphalan/ 5-fluorouaracil	52%	18%	not reported	not reported
		MCAF	31%	0		
Horton, 1982 (21)	111	MCA	32%	5%	not reported	not reported
		MCAF	18%	5%		

Note: GOG, Gynecologic Oncology Group; MCA, megestrol/cyclophosphamide/doxorubicin (Adriamycin); MCAF, MCA + /5-fluorouracil

Hormonal Therapy for Advanced or Recurrent Endometrial Cancer

Survival

Survival data have been reported from two randomized studies that considered hormonal therapy (Table 6). Median survival ranged from seven to 12 months in these studies. However, the median survival data could not be pooled across studies because of the variability among the studies due to chemotherapy regimens and outcome measures.

Table 6. Survival data of hormonal therapy for advanced or recurrent endometrial cancer.

Study	Hormonal therapy	Median Survival (months)	Log-rank p-value
Pandya, 2001 (23) (phase II randomized)	megestrol	12	(no p-value)
	megestrol/tamoxifen	8.6	
Thigpen, 1999 (8)	MPA 200 mg	11.1	p=0.026
	MPA 1,000 mg	7.0	

Note: MPA, medroxyprogesterone acetate

Tumour Response

Tumour response data from three randomized studies (8,23,24) appear in Table 7. Only the RCT by Thigpen et al (8) detected a difference between the treatment groups. They reported that low-dose medroxyprogesterone acetate (MPA) showed marginally better response rates than high-dose MPA (p=0.051). When Thigpen et al (8) calculated response rates for subgroups of participants, they reported that grade I, progesterone-receptor-positive or estrogen-positive tumours had response rates of 37%, 37%, and 26%, respectively, and median

survival of 18.8, 12.1, and 8.3 months, respectively. However, participants with grade III, progesterone-receptor-negative or estrogen-receptor-negative tumours had response rates of 9%, 8%, and 7%, respectively and survival of 6.9, 6.8, and 6.7 months, respectively, based on univariant analysis (8).

Table 7. Tumour response data from clinical trials of hormonal therapy for advanced or recurrent endometrial cancer.

Study	Regimen	# evaluated	# complete responses (CR)	# partial Responses (PR)	Response rate (CR + PR) (%)
Pandya, 2001 (23)	- megestrol - megestrol/tamoxifen	20 41	1 1	3 7	4 (20%) 8 (20%)
Thigpen, 1999 (8)	- MPA 200 mg - MPA 1,000 mg	145 154	25 14	11 10	36 (25%) 24 (15%) p=0.051
Rendina, 1984 (24)	- MPA - tamoxifen	48 45	8 6	14 10	22 (46%) 16 (36%)

Note: MPA = medroxyprogesterone acetate

Adverse Events

Three randomized trials examining the use of hormonal therapy in the treatment of endometrial cancer provided details of adverse effects (8,23,24). Pandya et al reported that 5% of patients on megestrol plus tamoxifen experienced life-threatening adverse events, including one case of pulmonary embolism (23). Rendina et al reported that none of the participants in their trial experienced adverse effects severe enough to require withdrawal of therapy (24). Thigpen et al (8) reported that thrombophlebitis (5%) was the most frequently reported adverse effect, followed by gastrointestinal upset, somnolescence, fatigue, edema (all less than 3%), and pulmonary embolus (1%) (8).

Combination Therapy for Advanced or Recurrent Endometrial Cancer

Ayoub et al (25) reported the results of the only randomized trial identified that compared chemotherapy to combined chemotherapy and hormonal therapy for advanced or recurrent endometrial cancer. The trial was not blinded and did not describe an appropriate method for concealing allocation up to the time of randomization. An intention-to-treat approach was not used for survival analysis, and the number of patients lost to follow-up was not described.

Forty-six women with metastatic endometrial cancer (37% newly diagnosed and 62% recurrent) and an ECOG performance status between 0 and 2 entered the trial. None had received previous chemotherapy or hormonal therapy, but all had been treated with radiation. Details of dose and schedule for the chemotherapy and hormonal therapy regimens evaluated are listed in Appendix 1.

Median survival was 11 months with chemotherapy alone (cyclophosphamide/doxorubicin/5-fluorouracil) and 14 months with chemotherapy plus cyclical hormonal therapy (Provera followed by tamoxifen) (p>0.05). Response rates were 15% with chemotherapy alone (1 complete and 2 partial, n=20) and 43% with chemotherapy plus hormonal therapy group (6 complete and 4 partial, n=23). The difference in response rates between groups was of borderline statistical significance (p=0.05). Quality of life was not assessed.

Ayoub et al reported that five of 23 women (22%) treated with combined chemo-hormonal therapy experienced phlebitis (25). Toxicity data were not presented separately for the two treatment groups, but 14% overall experienced grade 3 or 4 hematologic adverse events, and 12% grade 3 or 4 nausea or vomiting.

Chemotherapy for Advanced or Recurrent Uterine Papillary Serous Carcinoma (UPSC)

There were two prospective and two retrospective single-cohort studies of chemotherapy for advanced or recurrent UPSC (6,9,50,51) (Table 8). These studies included women with UPSC who received chemotherapy for early-stage, advanced or recurrent disease, but only data for patients with measurable disease in the latter two groups were extracted for this practice guideline.

There is limited survival and response data available from those studies. The Canadian prospective phase II study by Hoskins et al (6) reported response rates for both patients with UPSC and patients with non-papillary serous cancers. They reported that, out of the 46 women assessable for response, there was an overall response rate of 78%. Among the women with advanced non-papillary serous cancer there was a 78% response rate, compared to a 60% response rate among women with UPSC. The response rate for women with recurrent non-papillary serous cancer was 56% compared to 50% among women with recurrent UPSC. These findings need to be interpreted with caution because of the small sample size of the study.

Toxicity data are also sparse. Ninety percent of the participants in the study by Ramondetta et al experienced grade 3 or 4 neutropenia after treatment with paclitaxel; 45% were hospitalized for neutropenic fever (50). Ramondetta also reported that one patient developed congestive heart failure (50). Price et al reported that 64% of patients with recurrent disease treated with cisplatin/doxorubicin/ cyclophosphamide experienced grade 3 or 4 neutropenia, 9% experienced grade 3 or 4 thrombocytopenia, and 9% experienced grade 3 or 4 nausea or vomiting (51). In that study, Price et al also reported one death that was associated with cardiotoxicity from doxorubicin (51).

Table 8. Studies of chemotherapy for UPSC.

Study	Hoskins, 2001 (6)	Ramondetta, 2001 (50)	Zanotti, 1999 (9)	Price, 1993 (51)
Type of study	Prospective	Prospective	Retrospective	Retrospective
Dose	175 mg/m^2 paclitaxel over 3 hours + AUC 5-7 carboplatin, every 4 weeks	200 mg/m^2 paclitaxel over 24 hours, every 3 weeks	175 mg/m^2 paclitaxel over 3 hours + 75mg/m^2 cisplatin or AUC 5 carboplatin, every 3 weeks	50 mg/m^2 cisplatin + 50 mg/m^2 doxorubicin + 500 mg cyclophosphamide
Total UPSC patients	24	13	24	11
# with recurrent disease	4	9	Second line: 5 (platinum) 6 (no platinum)	11
# with advanced disease	20 (only 15 evaluable)	4	Second line: 8 (platinum) Initial chemotherapy: 9 (platinum)	0
% with prior chemotherapy	0%	0%	Second line: 0% (platinum) 83% (no platinum) Initial chemotherapy: 0% (platinum)	Not reported
Median survival for advanced patients (months)	26	11	56	Not applicable
Median survival for patients with recurrence (months)	15	19	Not reported	7
# complete responses (CR)	3 advanced 1 recurrent	4	11 second line	1
# partial responses (PR)	6 advanced 1 recurrent	6	4 second line	2
Response rate (CR + PR) (%)	9 (60%) advanced 2 (50%) recurrent	10 (77%)	15 (75%) second line 8 [a] (89%) initial chemotherapy	3 (30%)

Note: AUC, area under curve

[a] based on normalization of elevated pre-chemotherapy CA 125 level

V. INTERPRETIVE SUMMARY

Chemotherapeutic options studied for the treatment of advanced or recurrent carcinoma of the endometrium have included single-, double-, and triple-agent therapies. Single-agent chemotherapy has reported response rates as follows: doxorubicin 17-27% (7,12,18,22) and platinum agents 21% (19). For combination chemotherapy, randomized trials of doxorubicin/cisplatin reported response rates of 34%, 40%, 45%, and 43% (11,12,15,18); however, other agents in combination with doxorubicin revealed response rates of 30% (cyclophosphamide) (7) and 43% (paclitaxel) (15). When three agents are combined, the response rates seem to be higher. One RCT compared doxorubicin/cisplatin to doxorubicin/paclitaxel/cisplatin and reported a 57% response rate for the doxorubicin/paclitaxel/cisplatin arm compared to a 34% response for the doxorubicin/cisplatin arm (11).

Paclitaxel-containing regimens seem to be promising. A non-comparative study of paclitaxel/carboplatin reported a response rate of 78% and 50% in advanced and recurrent disease, respectively (6). Median survival was 15 months for recurrent disease and has not yet been reached in advanced disease (6). Although newer studies, particularly those using a combination of carboplatin and paclitaxel, report promising results, caution should be exercised in interpreting reported favourable response rates in the absence of a well-designed clinical trial.

One randomized trial compared whole abdominal radiotherapy to cisplatin/doxorubicin and detected an advantage in both progression-free survival and overall survival in the chemotherapy arm but also an increase in adverse events. Recurrences were frequent in both arms (13).

The only randomized phase III trial comparing the effects of hormonal therapy in patients with advanced or recurrent endometrial cancer concluded that patients receiving low-dose medroxyprogesterone acetate (MPA) survived longer and responded to treatment better than patients treated with high-dose MPA. The best response seems to be in patients with well-differentiated tumours and positive progesterone receptor status (8,24). However, response rates varied considerably from 15% to 46% (8,23,24). This variation suggests a considerable selection bias in the patient populations studied and again speaks to the need for a properly designed trial in the future. Hormonal agents are well tolerated with adverse events occurring at a rate of less than 5% (8), although thromboembolic events have been reported as a complication in a number of studies (23,44,46,48).

There have been no randomized controlled trials regarding a treatment for patients with UPSC; however, response rates in four small non-comparative (two prospective, two retrospective) studies have ranged from 30-89% (6,9,50,51). In a Canadian prospective trial, the response rates for UPSC were lower than in advanced or recurrent non-serous endometrial cancers (60% advanced UPSC and 50% recurrent UPSC versus 78% advanced non-UPSC and 56% recurrent non-UPSC) (6), which is unexpected since previous trials have reported better responses.

VI. ONGOING TRIALS

The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials) was searched in April 2004 for reports of ongoing randomized trials.

Protocol ID(s)	Title and details of trial
GOG-189:	Phase III randomized study of doxorubicin, cisplatin, paclitaxel, and filgrastim (G-CSF) versus tamoxifen and megestrol in patients with stage III or IV or recurrent endometrial cancer. This trial will recruit approximately 630 patients and will assess quality of life. This trial is closed.
GOG-0184:	Phase III randomized adjuvant study of tumour volume-directed pelvic radiotherapy with or without paraaortic radiotherapy followed by cisplatin and doxorubicin with or without paclitaxel in patients with stage III or IV endometrial carcinoma. This trial will recruit approximately 434 patients and will assess survival, progression-frees survival and short and long term toxicity. (Summary last modified June 2003)
EORTC-55984:	Phase III randomized study of doxorubicin and cisplatin with or without paclitaxel in patients with locally advanced, metastatic, and/or relapsed endometrial cancer. This trial will recruit 312 patients and will assess survival, progression-free survival, toxicity and quality of life. (Summary last modified July 2003).

VII. IMPLICATIONS FOR POLICY

This guideline was submitted to the Policy Advisory Committee (PAC) for their meeting on September 23, 2003. At that time, PAC chose not to recommend funding because they felt that the guideline did not have a specific enough recommendation regarding the use of paclitaxel. The Gynecology Cancer DSG re-examined the evidence and decided that there was insufficient evidence to make a stronger recommendation regarding the use of paclitaxel at this time. Sub-optimal toxicity comparisons between patients with ovarian and endometrial cancer

appear to demonstrate that paclitaxel/carboplatin is associated with less leukopenia, nausea, and vomiting than is doxorubicin/cisplatin, although neurotoxicity is comparable.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the Gynecology Cancer DSG drafted the following recommendations:

Target Population

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Draft Recommendations

- Non-taxane combination chemotherapy is favoured over single-agent chemotherapy, in terms of response rate but not survival. The optimum regimen is yet to be defined.
- Platinum/paclitaxel is associated with substantially less high-grade (3 and 4) leukopenia and nausea and vomiting than doxorubicin/platinum, although neurological adverse effects are comparable.
- The addition of paclitaxel to the combination of cisplatin/doxorubicin has shown a significant response and survival advantage over doxorubicin/cisplatin; however, the use of three agents increases toxicity.
- Hormonal therapy may present a therapeutic option for the treatment of patients with minimal symptoms or non-life threatening advanced or recurrent endometrial carcinoma.
- Evidence supporting or refuting various chemotherapy regimens for UPSC is limited.
- Patients should be encouraged to participate in randomized trials.

Qualifying Statements

- The recommendation that the combination of doxorubicin/cisplatin/paclitaxel is better than doxorubicin/cisplatin in terms of survival is based on one randomized trial whose results are only published in abstract form at this time.
- When considering chemotherapy regimens for advanced or recurrent endometrial cancer, it is important to consider the toxicity of treatments—the small improved survival benefit of combination (2 or 3 agents) may not outweigh the harms associated with toxicity.
- For UPSC treatment, the most studied regimen is a paclitaxel/platinum combination. The addition of paclitaxel in small, non-comparative studies is associated with improved response rates and survival compared to non-paclitaxel containing regimens.

Future Research

In terms of future studies, it is important to be able to control for prognostic factors that affect outcome in these patient populations. Patients should be properly stratified with respect to their disease status (advanced versus recurrent), the amount of previous treatment whether it is radiation or chemotherapy, and disease recurrence either in or out of the radiated field. Patients with UPSC should be analyzed separately. Results relating to systemic therapy should be first assessed and proven in those patients with measurable disease so that an accurate assessment of any prolongation in disease-free survival can be made with reasonable assurance that these improvements are due to treatment. Treatment-related toxicity must be studied very carefully in the future in this patient population in order to ensure that the treatment

itself has acceptable morbidity in relation to the patient's quality of life, as median survival is generally limited and rarely more than a year in this patient population. Survival, response, and toxicity should be studied with regard to impact on quality of life. Comparing tumour responses for both chemotherapy and hormonal agents, stratified by grade, would provide valuable data for making treatment decisions.

Related Guidelines

Practice Guidelines Initiative's Evidence Summary Report # 4-14: *Adjuvant Chemotherapy for Early Stage Endometrial Cancer and Uterine Papillary Serous Carcinoma (in progress).*

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 81 practitioners in Ontario (11 gynecologists, 39 medical oncologists, 18 radiation oncologists, and 13 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on October 27, 2003]. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology Cancer DSG reviewed the results of the survey.

Results

Thirty-five responses were received out of the 81 surveys sent (43% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 18 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 9.

Table 9. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	17 (94%)	1 (6%)	--
There is a need for a clinical practice guideline on this topic.	15 (83%)	3 (17%)	--
The literature search is relevant and complete.	15 (88%)	2 (12%)	--
The results of the trials described in the report are interpreted according to my understanding of the data.	13 (72%)	3 (17%)	2 (11%)
The draft recommendations in this report are clear.	10 (56%)	6 (33%)	2 (11%)
I agree with the draft recommendations as stated.	11 (61%)	6 (33%)	1 (6%)
This report should be approved as a practice guideline.	10 (59%)	4 (24%)	3 (17%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	9 (50%)	5 (28%)	4 (22%)

Summary of Written Comments

Seven respondents (39%) provided written comments. The main points contained in the written comments were:

1. It appears as if no recommendations can actually really be made, so why try to make them for endometrial cancer? The recommendations are vague.
2. The recommendations are a bit too soft on the benefits of taxanes, it is surprising that non-taxane is favoured over taxane.

Modifications/Action

1. The Gynecology Cancer DSG acknowledges that there is limited evidence to make recommendations and thus the recommendations are vague. Nonetheless, the Gynecology Cancer DSG felt it was important to present the available evidence and to make recommendations based on the evidence. This guideline will be updated as new evidence becomes available, and as the data emerges, the Gynecology Cancer DSG will revise their recommendations as necessary.
2. The Gynecology Cancer DSG reviewed their original recommendations regarding taxanes and non-taxanes. The DSG agreed that the recommendation regarding non-taxanes was misleading and thus have modified the recommendation.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the PGCC for review and approval. Seven of 14 members of the PGCC returned ballots. Four PGCC members approved the practice guideline report as written, and one member approved the report with a minor editorial change to the recommendations required. One member approved the report conditional on the Gynecology DSG clarifying the recommendations. One PGCC member did not approve the report because the member was concerned that the guideline placed too much emphasis on the abstract by Fleming et al comparing doxorubicin/cisplatin to doxorubicin/paclitaxel/cisplatin. The PGCC member thought that the Gynecology DSG should wait until the RCT was reported in a full publication before making recommendations based on the trial.

Modifications/Actions

The wording of the recommendations was clarified as per the suggestions of two PGCC members. This practice guideline was submitted to the PGCC members for review on May 15, 2004. On June 1, 2004 the Fleming et al RCT comparing doxorubicin/cisplatin to doxorubicin/paclitaxel/cisplatin was published in a full report in the *Journal of Clinical Oncology* (11). The Gynecology Cancer DSG has updated the guideline to include the full publication. The results of the full publication are consistent with the abstract data presented previously and thus the Gynecology Cancer DSG did not revise their recommendations based on the full publication.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Gynecology Cancer DSG and by the Practice Guidelines Coordinating Committee.

Target Population

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Recommendations

For women with advanced or recurrent endometrial cancer:

- Combination chemotherapy is favoured over single-agent chemotherapy because of higher response rates.
- Paclitaxel in combination with cisplatin/doxorubicin chemotherapy improves both response rate and median survival; however, the use of this three-drug combination is associated with increased toxicity.
- Hormonal therapy may be a therapeutic option for those patients with minimal symptoms or non-life threatening advanced or recurrent endometrial cancer.

For women with UPSC:

- Evidence supporting or refuting various chemotherapy regimens for UPSC is limited.
- Patients should be encouraged to participate in randomized trials.

Qualifying Statements:

- The decision to use the three-drug combination, consisting of cisplatin/doxorubicin/paclitaxel, should be made in consultation with the patient. Consideration needs to be given to both the greater toxicity and the three-month increase in median survival time achieved with the three-drug combination in comparison with the two drug doxorubicin/cisplatin regimen.
- For UPSC treatment, the most studied regimen is a paclitaxel/platinum combination. The addition of paclitaxel in small, non-comparative studies is associated with improved response rates and survival compared to non-platinum containing regimens.

Future Research

In terms of future studies, it is important to be able to control for prognostic factors that affect outcome in these patient populations. Patients should be properly stratified with respect to their disease status (advanced versus recurrent), the amount of previous treatment, type of previous treatment (radiation or chemotherapy), and disease recurrence either in or out of the radiated field. Patients with UPSC should be analyzed separately. Results relating to systemic therapy should be first assessed and proven in those patients with measurable disease so that an accurate assessment of any prolongation in disease-free survival can be made with reasonable assurance that these improvements are due to treatment. Treatment-related toxicity must be studied very carefully in the future in this patient population in order to ensure that the treatment itself has acceptable morbidity in relation to the patient's quality of life, as median survival is generally limited and rarely more than a year in this patient population. Survival, response and toxicity should be studied with regard to impact on quality of life. Comparing tumour responses for both chemotherapy and hormonal agents, stratified by grade, would provide valuable data for making treatment decisions.

Related Guidelines

Practice Guidelines Initiative's Evidence Summary Report # 4-14: *Adjuvant Chemotherapy for Early Stage Endometrial Cancer and Uterine Papillary Serous Carcinoma (in progress).*

X. JOURNAL REFERENCE

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For a complete list of the Gynecology Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at: http://www.cancercare.on.ca/access_PEBC.htm.

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Appendix 1.

Table A. Studies on systemic therapy for advanced or recurrent endometrial cancer.

Drug or combination	Evidence	Reference number
Chemotherapy		
carboplatin	2 phase II trials 1 prospective cohort	(40-42)
paclitaxel - alone paclitaxel - with carboplatin - with cisplatin - with epirubicin and cisplatin	3 phase II trials 2 phase II trials 1 prospective cohort 1 phase II trial 1 prospective cohort 1 prospective cohort	(5,37,39) (6,28) [1 abstract] (36) (29) (33) [abstract] (35)
oral etoposide	2 phase II trials	(32,38)
dactinomycin	1 phase II trial	(31)
topotecan - alone - with cisplatin	1 phase II trial 1 phase II trial	(26) (30) [abstract]
liposomal doxorubicin	1 phase II trial	(27)
vinorelbine – with carboplatin	1 prospective cohort	(34) [abstract]
Hormonal Therapy		
gonadotrophin-releasing hormone and luteinizing hormone-releasing hormone analogs	1 prospective cohort 2 phase II trials	(49) (47,48)
aromatase inhibitors	2 phase II trials	(44,46) [1 abstract]
LY353381 (selective estrogen receptor modulator)	2 phase II trials	(45) (43)[abstracts]

Table B. Description of participants in prospective single-cohort studies of chemotherapy.

Study	Chemotherapy	# entered (eligible)	Recurrent disease (%)	Advanced disease (%)	Performance status	% with prior HT	% with prior CT	% with prior RT
Muggia, 2002 (27)	liposomal doxorubicin	46 (42)	42 (100%)	0	GOG 0-1: 86% 2: 14%	26%	95%	69%
Hoskins, 2001 (6)	paclitaxel/ carboplatin	39 (39)	18 (46%)	21 (54%)	ECOG <=3	NR	none	NR
Miller, 2002 (26)	topotecan	29 (22)	NR	NR	0-1: 91% 2: 9%	14%	100%	41%
Scudder, 2001 (28)	paclitaxel/ carboplatin	57 (49)	NR	NR	NR	NR	none	NR
Dimopoulos, 2000 (29)	paclitaxel/ cisplatin	24 (24)	14 (59%)	10 (42%)	ECOG 0-1: 84% 2: 17%	NR	none	4%
Hall, 2000 (30)	topotecan/ cisplatin	8 (8)	NR	NR	0-2: 100%	NR	none	75%
Moore, 1999 (31)	dactinomycin	27 (27)	NR	NR	GOG 0-3: 100%	NR	100%	48%
Poplin, 1999 (32)	oral etoposide	47 (44)	23 (52%)	21 (48%)	0-1: 84% 2: 16%	47%	none	77%
Trudeau, 1999 (33)	paclitaxel/ cisplatin	8 (8)	NR	NR	NR	NR	none	NR
Santoro, 1998 (34)	vinorelbine/ carboplatin	13 (13)	0	13 (100%)	ECOG 0-3: 100%	NR	NR	NR
Lissoni, 1997 (35)	paclitaxel /cisplatin/ epirubicin	27 (27)	10 (37%)	17 (63%)	WHO 0-1: 100%	NR	none	20%
Price, 1997 (36)	paclitaxel/ carboplatin	14 (8)	5 (63%)	3 (37%)	NR	NR	NR	NR

Study	Chemotherapy	# entered (eligible)	Recurrent disease (%)	Advanced disease (%)	Performance status	% with prior HT	% with prior CT	% with prior RT
Ball, 1996 (5)	paclitaxel	30 (28)	NR	NR	GOG 0-1: 86% 2: 14%	18%	none	50%
Lissoni, 1996 (37)	paclitaxel	19 (19)	7 (37%)	12 (63%)	NR	NR	100% (PAC)	32%
Rose, 1996 (38)	oral etoposide	26 (25)	NR	NR	GOG 0-2: 100%	NR	96%	56%
Woo, 1996 (39)	paclitaxel	7 (7)	6 (86%)	1 (14%)	NR	NR	all platinum resistant	NR
Burke, 1993 (40)	carboplatin	33 (33)	16 (48%)	17 (52%)	Zubrod $\leq$2	21%	none	67%
Green, 1990 (41)	carboplatin	32 (23)	NR	NR	0-1: 70% 2: 30%	43%	none	78%
Long, 1988 (42)	carboplatin	26 (25)	NR	NR	ECOG 0-1: 72% 2-3: 28%	76%	none	80%

Note: CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; GOG, Gynecologic Oncology Group; HT, hormonal therapy; NR, not reported; PAC, paclitaxel; RT, radiotherapy; WHO, World Health Organization

Table C. Description of participants in trials of hormonal therapy.

Study	Hormonal therapy	# entered (eligible)	Performance status	Recurrent disease (%)	Advanced disease (%)	% with prior HT	% with prior CT	% with prior RT
McMeekin, 2001 (43)	LY353381	37 (29)	NR	NR	NR	allowed	none	NR
Sidhu, 2001 (44)	letrozole	17 (17)	NR	NR	NR	29%	none	82%
Klijn, 2000 (45)	LY353381	37 (35)	Karnofsky 50-100	NR	NR	NR	8%	53%
Rose, 2000 (46)	anastrozole	23 (23)	GOG 0-1: 74% 2-3: 26%	15 (65%)	8 (35%)	17%	none	35%
Lhomme, 1999 (47)	triptorelin	25 (24)	WHO 0-2	21 (84%)	4 (16%)	8%	12%	84%
Covens, 1997 (48)	leuprolide acetate	25 (25)	GOG 0-1: 68% 2-3: 32%	17 (68%)	8 (32%)	72%	8%	36%
Jeyarajah, 1996 (49)	leuprolide acetate	32 (32)	NR	32 (100%)	0	72%	NR	88%

Note: CT, chemotherapy; GOG, Gynecologic Oncology Group; HT, hormonal therapy; NR, not reported; RT, radiotherapy; WHO, World Health Organization

Table D. Survival data of chemotherapy for advanced or recurrent endometrial cancer.

Study	Chemotherapy	# patients	Median Survival (months)
Muggia, 2002 (27)	liposomal doxorubicin	41 [a]	8.2
Hoskins, 2001 (6)	paclitaxel/carboplatin	49	Advanced 23 [b] Recurrent 15
Scudder, 2001 (28) [abstract]	paclitaxel/carboplatin	49	10
Dimopoulos, 2000 (29)	paclitaxel/cisplatin	10	17.6 [d]
Poplin, 1999 (32)	oral etoposide	44 [c]	11
Ball, 1996 (5)	paclitaxel	28	9.5
Green, 1990 (41)	carboplatin	23	9.4
Long, 1988 (42)	carboplatin	25	7.2

[a] Includes five patients with UPSC
[b] Median failure-free survival (overall survival not yet reached)
[c] Patients with metastases
[d] Includes patients with stage I-IV disease

Table E. Tumour response data from clinical trials of chemotherapy for advanced or recurrent endometrial cancer.

Study	Regimen	# evaluated	# complete responses (CR)	# partial responses (PR)	Response rate (CR + PR) (%)
Miller, 2002 (26)	topotecan	22	1	1	2 (9%)
Muggia, 2002 (27)	liposomal doxorubicin	42	0	4	4 (10%)
Hoskins, 2001 (6)	paclitaxel/carboplatin	advanced 9 recurrent 18	2 1	5 9	7 (78%) 10 (50%)
Dimopoulos, 2000 (29)	paclitaxel/cisplatin	24	7	9	16 (67%)
Hall, 2000 (30) [abstract]	topotecan/cisplatin	6	3	0	3 (38%)
Moore, 1999 (31)	dactinomycin	24	1	2	3 (12%)
Poplin, 1999 (32)	oral etoposide	44	1	5	6 (14%)
Trudeau, 1999 (33) [abstract]	paclitaxel/cisplatin	8	1	5	6 (75%)
Santoro, 1998 (34) [abstract]	carboplatin/vinorelbine	13	3	6	9 (69%)
Lissoni, 1997 (35)	paclitaxel/cisplatin/epirubicin	27	6	15	21 (78%)
Price, 1997 (36)	paclitaxel/carboplatin	8	0	5	5 (63%)
Ball, 1996 (5)	paclitaxel	28	4	6	10 (36%)
Lissoni, 1996 (37)	paclitaxel	19	2	5	7 (37%)
Rose, 1996 (38)	oral etoposide	22	0	0	0
Woo, 1996 (39)	paclitaxel	7	0	3	3 (43%)
Burke, 1993 (40)	carboplatin	27	3	6	9 (33%)
Green, 1990 (41)	carboplatin	23	2	5	7 (30%)
Long, 1988 (42)	carboplatin	25	0	7	7 (28%)

Table F. Serious adverse event data (Grade 3/4) from clinical trials of chemotherapy for advanced or recurrent endometrial cancer.

Study	# patients	Treatment	Leukopenia	Thrombo-cytopenia	Gastro-intestinal
Miller, 2002 (26)	28	topotecan	75%	39%	14%
Scudder, 2001 (28) [abstract]	49	paclitaxel/carboplatin	33%	not reported	4%
Dimipoulos, 2000 (29)	24	paclitaxel/cisplatin/GCSF	22%	0%	9%
Hall, 2000 (30) [abstract]	6	topotecan/cisplatin	63%	25%	not reported
Moore, 1999 (31)	24	dactinomycin	44%	11%	15%
Poplin, 1999 (32)	44	oral etoposide	11%	2%	9%
Lissoni, 1997 (35)	27	paclitaxel/cisplatin/epirubicin	61%	8%	not reported
Price, 1997 (36)	8	paclitaxel/carboplatin	79%	5%	0
Ball, 1996 (5)	28	paclitaxel	62%	7%	17%
Lissoni, 1996 (37)	19	paclitaxel	11%	0	0
Rose, 1996 (38)	22	oral etoposide	52%	16%	4%
Long, 1988 (42)	25	carboplatin	not reported	not reported	28%

Note: GCSF, granulocyte-colony-stimulating factor

Table G. Survival data of hormonal therapy for advanced or recurrent endometrial cancer.

Study	Hormonal therapy	Median Survival (months)	Log-rank p-value
Rose, 2000 (46)	anastrozole	6	-
Lhomme, 1999 (47)	triptorelin	7.2	-
Covens, 1997 (48)	leuprolide acetate	9	-

Table H. Tumour response data from clinical trials of hormonal therapy for advanced or recurrent endometrial cancer.

Study	Regimen	# evaluated	# complete responses (CR)	# partial Responses (PR)	Response rate (CR + PR) (%)
Sidhu, 2001 (44) [abstract]	letrozole	10	0	2	2 (20%)
Klijn, 2000 (45) [abstract]	LY353381	32	0	7	7 (22%)
Rose, 2000 (46)	anastrozole	23	0	2	2 (9%)
Lhomme, 1999 (47)	triptorelin	23	1	1	2 (9%)
McMeekin, 1999 (43) [abstract]	LY353381	29	1	8	9 (31%)
Covens, 1997 (48)	leuprolide acetate	25	0	0	0
Jeyarajah, 1996 (49)	leuprolide acetate	32	2	7	9 (28%)

Appendix 2. Regimens studied in clinical trials of systemic therapy for advanced or recurrent endometrial cancer.

Table A. Chemotherapy.

Study	Drugs*	Doses	Schedule
Comparative studies (Randomized trials)			
Fleming, 2004 (11)	Doxorubicin + cisplatin Doxorubicin + cisplatin + paclitaxel	60 mg/m^2 50 mg/m^2 45 mg/m^2 50 mg/m^2 160 mg/m^2	every 3 weeks
Aapro, 2003 (12)	doxorubicin doxorubicin + cisplatin	60 mg/m^2 60 mg/m^2 50 mg/m^2	every 4 weeks
Fleming, 2000 [abstract] (15)	doxorubicin + cisplatin doxorubicin + paclitaxel	60 mg/m^2 50 mg/m^2 50 mg/m^2 150 mg/m^2 over 24 hours	every 3 weeks
Pawinski, 1999 (16)	cyclophosphamide ifosfamide	1200 mg/m^2 5g/m^2	every 3 weeks
Thigpen, 1994 (7)	doxorubicin doxorubicin + cyclophosphamide	60 mg/m^2 60 mg/m^2 500 mg/m^2	every 3 weeks
Thigpen, 1993 [abstract] (18)	doxorubicin doxorubicin + cisplatin	60 mg/m^2 60 mg/m^2 50 mg/m^2	every 3 weeks
Edmonson, 1987 (19)	cisplatin cyclophosphamide + doxorubicin + cisplatin	60 mg/m^2 400 mg/m^2 40 mg/m^2 40 mg/m^2	every 3 weeks every 4 weeks
Cohen, 1984 (20)	megestrol (oral) + melphalan (oral) + 5-fluorouaracil megestrol (oral) + cyclophosphamide + doxorubicin + 5-fluorouracil	180 mg 7 mg/m^2 525 mg/m^2 180 mg 400 mg/m^2 40 mg/m^2 400 mg/m^2	daily for 8 weeks day 1-4 of 28 day 1-4 of 28 daily for 8 weeks day 1 of 21 day 1 of 21 day 1 of 21
Horton, 1982 (21)	megestrol (oral) + cyclophosphamide + doxorubicin megestrol (oral) + cyclophosphamide + doxorubicin + 5-fluorouracil	80 mg 400 mg/m^2 40 mg/m^2 80 mg 250 mg/m^2 30 mg/m^2 300 mg/m^2	three times daily day 1 of 28 day 1 of 28 three times daily day 1 of 28 day 1 of 28 days 1-3 of 28
Horton, 1978 (22)	doxorubicin cyclophosphamide	50 mg/m^2 666 mg/m^2	every 3 weeks

* intravenous unless noted otherwise

Table A. Chemotherapy (cont.).

Study	Drugs*	Doses	Schedule
Non-comparative studies (single-cohort)			
Muggia, 2002 (27)	liposomal doxorubicin	50 mg/m^2	every 4 weeks
Miller, 2002 (26)	topotecan	1.5 mg^2/day X 5 days	every 3 weeks
Scudder, 2001 [abstract] (28)	paclitaxel + carboplatin	175 mg/m^2 over 3 hours area under the curve = 5	not reported
Dimopoulos, 2000 (29)	paclitaxel + cisplatin	175 mg/m^2 over 3 hours 75 mg/m^2	every 3 weeks
Hall, 2000 [abstract] (30)	topotecan + cisplatin	0.75 mg^2/day X 5 days 50 mg/m^2	not reported
Moore, 1999 (31)	dactinomycin	2 mg/m^2	every 4 weeks
Poplin, 1999 (32)	etoposide (oral)	50 mg on days 1-21	every 4 weeks
Trudeau, 1999 [abstract] (33)	paclitaxel + cisplatin	135 mg/m^2 over 24 hours 75 mg/m^2	every 3 weeks
Santoro, 1998 [abstract] (34)	carboplatin + vinorelbine	300 mg/m 25 mg/m^2 on days 1 & 8	every 3 weeks
Lissoni, 1997 (35)	paclitaxel + cisplatin + epirubicin	175 mg/m^2 over 3 hours 50 mg/m^2 70 mg/m^2	every 3 weeks
Price, 1997 (36)	paclitaxel + carboplatin	175 mg/m^2 over 3 hours area under the curve = 5	every 4 weeks
Ball, 1996 (5)	paclitaxel	250 mg/m^2 over 24 hours	every 3 weeks
Lissoni, 1996 (37)	paclitaxel	175 mg/m^2 over 3 hours	every 3 weeks
Rose, 1996 (38)	etoposide (oral)	50 mg/m^2 on days 1-21	every 4 weeks
Woo, 1996 (39)	paclitaxel	170 mg/m^2 over 3 hours	every 3 weeks

* intravenous unless noted otherwise

Table B. Hormonal therapy.

Study	Drugs	Doses	Route	Schedule
Comparative studies (Randomized trials)				
Pandya, 2001 (23)	megestrol acetate megestrol acetate + tamoxifen	80 mg 80 mg 10 mg	oral oral	twice daily
Thigpen, 1999 (8)	medroxyprogesterone acetate vs medroxyprogesterone acetate	200 mg 1,000 mg	Oral oral	Daily Daily
Rendina, 1984 (24)	medroxyprogesterone acetate tamoxifen	1 g 20mg	intramuscular oral	weekly twice daily
Non-comparative studies (single-cohort)				
McMeekin, 2001 [abstract] (43)	LY353381	20 mg	oral	Daily
Sidhu, 2001 [abstract] (44)	letrozole	2.5 mg	oral	daily
Klijn, 2000 [abstract] (45)	LY353381	20 mg	oral	daily
Rose, 2000 (46)	anastrozole	1 mg	oral	daily
Lhomme, 1999 (47)	triptorelin	3.75 mg	intramuscular	every 4 weeks
Covens, 1997 (48)	leuprolide acetate	7.5 mg	intramuscular	every 4 weeks
Jeyarajah, 1996 (49)	leuprolide acetate	3.5 - 7.5 mg	intramuscular	monthly

Table C. Combined chemotherapy and hormonal therapy.

Study	Drugs	Doses	Route	Schedule
Ayoub, 1988 (25) (randomized trial)	cyclophosphamide	400 mg/m^2	intravenous	days 1 and 8 of 28
	+ doxorubicin	30 mg/m^2	intravenous	day 1 of 28
	+ 5-fluorouracil	400 mg/m^2	intravenous	days 1 and 8 of 28
	cyclophosphamide	400 mg/m^2	intravenous	days 1 and 8 of 28
	+ doxorubicin	30 mg/m^2	intravenous	day 1 of 28
	+ 5-fluorouracil	400 mg/m^2	intravenous	days 1 and 8 of 28
	+ medroxyprogesterone*	200 mg	oral	daily for 3 weeks*
	followed by tamoxifen*	20 mg	oral	daily for 3 weeks*

* medroxyprogesterone and tamoxifen were given sequentially for one year

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 4-8 Version 4: Section 2

Systemic Therapy for Advanced or Recurrent Endometrial Cancer, and Advanced or Recurrent Uterine Papillary Serous Carcinoma

Guideline Review Summary

A. Covens, L. Durocher-Allen, and Members of the Expert Panel on Endometrial Cancer or Uterine Papillary Serous Carcinoma

July 23, 2019

The 2004 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2004. In 2013, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (RP) conducted an updated search of the literature from 2004 to 2013 and the data supported the 2004 recommendations. Please see Appendix A for this document summary and review table. In 2016, this document was assessed again and in accordance with the PEBC Document Assessment and Review Protocol, was determined to require a review. As part of the review, a PEBC methodologist (DS) conducted an updated search of the literature from 2013 to 2017 and the data supported the 2004 recommendations. Please see Appendix B for this document summary and review table.

In 2018, this document was assessed again and in accordance with the PEBC Document Assessment and Review Protocol was determine to require a review. An updated search of the literature from 2017 to 2019 was performed by a PEBC methodologist (LDA) and a clinical expert (AC) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Expert Panel on Endometrial Cancer and Uterine Papillary Serous Carcinoma (Appendix 1) endorsed the recommendations found in Section 1 (Practice Guideline Report) on July 23, 2019.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

1. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?
2. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma?

Literature Search and New Evidence

The literature search strategy is shown in Appendix 2. The new search (May 2017 to May 2019) yielded 1 practice guideline, 1 RCT, and 2 non-randomized phase II trials. An additional search for ongoing studies on clinicaltrials.gov yielded 7 potentially relevant ongoing trials. Brief results of these publications are shown in the Document Summary and Review Tool.

Impact on the Guideline and Its Recommendations

The new data from the latest updated literature search do not change the existing recommendations. Recently, there has been one small randomized phase II study showing a benefit of adding trastuzumab to carboplatin/paclitaxel in patients with overexpression of Her2/Neu in advanced (stage III or IV) or recurrent uterine serous carcinoma (3). To highlight that new research results are becoming available, this has been noted in a qualifying statement accompanying the recommendations in Section 1. The Expert Panel ENDORSED the 2004 recommendations on the chemotherapeutic and hormonal therapy options for advanced or recurrent endometrial cancer and advanced or recurrent uterine papillary serous carcinoma.

Number and Title of Document under Review	Guideline 4-8 Version 3: Systemic therapy for advanced or recurrent endometrial cancer and advanced or recurrent uterine papillary serous carcinoma
Current Report Date	March 6, 2014
Clinical Expert	Dr. Allan Covens
Research Coordinator	Lisa Durocher-Allen
Date Assessed	October 26, 2018
Approval Date and Review Outcome (once completed)	July 23, 2019 ENDORSED

Original Question(s):

1. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?
2. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma?

Target Population:

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Study Selection Criteria:

Inclusion Criteria
Evidence-based clinical practice guidelines or systematic reviews regarding systemic therapy for advanced disease from other guideline-development groups were eligible for inclusion.

To address the question regarding the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer, full articles or abstracts of randomized controlled trials (RCTs) were selected for inclusion if they met the following criteria:

1. RCTs or meta-analyses comparing regimens of systemic chemotherapy or hormonal therapy to the standard treatment for advanced or recurrent endometrial cancer reporting at least one of the following outcomes: survival, quality of life, response

rate, or toxicity.
2. RCTs that reported on heterogeneous populations (e.g., included women with a range of disease stages) were eligible if results were given separately for the group with advanced or recurrent endometrial cancer.
3. When RCTs were not available, phase II trials of chemotherapy and hormonal therapy agents were included.

To address the question regarding the chemotherapeutic options for women with advanced or recurrent UPSC, full articles or abstracts of RCTs were selected for inclusion if they met the following criteria:

1. RCTs comparing systemic therapy regimens that included women with stage IIIc or IV UPSC with measurable or evaluable disease at the start of systemic therapy, and reported at least one of the following outcomes: survival, quality of life, response rate, or toxicity.
2. When RCTs were not available, phase II trials of chemotherapy agents were included.

Exclusion Criteria

1. Non-English language publications were excluded.
2. Studies evaluating the role of radiotherapy, administered with chemotherapy or hormonal therapy, were excluded.

Search Details:

- March 8 2017 to March 21, 2019(MEDLINE, EMBASE)
- March 8, 2018 to May 21, 2019 (ASCO annual meetings, the Cochrane library, clinicaltrials.gov, the National Guidelines Clearinghouse, and the Canadian Medical Association Infobase)

Summary of New Evidence:

Of 204 totals hits from MEDLINE and EMBASE + 362 hits from ASCO and 24 hits from clinicaltrials.gov + 15 hits from Canadian Medical Association Infobase, 4 references representing 1 practice guideline, 1 RCT (full publication) and 2 non randomized phase II trials (1 full publication and 1 abstract) were included. There were 7 ongoing trials identified. Details from the included trials are summarized in the tables below.

Clinical Expert Interest Declaration:

None.

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
2. Does the newly identified evidence support the existing recommendations?	Yes

3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes
Review Outcome as recommended by the Clinical Expert	Endorse
If outcome is UPDATE, are you aware of trials now underway (not yet published) that will impact recommendations?	N/A
DSG/GDG Commentary	The emerging role of immunotherapy should be mentioned in the Future Research section. A statement was added to the section. It is acknowledged that the guideline will require a full update when next reviewed.

Guidelines

Reference	Recommendations
Santaballa et al. (2017) (1) Spanish Society of Medical Oncology (SEOM) guideline Consensus based	• Endocrine therapy is recommended as a therapeutic alternative for those patients with G1-2 tumors, hormones receptor positive and no rapid progressive disease [IV, A]. • Carboplatin and paclitaxel is the standard option in metastatic or advanced endometrial cancer [I, A]. There is no standard CT for second line.

Abbreviations: CT: computed tomography

Published Controlled Trials

Author, year, reference	Population	N	Median Follow-up	Intervention/ Comparison	Outcomes of interest	Brief results
Aghajanian et al. 2018 (2) 3 arm single stage, historically controlled, randomized phase II	Eligible patients had FIGO stage III or IVA (with measurable disease) or Stage IVB or recurrent (with or without measurable disease) endometrial cancer	349		Arm 1: D1 : paclitaxel 175 mg/m2 IV over 3 h, carboplatin AUC 6 IV over 30 min,followed by bevacizumab 15 mg/kg IV.Pts with prior pelvic radiation received paclitaxel at 135 mg/m2 and carboplatin at AUC 5 Arm 2: D1: paclitaxel 175 mg/m2 IV over 3 h and carboplatin AUC 5 IV over 30 min. Temsirolimus 25 mg IV on d1 & 8 (concurrent with chemo) and d1, 8 and 15 (during maintenance). Pts with prior pelvic radiation therapy received paclitaxel at 135 mg/m2 and temsirolimus at 20mg Arm 3: D1 ixabepilone 30 mg/m2 IV over 1 h, carboplatin AUC 6 IV over 30 min, followed by bevacizumab 15mg/kg IV. Pts with prior pelvic radiation received ixabepilone at 25mg/m2 and carboplatin at AUC 5. 462 patients from	PFS Response rate OS duration (censoring at 36 months) Any adverse event grades ≥3 Serious adverse	• PFS compared using a log-rank test on data grouped by time intervals was not statistically significantly better in any experimental Arm ($p > 0.039$) when each Arm was compared to historical controls • HR (92.2% CI) for Arms 1, 2, and 3 relative to the historical reference Arm were 0.81 (0.63 to 1.02), 1.22 (0.96 to 1.55), and 0.87 (0.68 to 1.11), • Overall response rates were 59%, 55%, 53%, and 51% in Arms 1, 2, 3, and the historical reference Arm. • Overall survival in Arm 1

				another study with similar disease characteristics formed a historical control group.	event grades ≥3	significantly (p<0.039) increased relative to the historical reference. • HR (92.2%CI) for Arms 1, 2, and 3 relative to the historical reference Arm were 0.71 (0.55 to 0.91), 0.99 (0.78 to 1.26), and 0.97 (0.77 to 1.23), • PC + bevacizumab = 93.7% • PC + temsirolimus = 98.2% • IC + bevacizumab= 95.6% • PC + bevacizumab = 40.2% • PC + temsirolimus = 44.2% • IC + bevacizumab= 44.7%
Fader et al. 2018 (3) Aug 2011-Mar 2017 Phase II, 11 academic institutions in US, randomized (1:1)	Pts with advance (stage III or IV) or recurrent uterine serous carcinoma who overexpress Her2/neu-positive disease	61	N/A	Carboplatin/paclitaxel (control) vs Carboplatin/paclitaxel + trastuzumab	PFS	• all pts: 8.0 (control) vs 12.6 (experimental) months, HR 0.44 (90% CI 0.26 to 0.76); p=0.005 • stage III-IV undergoing primary treatment (n=41): 9.3 (control) vs 17.9 (experimental)

						months, HR 0.40 (90% CI, 0.20 to 0.80); p = 0.013 • Recurrent disease (n=17): 6.0 (control) vs 9.2 (experimental) months, HR 0.14 (90% CI 0.05 to 0.54); p = 0.003

Abbreviations: AE- adverse events, AUC- Area under the curve, CI – confidence interval, D1: Day 1, FIGO: International Federation of Gynecology and Obstetrics, HR: hazard ratio, IC- ixabepilone and carboplatin, IV- Intravenously, NS- not significant, OS- overall survival, PC- paclitaxel and carboplatin, PFS- progression-free survival, STS- steroid sulphatase

Abstracts

Author, year, reference	Population	N	Median Follow-up	Intervention/ Comparison	Outcomes of interest	Brief results
Makker et al. 2018 (4) Phase II NCT02501096	Pts with histologically confirmed EC irrespective of MSI/MMR Status and measurable disease	54	4 months	Lenvatinib 20mg PO QD plus pembrolizumab 200mg Q3W, IV.	ORR (24 wks) ORR PFS	• ORR 50.0% (95% CI, 32.4 to 67.6) • ORR 36.7% (95% CI,23.4 to 51.7) • median PFS 10.1 months (95% CI, 5.3 to NE).

CI: Confidence interval; EC: endometrial cancer; HR: hazard ratio; IV: intravenous; MSI: microsatellite instability; MMR: mismatch repair; NE: not estimable; ORR: objective response rate; PFS: progression free survival; PO QD: per os quaque die (Latin: one tablet by mouth once a day); Q3W: every 3 weeks

Ongoing Trials

Protocol ID	Official Title	Intervention/ Comparison	Status
NCT01461759	A Phase II Trial of Docetaxel / Cisplatin in Patients With Recurrent or Stage IVb Endometrial Cancer	Doctaxel + Cisplatin	Recruiting
NCT03884101	A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma (LEAP-001)	Lenvatinib + Pembrolizumab vs Pacilitaxel + Carboplatin	Recruiting
NCT02584478	A Phase 1/2a Evaluation of the Safety and Efficacy of Adding AL3818, a Dual Receptor Tyrosine Kinase Inhibitor, to Standard Platinum-Based Chemotherapy, in Subjects With Recurrent or Metastatic Endometrial, Ovarian, Fallopian, Primary Peritoneal or Cervical Carcinoma (AL3818-US-002)	AL3818 + Carboplatin + Pacilitaxel vs Paciltaxel _ Carboplatin	Recruiting
NCT03570437	A 3-Arm Randomised Phase II Evaluation of Cediranib in Combination With Weekly Paclitaxel or Olaparib Versus Weekly Paclitaxel Chemotherapy for Advanced Endometrial Carcinoma or for Disease Relapse Within 18 Months of Adjuvant Carboplatin-paclitaxel Chemotherapy.	Pacilataxel vs Cediranib vs Olaparib	Recruiting
NCT02725268	A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3Kα Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer	Pacilitazel vs MLN0128 + MLN1117	Active, not recruiting
NCT02730416	ENGOT-EN1/FANDANGO: A Randomized Phase II Trial of First-line Combination Chemotherapy With Nintedanib / Placebo for Patients With Advanced or Recurrent Endometrial Cancer	Nintedanib vs Carboplatin + Paclitaxel	Recruiting
NCT03914612	A Phase III Randomized, Placebo-Controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer	Paclitaxel + Carboplatin vs Pembrolizumab +Paclitaxel + Carboplati	Not yet recruiting

References

1. Santaballa A, Matias-Guiu X, Redondo A, Carballo N, Gil M, Gomez C, et al. SEOM clinical guidelines for endometrial cancer (2017). Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico. 2018 Jan;20(1):29-37. PubMed PMID: 29238915. English.
2. Aghajanian C, Filiaci V, Dizon DS, Carlson JW, Powell MA, Secord AA, et al. A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. Gynecol Oncol. 2018 08;150(2):274-81. PubMed PMID: 29804638. English.
3. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu. J Clin Oncol. 2018 Jul 10;36(20):2044-51. PubMed PMID: 29584549. Epub 2018/03/28. eng.
4. Makker V, Rasco D, Vogelzang NJ, Messing M, Brose MS, Cohn AL, et al. Lenvatinib+pembrolizumab in patients with advanced endometrial cancer: Updated results. Asia Pac J Clin Oncol. 2018 November;14 (Supplement 7):175. PubMed PMID: 625147390. English.

Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest
Laurie Elit Gynecologic Oncology	Juravinksi Cancer Centre Hamilton, ON	No conflict of interest declared
Anthony Fyles Radiation Oncology	Princess Margaret Hospital Toronto, ON	No conflict of interest declared
Hal Hirte Medical Oncology	Juravinksi Cancer Centre Hamilton, ON	Received $500 or more in a single year in a consulting capacity for AstraZeneca - consultant, speaker; Merck - consultant
Lua Eiriksson Gynecologic Oncology	Juravinksi Cancer Centre Hamilton, ON	No conflict of interest declared
Kara Schnarr Radiation Oncology	Juravinksi Cancer Centre Hamilton, ON	Received a grant from the Juravinski Cancer Centre foundation for an ICES database project that is looking into the use of preoperative imaging in endometrial cancer
Neesha Dhani Medical Oncology	Princess Margaret Hospital Toronto, ON	No conflict of interest declared

Appendix 2. LITERATURE SEARCH STRATEGY

MEDLINE

1 exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/ (116958)
2 (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt. (451866)
3 random allocation/ or double blind method/ or single blind method/ (246188)
4 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. (174430)
5 or/1-4 (736996)
6 (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/ (1038049)
7 (clinical trial or clinical trial, phase II or controlled clinical trial).pt. (547410)
8 (6 or 7) and random$.tw. (417618)
9 (clinic$ adj trial$1).tw. (288304)
10 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw. (153373)
11 placebos/ (34211)
12 (placebo? or random allocation or randomly allocated or allocated randomly).tw. (211842)
13 (allocated adj2 random).tw. (777)
14 or/9-13 (528750)
15 5 or 8 or 14 (1015338)
16 (systematic adj (review: or overview:)).mp. (99583)
17 (meta-analy: or metaanaly:).mp. (134852)
18 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp. (8233)
19 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (97245)
20 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (143815)
21 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab. (34848)
22 or/16-21 (285724)
23 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic:
quality).ab. (56553)
24 (stud: adj1 select:).ab. (18816)
25 (23 or 24) and review.pt. (37270)
26 22 or 25 (289745)
27 (guideline or practice guideline).pt. (29068)
28 exp consensus development conference/ (10553)
29 consensus/ (7502)
30 (guideline: or recommend: or consensus or standards).ti. (132461)
31 27 or 28 or 29 or 30 (151002)
32 26 or 31 (432799)
33 exp endometrial neoplasms/ (18308)
34 exp uterine neoplasms/ (118292)
35 (endometri$ and (cancer$ or neoplas$ or carcin$ or malig$ or tumo$)).tw. (36268)
36 uterine papillary serous carcinoma.tw. (258)
37 or/33-36 (133262)
38 (advance$ or recur$).tw. (1056753)
39 37 and 38 (17084)
40 exp drug therapy/ (1198463)
41 exp drug therapy combination/ (292014)
42 exp chemotherapy/ (1198463)
43 exp hormone/ (1282465)
44 exp antineoplastic agents/ (942137)

45 chemothera$.tw. (337247)
46 (hormon$ adj3 thera$).tw. (37250)
47 or/40-46 (3050235)
48 39 and 47 (6447)
49 15 or 32 (1355555)
50 48 and 49 (1213)
51 (comment or letter or editorial or news or newspaper article or patient education handout or case reports or historical article).pt. (3696809)
52 50 not 51 (1176)
53 exp animal/ not human/ (4327457)
54 52 not 53 (1172)
55 limit 54 to english language (1098)
56 (201312: or 2014: or 2015: or 2016: or 2017:).ed. (3384919)
57 55 and 56 (234)

EMBASE

1 exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/ (462121)
2 randomization/ or single blind procedure/ or double blind procedure/ (231987)
3 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. (241506)
4 or/1-3 (693712)
5 (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/ (1511667)
6 5 and random$.tw. (458648)
7 (clinic$ adj trial$1).tw. (385919)
8 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw. (199194)
9 placebo/ (304439)
10 (placebo? or random allocation or randomly allocated or allocated randomly).tw. (278421)
11 (allocated adj2 random).tw. (861)
12 or/7-11 (805988)
13 4 or 6 or 12 (1264138)
14 (systematic adj (review: or overview:)).mp. (186992)
15 (meta-analy: or metaanaly:).mp. (201408)
16 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or
quantitative synthes?s or quantitative overview:).mp. (12253)
17 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (131700)
18 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index
or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (176557)
19 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
(41384)
20 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. (68647)
21 (stud: adj1 select:).ab. (22957)
22 (20 or 21) and review.pt. (31613)
23 or/14-19 (405938)
24 22 or 23 (410136)

25 consensus development conference/ (19344)
26 practice guideline/ (299081)
27 *consensus development/ or *consensus/ (7203)
28 *standard/ (4065)
29 (guideline: or recommend: or consensus or standards).kw. (39580)
30 (guideline: or recommend: or consensus or standards).ti. (165853)
31 or/25-30 (425284)
32 13 or 24 or 31 (1921836)
33 exp endometrial neoplasms/ (53038)
34 exp uterine neoplasms/ (130546)
35 (endometri$ and (cancer$ or neoplas$ or carcin$ or malig$ or tumo$)).tw. (50586)
36 uterine papillary serous carcinoma.tw. (377)
37 or/33-36 (158711)
38 (advance$ or recur$).tw. (1417688)
39 37 and 38 (26425)
40 exp drug therapy/ (2168880)
41 exp drug therapy combination/ (150782)
42 exp chemotherapy/ (551089)
43 exp hormone/ (54553)
44 exp antineoplastic agents/ (1837292)
45 chemothera$.tw. (495924)
46 (hormon$ adj3 thera$).tw. (51269)
47 or/40-46 (3463998)
48 39 and 47 (13406)
49 32 and 48 (2803)
50 (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/ (2637311)
51 49 not 50 (2750)
52 exp animal/ not human/ (4734313)
53 51 not 52 (2745)
54 limit 53 to english language (2616)
55 (201312: or 2014: or 2015: or 2016: or 2017:).dd. (3574548)
56 54 and 55 (437)

clinicaltrials.gov

Searched with keywords: (“advanced” OR “recurrent”) AND (“endometrial” OR “uterine papillary serous carcinoma”). Filter was used to limit results to phase II-IV trials and studies that were of open, active but not recruiting and unknown status.

The Canadian Medical Association Infobase

Searched by conditions: cancer, endometrial.

Cochrane Library, National Guidelines Clearinghouse, ASCO Meeting Abstracts

Searched between 2013 and 2017 with keywords: (“advanced” OR “recurrent”) AND (“endometrial” OR “uterine papillary serous carcinoma”).

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.

Appendix A: Document Summary and Review Conducted in 2013

Number and title of document under review	#4-8 Systemic Therapy for Advanced or Recurrent Endometrial Cancer, and Advanced or Recurrent Uterine Papillary Serous Carcinoma
Current Report Date	August 17, 2004
Clinical Expert	Dr. Allan Covens
Research Coordinator	Raymond Poon
Assessment Date	November 2013
Approval Date and Review Outcome (once completed)	March 6, 2014 (ENDORSE)

Original Question(s):

1. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?
2. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma?

Target Population:

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Study Section Criteria:

Inclusion Criteria

Evidence-based clinical practice guidelines or systematic reviews regarding systemic therapy for advanced disease from other guideline-development groups were eligible for inclusion.

To address the question regarding the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer, full articles or abstracts were selected for inclusion if they met the following criteria:

1. Randomized controlled trials (RCT) or meta-analyses comparing regimens of systemic chemotherapy or hormonal therapy to the standard treatment for advanced or recurrent endometrial cancer reporting at least one of the following outcomes: survival, quality of life, response rate, or toxicity.
2. RCTs that reported on heterogeneous populations (e.g., included women with a range of disease stages) were eligible if results were given separately for the group with advanced or recurrent endometrial cancer.
3. When RCTs were not available, phase II trials of chemotherapy and hormonal therapy agents were included.

To address the question regarding the chemotherapeutic options for women with advanced or recurrent UPSC, full articles or abstracts were selected for inclusion if they met the following criteria:

1. RCTs comparing systemic therapy regimens that included women with stage IIIc or IV UPSC with measurable or evaluable disease at the start of systemic therapy, and reported at least one of the following outcomes: survival, quality of life, response rate, or toxicity.
2. When RCTs were not available, phase II trials of chemotherapy agents were included.

Exclusion Criteria

1. Non-English language publications were excluded.
2. Studies evaluating the role of radiotherapy, administered with chemotherapy or hormonal therapy, were excluded.

Search Details:

April 2004 to December 6, 2013 (Medline, Embase, ASCO annual meetings, the Cochrane Library, clinicaltrials.gov, the National Guidelines Clearinghouse, and the Canadian Medical Association Infobase)

Brief Summary/Discussion of New Evidence:

Of 917 total hits from Medline and Embase + 104 hits from ASCO + 30 hits from clinicaltrials.gov + 5 hits from the Cochrane Library + 7 hits from the National Guidelines Clearinghouse + 8 hits from the Canadian Medical Association Infobase, 72 references representing 2 practice guidelines, 2 meta-analyses, 6 randomized control trials (2 RCTs had two publications each and 1 RCT as an abstract), and 42 non-randomized phase II trials (including 19 abstracts) were found. There were 8 ongoing trials identified.

Guidelines		
Working Group	**Recommendations**	**References**
SOGC-GOC-SCC Policy and Practice Guideline Committee	● A combination regimen of cisplatin and doxorubicin or carboplatin and paclitaxel has demonstrated efficacy in phase III studies for the treatment of advanced stage en om trial c ncer. (Qualit of evidence asse sment: II-2)	Kupets et ., 013
The Soci ty of Gynecologic Oncologists Clinical Practice C mmittee	● Advanced-stage and recurrent uterine papillary serous carcinoma are best managed with cytoreductive surgery he possible followed by platinum-based chemotherapy (carboplatin a pa litaxel or ci plati and adriamycin) with or without tumor-dire ted rad otherapy.	Boruta t al., 2009

Meta-Analyses/Systematic eviews					
Interventions	**Study**	**Population (N)**	**Outcomes**	**Brief results**	**Re eren es**
Comparison 1: doxorubicin combination vs. single-agent doxorubicin	3 RCTs	814	● OS	● The evidence indicates a non-significant benefit in OS in favor of doxorubicin combination. HR=0.89 (95% CI: 0.77-1.03; p=0.12).	Vale et al., 2012 and Humber et al., 2007
			● PFS	● PFS was significantly improved with doxorubicin combination. HR=0.85 (95% CI: 0.74-0.97; p=0.016).	
			● Toxicity	● Pooled data for 2 of the 3 trials showed that doxorubicin combination regimens were associated with significantly more grade 3/4 nausea/vomiting (OR=3.95; 95%	

				CI: 2.27-6.89; p<0.00001), white blood cell toxicity (OR=2.51; 95% CI: 1.73-3.65; p<0.00001), and thrombocytopenia (OR=4.12; 95% CI: 2.08-8.14; p=0.000047). One trial demonstrated significantly higher occurrence of grade 3/4 anaemia for doxorubicin combination. OR=5.32 (95% CI: 2.62-10.81; p<0.00001).	
Comparison 2: doxorubicin + cisplatin + other drugs vs. doxorubicin + cisplatin	2 RCTs	291	● OS ● PFS ● Toxicity	● The evidence indicates a significant benefit in OS in favor of doxorubicin + cisplatin + other drugs. HR=0.75 (95% CI: 0.58-0.97; p=0.03). ● PFS was significantly improved with doxorubicin + cisplatin + other drugs. HR=0.64 (95% CI: 0.49-0.82; p=0.00037). ● Doxorubicin + cisplatin + other drugs chemotherapy regimens were associated with significantly less grade 3/4 white blood cell toxicity (OR=0.45; 95% CI: 0.29-0.72; p=0.00090) but significantly more thrombocytopenia (OR=5.65; 95% CI: 2.60-12.28; p=0.000013).	
Comparison 3: Three-drug combination + hormones vs. Two-drug combination + hormones	2 RCTS	384	● OS ● PFS ● Toxicity	● The evidence indicates a non-significant benefit in OS in favor of three-drug combination + hormones. HR=0.88 (95% CI: 0.71-1.08; p=0.21). ● PFS was non-significantly improved with three-drug combination + hormones. HR=0.88 (95% CI: 0.72-1.08; p=0.23). ● Three-drug combination + hormones chemotherapy regimens were associated with significantly less grade 3/4 white blood cell toxicity. OR=0.51 (95% CI: 0.33-0.78; p=0.0017). One trial reported significantly less grade 3/4 thrombocytopenia f r three-drug om ination + hormones ch motherapy regimens. OR=0.12 (95% CI: 0.05-0.29; p<0.00001).	

Randomized Control Trials

Intervent o s	Population	N	Median follow up	Outcomes	Brief results	References
doxorubicin + 24-h paclitaxel + filgrastim (DxPF) vs. doxorubicin + cisplatin (DxC)	Chemotherapy-naïve women (GOG PS of 0-2) with histologically confirmed stage III, stage IV or recurrent endometrial carcinoma. Proportion of patients who had prior radiotherapy: 51% vs. 53%. Proportion of patients who had prior hormonal therapy: 80% vs. 82%.	317	61 months	● OS ● PFS ● ORR	● The median OS for DxPF was 13.6 months compared with 12.6 months for DxC. The difference was not significant. HR=1.00 (95% CI: 0.78-1.27; p=0.49). ● There was no significant difference in PFS between DxPF (6 months) and DxC (7.2 months). HR=1.01 (95% CI: 0.80-1.28; p=0.46). ● ORR was 43% for DxPF and 40% for DxC. The difference was not significant. OR=1.12 (95% CI: 0.69-1.79; p=0.36). The ORR for both arms in patients with prior pelvic	Fle i g et al., 2004

				● Toxicity	radiotherapy was 35%. ● Grade 4 granulocytopenia was the most common adverse event occurring in 50% and 54% of patients receiving DxPF and DxC, respectively. Grade 3/4 gastrointestinal sym toms, primarily nausea a d vomiting were similar in both groups (12.1% v . 16.0%).	
docetaxel + cisplatin (DC) vs. docetaxel + carboplatin (DCb) vs. paclitaxel + carboplatin (PCb)	Patients (ECOG PS of 0-2) with histologically confirmed stage III, stage IV, or recurrent endometrial carcinoma. Proportion of patients with prior surgery: 72% vs. 69% vs. 63%. Proportion of patients with prior radiotherapy: 14% vs. 14% vs. 17%. Proportion of patients with prior chemotherapy: 17% vs. 45% vs. 37%. Median age=62.5 years	88	Not reported	● OS ● PFS ● ORR ● Toxicity	● There were no significant differences in median OS between DC (629 days), DCb (731 days), and PCb (854 days). ● There were no significant differences in median PFS between DC (232 days), DCb (238 days), and PCb (289 days). ● The ORR for the DC, DCb, and PCb groups were 51.7%, 48.3%, and 60.0%, respectively. The OR comparing DC to DCb was 1.1480. The OR comparing DC to PCb was 0.7143. The OR comparing DCb to PCb was 0.6222. The differences were not significant (p=0.6492). ● The toxicity profiles of the three treatment groups were comparable. Most notable toxic effects were grade 3/4 neutropenia (DC=83.3% vs. DCb=90.0% vs. PCb=76.6%), febrile neutropenia (10.0% vs. 6.7% vs. 3.3%), thro bocytopenia (6.7% vs. 0.0% vs. 10.0%), and diarrhea (13.3% vs. 3.3% vs. 0%). Grade 3 neurotoxicity occurred only in patients treated with PCb (10.0%) but in all instances, the differences were not significant.	Nomu a et al., 201 and Nomura et al., 2008 (Abstract)
doxorubicin + cisplatin + paclitaxel (DxCP) vs. doxorubicin + cisplatin (DxP)	Patients (GOG PS of ≤2) with stage III or IV endometrial carcinoma of any histology who have undergone surgical debulking an volume-direc ed irradiation of the pe vis/para-aortic lymph odes. Median age=58 years	552	47 months	● RFS ● Toxicity ● QOL	● The proportion of patients treated with DxCP alive and recurrence-free at 36 months was 64% compared with 62% in the DxP group. The difference was not significant (p=0.21). ● The incidences of all grade leukopenia, neutropenia, thrombocytopenia, anemia, infection/fever, febrile neutropenia, sensory neuropathy, pain, and myalgia were significantly more frequent with the addition of paclitaxel (p<0.01). ● After adjusting for baseline score, the mean neuropathy (FACT/GOG-Ntx) score of DxCP-treated patients was 5.2 points lower/worse than the mean score of DxP-treated patients	Homesley et al., 2009 and Cella et al., 2010

					within 4 weeks of last course. The difference was significant (p<0.001). At 6 month post last course, the difference remained significant (p=0.014) but reduced to 1.6 point in favor of DxP-treated patients.	
doxorubicin + cisplatin (DxC) vs. methotrexate + vinblastine + doxorubicin + cisplatin (MVDxC)	Chemotherapy-naïve patients (ECOG PS of 2 or better) with histologically confirmed advanced, recurrent, or metastatic endometrial carcinoma not curable by surgery or radiotherapy. Proportion of patients with prior radiotherapy: 53% vs. 54%. Median age=65 vs. 67 years	28	Not reported (trial was closed prematurely due to slow accrual)	● OS ● PFS ● ORR ● Toxicity	● The median OS was 13.2 months for DxC and 16.8 months for MVDxC. The 2-year survival was 20% for DxC and 31% for MVDxC. ● The median PFS was 4.0 months for DxC and 6.9 months for MVDxC. The 1-year PFS was 27% for DxC and 9% for MVDxC. ● The ORR for patients who received DxC and MVDxC were 40% and 69%, respectively. ● Severe leukopenia (MVDxC=69% vs. DxC=47%) and thrombocytopenia (23% vs. 0%) were substantial for MVDxC compared with DxC. In addition, severe nau ea (38% vs. 27%), emesis (31% vs. 20%), stomatitis (31% vs. 7%), diarrhea (8% vs. 0%), and renal (8% vs. 0%) were more common for th MVDxC-treated patients.	Long et al., 2006
doxorubicin + cisplatin (DxC) vs. doxorubicin (Dx)	Patients (GOG PS of 0-2) with histologically confirmed stage III, IV, or recurrent endometrial carcinoma after previous surgery and/or radiotherapy and no prior cytotoxic chemotherapy. Proportion of patients with prior radiotherapy: 68% vs. 62%. Proportion of patients with prior hormonal therapy: 35% vs. 29%. Median age=64.4 vs. 66.9 years	281	Not reported	● OS ● PFS ● ORR ● Toxicity	● There was no significant difference in median OS between the DxC (9.0 months) and Dx (9.2 months) group. HR=0.928 (95% CI: 0.727-1.185). ● The median PFS was significantly prolonged in patients treated with DxC (5.7 months) compared with 3.8 months in those treated with Dx. HR=0.736 (95% CI: 0.577-0.939; p=0.014). ● The ORR for DxC and Dx were 42% and 25%, respectively. The difference was significant (p=0.004). ● The addition of cisplatin resulted in higher rates of grade 3/4 leukopenia (62% vs. 40%), thrombocytopenia (14% vs. 2%), anemia (22% vs. 4%), and nausea/vomiting (13% vs. 3%).	Thigpen et al., 2004
Non-Randomized Phase II Trials						
Interventions	**Population**	**N**	**Median follow up**	**Outcomes**	**Brief result**	**References**
docetaxel	Patients (ECOG PS of 0-2) with histologically confirmed stage III, stage IV, or recurrent	50	18 months	● OS ● PFS	● The median survival time was 18 months. ● The median PFS was 4 months.	Hamed et al., 2012

	endometrial carcinoma. Prior treatment with a taxane was not permitted. Forty-five patients (90%) had prior surgery, 25 patients (50%) had prior radiotherapy, 5 patients (10%) had prior hormonal therapy, and 17 patients (34%) had prior chemotherapy. Median age=60 years			● ORR ● Toxicity	● The ORR was 34%. Of 17 patients who received prior chemotherapy, the ORR was 29%. ● The most common grade 3/4 hematological adverse effects were neutropenia (92%) and leucopenia (50%). The most common grade 3/4 nonhematologic adverse effects were anorexia (20%), constipation (12%), and febrile neutropenia (10%).	
paclitaxel + carboplatin	Patients (ECOG PS of 0-2) with no prior history of chemotherapy and histologically proven advanced or recurrent epithelial endometrial carcinoma not curable by surgery or radiation therapy. Twenty-one patients (70%) had prior surgery. Median age=62 years	30	>30 months	● OS ● PFS ● ORR ● Toxicity	● The median OS was 15 months. The 6-month survival rate was 80%. ● The media PFS was 8.2 months. ● The ORR was 54%. ● Toxicities were generally tolerable. Fourteen patients developed grade 1/2 sensory neuropathy or neuropathic pain. Fifteen patients developed grade 4 neutropenia and 2 patients developed grade III thrombocytopenia and anemia.	Attarian et al., 2009
paclitaxel + epirubicin + carboplatin (PECb)	Patients (relative PS of 0-2) with histologically diagnosed advanced primary or recurrent endometrial carcinoma. Median age=57 years	30	Advanced disease: OS=26 months, PFS=12 months; Recurrent disease: OS=18 months, PFS=6 months	● OS ● PFS ● Response rate	● The median OS for advanced cases was 26 months compared with 19 months for recurrent cases. ● The median PFS for advanced cases was 12 months compared with 6 months for recurrent cases. ● Response rates were 74% in advanced cases and 50% in recurrent cases.	Egawa-Takata et al., 2011
tamoxifen + medroxyprogesterone acetate	Patients (GOG PS of 0-2) with histologically confirmed advanced or recurrent endometrial carcinoma not considered curable by local therapy. Prior chemotherapy and hormonal therapy were not allowed. Thirty-six patients (60%) had prior radiotherapy.	60	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 13 months. ● The median PFS was 3 months. ● The ORR was 33%. ● The frequencies of grade 3/4 thromboembolic episode, hepatic and genitourinary toxicities, anemia, hypertension, or weight gain/loss were ≤3.5%.	Whitney et al., 2004
bevacizumab	Patients (GOG PS of 0-2) with histologically confirmed primary persistent or recurrent endometrial cancer. Thirty-three (63.5%)	52	Not reported	● OS ● PFS	● The median OS was 10.55 months. ● The median PFS was 4.17 months. The proportion of patients who survived progression free for at least 6 months was 40.4%.	Aghajanian et al., 2011

	and nineteen (36.5%) patients had one or two prior cytotoxic regimens, respectively. Twenty-nine patients (55.8%) had prior radiotherapy. Median age=62 years			● ORR ● Toxicity	● The ORR was 13.5%, ● Two patients had grade 3/4 hemorrhage (1 stomach and 1 rectum). Two patients developed grade 3/4 thrombosis/embolism. Two patients experienced grade 3/4 proteinuria, and four patients had grade 3 hypertension. One case of grade 3 hypotension was reported.	
bevacizumab + temsirolimus	Patients (GOG PS of 0-2) with histologically confirmed primary persistent or recurrent endometrial carcinoma and no prior treatment with bevacizumab or temsirolimus. Forty (81.6%) and nine (18.4%) patients had one or two prior cytotoxic regimens. Twenty patients (40.8%) had prior radiation therapy and forty-eight (98.0%) patients had prior surgery. Median age=63 years	49	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 16.9 months. ● The median PFS was 5.6 months. The proportion of patients who survived progression free for at least 6 months was 46.9%. ● The ORR was 24.5%. ● Two patients had grade 3 gastrointestinal-vaginal fistulae, one patient suffered from grade 3 hemorrhage (epistaxis), and one patient experienced grade 4 thrombosis/embolism. Fourteen patients had grade 3/4 metabolic toxicities. There were 3 possible treatment-related deaths.	Alvarez et al., 2013
gemcitabine + cisplatin	Patients (Zubrod PS of 0-2) with histologically proven stage III or IV or recurrent endometrioid endometrial carcinoma not curable by surgery and/or radiotherapy and no prior treatment with gemcitabine. Six (29%) and three (14%) patients had one or two prior chemotherapy regimens. Fourteen patients (67%) had prior radiotherapy. Median age=62 years	21	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 18.2 months. ● The median PFS was 7.5 months. ● The ORR was 50%. Eight chemotherapy-naive patients (67%) responded, compared with 2 responding patients (25%) with prior chemotherapy. The difference was not significant (p=0.17). Similarly, five radiotherapy-naïve patients (83%) responded, compared with 5 responding patients (36%) who had prior radiotherapy. The difference was not significant (p=0.14). ● Eleven patients had grade 3/4 neutropenia, ten patients had grade 3/4 thrombocytopenia, and seven patients had grade 3 anemia. The most common grade 3/4 nonhematologic toxicities were hypokalemia (4 patients), fatigue (4 patients), and hyperglycemia (3 patients).	Brown et al., 2010
ridaforolimus	Women (EGOG PS 0-2) with histologically confirmed recurrent or persistent endometrial cancer.	45	24 months	● PFS ● ORR ● Toxicity	● The 6-month PFS was 18%. ● The ORR was 11%. ● The most common grade 3/4	Colombo et al., 2013 and Colombo et al., 2007

	Prior therapy with rapmycin or a rapmycin analogue was not allowed. Fourteen (31%) and twenty-nine (64%) patients had one and 2 or more prior chemotherapy regimens, respectively. Thirty (67%) patients had prior radiotherapy and forty-four (98%) patients had prior surgical therapy. Median age=66.7 years				adverse events were anaemia (22%), mouth sores (9%), and hyperglycaemia (9%).	(Abstract)
fulvestrant	Patients (GOG PS of 0-1) with histologically proven recurrent, persistent, or metastatic endometrial cancer not amenable to curative surgery. Twenty-four (45%) patients had prior adjuvant chemotherapy.	53	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS in the estrogen negative patients was 3 months and in estrogen positive patients, median OS was 26 months. ● The median PFS in estrogen negative and positive patients were 2 and 10 months, respectively. ● The ORR in estrogen positive patients was 16% and none in estrogen negative patients. ● Treatment was overall well tolerated with only 4 patients experiencing grade 4/5 thrombotic adverse events.	Covens et al., 2011
nonpegylated doxorubicin (Myocet)	Patients (ECOG PS of 0-2) with advanced or recurrent endometrial cancer failing 1 previous carboplatin-paclitaxel chemotherapy. Six (33%) patients had prior radiotherapy. Median age=66 years	18	Not reported	● OS ● TTP ● ORR ● Toxicity	● The median OS was 24 weeks. ● The median TTP was 9 weeks. ● The ORR was 0%. ● Grade 3/4 anemia was observed in 2 patients (11%) and grade 3/4 neutropenia was reported in 61% of patients. The most common grade 3/4 nonhematologic toxicities were fatigue (22%), hair loss (89%), constipation (11%), and diarrhea, nausea and vomiting, each at 5.5%.	Di Legge et al., 2011
ixabepilone	Patients (GOG PS of 0-2) with histologically confirmed recurrent or persistent endometrial cancer and had one prior chemotherapeutic regimen. Prior treatment with ixabepilone was not allowed. Twenty-one (42%) patients had prior radiotherapy and eight (16%) had prior hormonal	50	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was at least 8.7 months. ● The median PFS was 2.9 months and the 6-month PFS was 20%. ● The ORR was 12%. ● The major grade 3/4 toxicities were neutropenia (52%), leukopenia (48%), gastrointestinal (24%), constitutional (20%), neurologic (18%), infection (16%), and anemia (14%).	Dizon et al., 2009

	therapy. Median age=64 years					
pegylated liposomal doxorubicin + carboplatin	Patients (ECOG PS of 0-2) with histologically confirmed recurrent or advanced endometrial carcinoma and could have received up to two prior chemotherapy regimens. ≥18 years	31	24.7 months	● OS ● PFS ● ORR	● The median OS was 21.4 months. ● The median PFS was 9.5 months. ● The ORR was 44%.	du Bois et al., 2007
fulvestrant	Postmenopasual patients (WHO PS of at least 2) with histologically confirmed stage IVB or recurrent endometrial cancer not curable to surgery and/or radiotherapy. Patients with estrogen and progesterone receptor negative tumors were excluded. Thirty-four (97%), twenty-two (63%), and fourteen (40%) patients had prior surgery, radiotherapy, and chemotherapy, respectively. Median age=68.5 years	35	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 13.2 months. ● The median PFS was 2.3 months. ● The ORR was 11.4%. ● Grade 3/4 adverse events were rare with only one treatment-related serious adverse event reported (vomiting).	Emons et al., 2013 and Emons et al., 2009 (Abstract)
trastuzumab	Patients (GOG PS of 0-2) with histologically proven stage III, stage IV, or recurrent HER2 positive endometrial carcinoma. Sixteen (48%), six (18%), and three (9%) patients had 1, 2 and 3+ prior chemotherapy regimens. Seventeen (52%) patients had prior radiotherapy.	33	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS for patients with ICH-positive and FISH-positive tumors were 7.85 and 6.80 months, respectively. ● The median PFS for patients with ICH-positive and FISH-positive tumors were 1.84 and 1.81 months, respectively. ● The ORR was 0%. ● Two possible treatment-related deaths due to infarction and cardiopulmonary arrest. The major grade 3/4 adverse events were gastrointestinal (3 cases), pulmonary (3 cases), and anemia (2 cases).	Fleming et al., 2010
oxaliplatin	Patients (GOG PS of 0-2) with recurrent or persistent endometrial carcinoma who received one previous chemotherapy treatment. Prior therapy with oxaliplatin was not allowed. Twenty-four (46.2%) patients had prior radiotherapy. Median age=67 years	52	Not reported	● ORR ● Toxicity	● The ORR was 13.5%. ● There were 3 cases of grade 3 neurotoxicity. Grade 3 gastrointestinal toxicity occurred in 6 patients. Grade 3 pulmonary toxicity was reported in 4 patients and two patients had grade 3 anemia. Three patients developed grade 3 thrombocytopenia and 1 patient experienced grade 3 hemorrhage.	Fracasso et al., 2006

flavopiridol	Patients (GOG PS of 0-2) with recurrent or persistent endometrial carcinoma who have had one prior cytotoxic chemotherapy regimen. Fourteen (61%) and five (22%) patients had prior radiotherapy and hormonal therapy, respectively. Median age=63 years	23	Not reported	● PFS ● ORR ● Toxicity	● The median PFS was 3.2 months. ● The ORR was 0%. ● The most common toxicity was diarrhea with 14 (61%) patients reporting grade ≥2. Grade 2/3 anemia occurred in 8 (43%) patients and grade ≥2 neutropenia occurred in 5 (22%) patients.	Grendys et al., 2005
docetaxel	Patients (GOG PS of 0-2) with histologically proven primary and recurrent or persistent endometrial carcinoma who have received one prior chemotherapeutic regimen. Eight (31%) and five (19%) patients had prior radiotherapy and hormonal therapy, respectively.	26	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 6.4 months. ● The median PFS was 2.0 months. ● The ORR was 7.7% ● Grade 3/4 neutropenia occurred in 23% of patients and only one case of grade 3 anemia. Grade 3 neurotoxicity and metabolic toxicities were reported in 11% of patients. Other grade 3 toxicities (gastrointestinal, nausea, vomiting, constitutional, infection, and pulmonary) occurred in <10% of patients.	Garcia et al., 2008
docetaxel	Patients (WHO PS of at least 2) with histologically confirmed recurrent or metastatic endometrial cancer and no previous chemotherapy. Median age=65 years	35	Not reported	● OS ● TTP ● ORR ● Toxicity	● The median OS was 43 weeks. ● The median TTP was 12 weeks. ● The ORR was 21%. ● The most common grade 3 nonhematologic toxicities were alopecia (9%) and pain (9%). One patient experienced severe anaphylactic reaction and another developed grade 3 epistaxis.	Gunthert et al., 2007 and Gunthert et al., 2005 (Abstract)
paclitaxel	Patients (ECOG PS of 0-2) with histopathologically confirmed stage III or IV or recurrent endometrial adenocarcinoma. Prior treatment with paclitaxel or docetaxel was not allowed. Thirteen (56.5%), two (8.7%), one (4.3%), twenty-one (91.3%), and three (13%) patients had prior chemotherapy, hormonal therapy, immunotherapy, surgery, and radiotherapy,	23	Not reported	● ORR ● Toxicity	● The ORR was 30.4%. ● The most common grade 3/4 symptoms were febrile neutropenia and constipation (each at 8.7%). Grade 3/4 laboratory abnormalities included neutropenia (78.3%), leucopenia (47.8%), lowered hemoglobin (13.0%), decreased potassium (8.7%), and decreased sodium (4.3%).	Hirai et al., 2004 and Miyagi et al., 2004 (Abstract)

	respectively. Median age=60 years					
liposomal doxorubicin	Patients (GOG PS of 0-2) with histologically confirmed disseminated or recurrent endometrial carcinoma who had not received prior chemotherapy. Twenty-seven (52%) patients had prior radiotherapy. Median age=65 years	52	Not reported	● OS ● ORR ● Toxicity	● The median survival was 10.9 months. ● The ORR was 11.5%. ● The most common grade 3/4 adverse events were anemia (15%), gastrointestinal (15%), pain (13%), genito-urinary (10%), neurologic (10%), and leukopenia (10%).	Homesley et al., 2005
paclitaxel	Patients (GOG PS of 0-2) with initial histologic diagnosis of persistent or recurrent endometrial carcinoma and had no more than one prior chemotherapeutic regimen.	15	Not reported	● ORR ● Toxicity	● The ORR was 26.7%. ● There were minimal grade 3/4 toxicities reported.	Homesley et al., 2008 and Homesley et al., 2006 (Abstract)
docetaxel	Patients (ECOG PS of 0-2) with histologically documented primary stage III, IV or recurrent endometrial carcinoma. Prior treatment with a taxane was not allowed. Fourteen (42%), twenty-nine (88%), nine (27%), and five (15%) patients had prior chemotherapy, surgery, radiotherapy, and hormonal therapy, respectively. Median age=59 years	33	17.6 months	● OS ● TPP ● ORR ● Toxicity	● The median OS was 17.8 months. ● The median TTP was 3.9 months. ● The ORR was 31%. ● The most common grade 3/4 toxicities were neutropenia (94%), anorexia (18%), and constipation (12%). Grade 3/4 fatigue, vomiting, and diarrhea each occurred in 9% of the patients.	Katsumata et al., 2005
gefitinib	Patients (GOG PS of 0-2) with histologically confirmed, recurrent or persistent endometrial carcinoma after at least one prior chemotherapeutic regimen. Eight (31%) and eighteen (69%) patients had prior hormonal therapy and radiotherapy, respectively.	26	24 months	● OS ● PFS ● ORR ● Toxicity	● The median OS was 7.1 months. ● The median PFS was 1.8 months. The proportion of patients who survived progression free for at least 6 months was 15.4%. ● The ORR was 3.8%. ● Grade 3/4 adverse effects included gastrointestinal (19%), fatigue (19%), pain (15%), dermatologic (15%), neurologic (11.5%), hematologic (11.5%), anemia (8%), and cardiovascular, metabolic, ocular, and pulmonary (each at 4%).	Leslie et al., 2013
lapatinib	Patients (GOG PS of 0-2) with a	30	6 months	● OS	● The median OS was 7.33 months.	Leslie et al., 2012

	histological diagnosis of recurrent or persistent endometrial carcinoma following one or two prior cytotoxic regimens. Eleven (36.7%) and twenty-nine (96.7%) patients had prior radiation and surgery, respectively. 18 years of age and older.			● PFS ● ORR ● Toxicity	● The median PFS was 1.82 months. The proportion of patients who survived progression free for at least 6 months was 10%. ● The ORR was 3.3%. ● The most common grade 3/4 toxicities were gastrointestinal (20%) and metabolic (10%). Other grade 3/4 toxicities each occurred in 3.3% of the patients (anemia, cardiovascular, dermatologic, genitourinary/renal, hemorrhage, and pulmonary)	
letrozole	Postmenopausal women (ECOG PS of 0-2) with histologically confirmed recurrent or advanced (stage IV) adenocarcinoma or adenosquamous carcinoma of the endometrium not amenable by surgery or radiotherapy. Except adjuvant, no prior chemotherapy was allowed. Ten (31%) and twenty-six (81%) patients had prior progestins and radiotherapy, respectively. Median age=71 years	32	Not reported	● OS ● TTP ● ORR ● Toxicity	● The median OS was 8.8 months. ● The median TTP was 3.9 months. ● The ORR was 9.4%. ● One patient experienced grade 3 depression and another patient developed deep vein thrombosis. Other nonhematological toxicities were grade 1/2 hot flashes (28%) and fatigue (12.5%). One patient had grade 4 elevation in serum creatinine level and two patients developed transient grade 2/3 hyperbilirubinemia.	Ma et al., 2004
trabectedin	Women (ECOG PS of 0-1) with histologically proven persistent or recurrent endometrial cancer following exposure to only one cytotoxic chemotherapy regimen. Median age=63 years	50	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 6.7 months. ● The median PFS was 1.8 months. ● The ORR was 2.2%. ● The most frequent grade 3/4 adverse events were increased alanine aminotransferase (40%), asthenia (14%), and neutropenia (14%).	McMeekin et al., 2009 and McMeekin et al., 2004 (Abstract)
thalidomide	Women (GOG PS of 0-2) with histologically confirmed persistent or recurrent endometrial cancer of any subtype and received one or two prior chemotherapy regimens. Fifteen (62%) and twenty-three (96%) patients had prior radiation therapy and hysterectomy, respectively. Median age=70 years	24	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 6.3 months. ● The median PFS was 1.7 months. The proportion of patients who survived progression free for at least 6 months was 8%. ● The ORR was 12%. ● The most common grade 3 toxicities were hematologic (12.5%), cardiovascular (12.5%), constitutional (12.5%), gastrointestinal (8%), and other neurological symptoms (8%).	McMeekin et al., 2007

pemetrexed	Patients (GOG PS of 0-2) with recurrent or persistent endometrial adenocarcinoma refractory to curative treatments and received one prior chemotherapy regimen. Twelve (46%) patients had prior radiotherapy. Median age=63 years	25	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 9.4 months. ● The media PFS was 2.7 months. ● The ORR was 4%. ● The most common grade 3/4 adverse events were neutropenia (48%), leukopenia (40%), anemia (20%), and constitutional (16%).	Miller et al., 2009a and Miller et al., 2009b (Abstract)
erlotinib	Chemotherapy-naïve patients (ECOG PS of 0-2) with histologically confirmed metastatic/locally advanced adenocarcinoma or adenosquamous carcinoma of the endometrium not curable by standard therapies. Six (18%) and nineteen (58%) patients had prior hormonal therapy and radiation, respectively. Median age=66 years	33	Not reported	● ORR ●Toxicity	● The ORR was 12.5%. None of the responders received prior hormonal therapy. ● The most frequent adverse events reported were rash (88%), dry skin (61%), and diarrhea (57.6%, including four patients with grade 3 severity). One patient had grade 3 anemia, one patient had grade 3 bilirubin elevation and one patient had a grade 4 transient increase of hepatic transaminases.	Oza et al., 2008a and Jasas et al., 2004 (Abstract)
temsirolimus	Chemotherapy-naïve or chemotherapy-treated patients (PS of 0-2) with histologically proven metastatic or locally advanced adenocarcinoma or adenosquamous carcinoma of the endometrium not curable by standard therapies. Patients could have had prior radiation or up to one prior hormonal treatment. Median age=chemotherapy-naïve (66 years) and chemotherapy-treated (60 years)	60	Not reported	● PFS ● ORR ● Toxicity	● The median PFS for the chemotherapy-naïve patients was 7.33 months compared with 3.25 months in chemotherapy-treated patients. ● The ORR were 14% and 4% for the chemotherapy-naïve and chemotherapy-treated groups, respectively. ● The most common toxicities were fatigue (61-63%), rash (37-45%), mucositis (11-58%), nausea (27-67%), and pneumonitis (37-45%). The most frequent hematologic toxicity was anemia (77-78%).	Oza et al., 2011a and Oza et al., 2008b (Abstract) and Oza et al., 2006 (Abstract)
paclitaxel + epirubicin + carboplatin	Patients (ECOG PS of 0-2) with histologically confirmed primary stage IV or recurrent endometrial carcinoma no longer amenable to initial surgery and/or radiation therapy and had no prior chemotherapy treatment for advanced disease. Median age=67 years	57	84.2 months	● OS ● TTP ● ORR ● Toxicity	● The median OS was 13.8 months. ● The median TTP was 7.8 months. ● The ORR was 63.2%. ● Nine (15.5%) patients reported grade 3/4 neutropenia. Three (5%) patients had grade 3/4 anemia and three (5%) had grade 3 peripheral neuropathy. There were two cardiac deaths but these were not clearly	Papadimitriou et al., 2008a

					determined to be treatment-related. Thirty-eight (67%) patients reported grade 3 alopecia.	
paclitaxel + topotecan + carboplatin	Patients (ECOG PS of 0-2) with histologically proven primary stage IV or recurrent endometrial carcinoma no longer amenable to initial surgery and/or radiation therapy and had no prior chemotherapy treatment for advanced disease. Median age=68 years	39	35.8 months	● OS ● TTP ● ORR ● Toxicity	● The median OS was 17.7 months. ● The median TTP was 8.9 months. ● The ORR was 60%. ● The most frequent grade 3/4 hematologic adverse effect was thrombocytopenia (13%). Grade 3/4 neutropenia occurred in 10% of patients. Twenty-eight (72%) patients reported grade 3 alopecia.	Papadimitriou et al., 2008b
carboplatin + pegylated liposomal doxorubicin	Chemotherapy-naïve patients (ECOG PS of 0-2) with cytologically or histologically documented advanced (stage III or IV) or recurrent endometrial carcinoma. Median age=64 years	42	74 weeks	● OS ● PFS ● ORR ● Toxicity	● The median OS was 80.1 weeks. ● The median PFS was 52.9 weeks. ● The ORR was 59.5%. ● Grade 3/4 anemia was reported in 33% of patients. Grade 3/4 leukopenia occurred in 28% of patients. Other common grade 3/4 adverse events were neutropenia (47%) and thrombocytopenia (22%).	Pignata et al., 2007 and Lorusso et al., 2006 (Abstract)
everolimus	Patients (ECOG PS of 0-2) with histologically confirmed metastatic or locally advanced endometrial adenocarcinoma not eligible for surgery that progressed after one or two prior chemotherapy regimens. The proportion of patients who received prior surgery was 89% and 14% had previous hormonal treatment. Median age=65 years	44	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 8.1 months. ● The median PFS was 2.8 months. ● The ORR was 5% at 3 months and 9% at 6 months. ● The most common grade 3/4 non-hematological toxicities were fatigue (42%), anorexia (26%), infection (16%) and diarrhea and thromboembolism (each at 12%). Frequent grade 3/4 hematological adverse events were lymphopenia (23%) and anemia (14%). Grade 3/4 hypercholesterolemia and hyperglycemia were observed in 8% and 10% of patients, respectively.	Ray-Coquard et al., 2013 and Ray-Coquard et al., 2009 (Abstract)
irofulven	Patients (GOG PS of 0-2) with documented recurrent or persistent endometrial carcinoma of any histologic cell type and have one prior chemotherapy treatment. Fourteen (56%) and three (12%) patients had prior radiotherapy and hormonal therapy,	25	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 9.4 months. ● The median PFS was 2.0+ months. ● The ORR was 4%. ● There were three early treatment-related deaths as a result to renal failure and severe electrolyte disturbances. Grade 3/4 toxicities included anemia	Schilder et al., 2004

	respectively. Median age=67 years				(12%), neutropenia (20%), thrombocytopenia (20%), nausea (12%), emesis (20%), and metabolic (28%).	
paclitaxel + carboplatin + amifostine	Patients (SWOG PS of 0-2) with histologically proven advanced or recurrent epithelial endometrial carcinoma not amenable to surgery or radiation therapy and have not received prior cytotoxic chemotherapy. Twenty-eight (60%) and forty-four (94%) patients had prior radiotherapy and surgery, respectively. Median age=66 years	47	Not reported	● OS ● PFS ● ORR ● Toxicity	● The median OS was 14 months and the 6-month OS was 85%. ● The median PFS was 7 months and the 6-month PFS was 64%. ● The ORR was 40%. ● The common grade 3/4 toxicities were neutropenia (79%), anemia (17%), febrile neutropenia (13%), thrombocytopenia (13%), non-neuropathic pain (11%), and thrombosis/embolism (9%).	Scudder et al., 2005
weekly low-dose paclitaxel + carboplatin	Patients (GOG PS of 0-2) with histologically proven primary advanced or recurrent endometrial cancer. Five (38%) and seven (54%) patients had prior radiation therapy and chemotherapy, respectively.	13	Not reported	● OS ● PFS ● ORR	● The median OS was 15.4 months. ● The median PFS was 5.5 months. ● The ORR was 61.5%.	Secord et al., 2007
everolimus	Patients (Zubrod PS of 0-2) with histologically confirmed progressive or recurrent endometrial carcinoma. Thirty-four (97%) and nine (26%) patients had prior chemotherapy (up to 3 regimens) and hormonal/other therapy, respectively. Median age=58 years	35	Not reported	● ORR ● Toxicity	● The ORR was 0%. ● The most common grade 3/4 adverse events were lymphopenia (29%), fatigue (23%), nausea (11%), anemia (9%) and elevated glucose (9%).	Slomovitz et al., 2010
carboplatin + paclitaxel	Patients (WHO PS of 0-2) with primary advanced or recurrent endometrial carcinoma. Sixty-three (95.5%) and twenty-nine (44%) patients had prior surgery and radiotherapy, respectively. Five (7.6%) patients had prior hormonal therapy. Mean age=67.9 years	66	57 months	● OS ● PFS ● ORR ● Toxicity	● The median OS was 26 months. The 1-, 3- and 5-year survival rates were 81.8%, 33.3% and 19.9%, respectively. ● The median PFS was 14 months. The 1-, 3- and 5-year PFS rates were 59.0%, 18.2% and 10.5%, respectively. ● The ORR was 66.7%. ● The grade 3/4 adverse effects included nausea/vomiting (6.1%), neurologic (13.6%), neutropenia (7.6%), and thrombocytopenia (4.5%).	Sorbe et al., 2008 and Sorbe et al., 2005 (Abstract)
gemcitabine	Patients (GOG PS of 0-2) with histologically	23	Not reported	● PFS	● The median PFS was 1.7 months.	Tait et al., 2011

	confirmed recurrent or persistent endometrial adenocarcinoma that was refractory to curative therapy and had only one prior chemotherapy regimen. Nine (39%) and four (17%) patients had prior radiotherapy and hormonal therapy, respectively. Median age=64 years			● ORR ● Toxicity	● The ORR was 4%. ● Grade 3/4 adverse events were confined mainly to hematological toxicities with neutropenia (22%), anemia (22%), leukopenia (13%) and thrombocytopenia (9%). Grade 4/5 pulmonary toxicity was observed in 13% of patients with one treatment-related death due to pulmonary complications.	
Leuven dose-dense paclitaxel + carboplatin	Patients with histologically confirmed primary advanced or recurrent endometrial cancer. Four (9.5%) and seven (17%) patients had previous hormonal therapy and irradiation, respectively. Median age=chemotherapy-naïve (63 years) and chemotherapy-treated (65 years)	42	Chemotherapy-naïve=10 months; Chemotherapy-treated=16 months	● PFS ● ORR ● Toxicity	● The median PFS for the chemotherapy-naïve patients was 10 months compared with 11 months in chemotherapy-treated patients. ● The ORR for the chemotherapy-naïve patients was 71% compared with 21% in chemotherapy-treated patients. ● Grade 3/4 hematological toxicities included anemia (14%), leucopenia (74%), neutropenia (81%) and thrombocytopenia (26%). Neutropenic fever was reported in 7% of patients with one treatment-related death due to neutropenia and nephrotoxicity.	Vandenput et al., 2009
weekly paclitaxel + carboplatin	Patients with histologically confirmed primary advanced or recurrent endometrial cancer. None of the recurrent cases had prior irradiation or hormonal therapy. Median age=chemotherapy-naïve (60 years) and chemotherapy-treated (62 years)	29	Chemotherapy-naïve=7 months; Chemotherapy-treated=9 months	● OS ● PFS ● ORR ● Toxicity	● The median OS for the chemotherapy-naïve and chemotherapy-treated patients were 12 and 9 months, respectively. ● The median PFS for the chemotherapy-naïve and chemotherapy-treated patients were 9 and 8 months, respectively. ● The ORR for the chemotherapy-naïve patients was 50% compared with 39% in chemotherapy-treated patients. ● Grade 3/4 hematological toxicities included anemia (55.5%), neutropenia (89%) and thrombocytopenia (52%). Only one case of neutropenic fever was reported.	Vandenput et al., 2012

Ongoing Randomized Control Trials
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Interventions	Official title	Status	Protocol ID	Estimated primary completion date	Last updated
docetaxel + cisplatin	A Phase II Trial of Docetaxel/Cisplatin in Patients With Recurrent or Stage IVb Endometrial Cancer.	Recruiting	NCT01461759	September 2013	October 27, 2011

temsirolimus	Efficacy, Tolerability and Safety of Temsirolimus in Women With Platinum-refractory Ovarian Carcinoma or Advanced Endometrial Carcinoma.	Active	NCT01460979	October 2014	March 4, 2014
paclitaxel + carboplatin + bevacizumab vs. paclitaxel + carboplatin	A Randomized Phase II Trial of Carboplatin-Paclitaxel Compared to Carboplatin-Paclitaxel-Bevacizumab in Advanced (Stage III-IV) or Recurrent Endometrial Cancer.	Recruiting	NCT01770171	December 2017	January 15, 2013
AEZS-108 + doxorubicin vs. doxorubicin	Randomized Controlled Study Comparing AEZS-108 With Doxorubicin as Second Line Therapy for Locally Advanced, Recurrent or Metastatic Endometrial Cancer.	Recruiting	NCT01767155	December 2015	March 14, 2014
Liposome-encapsulated doxorubicin citrate + carboplatin	Phase II Multicenter Trial of the Austrian AGO With the Combination of Liposomal Doxorubicin (Myocet®) and Carboplatin in Primary Advanced or Metastatic and Recurrent Endometrial Cancer.	Unknown	NCT01100359	October 2010	August 6, 2013
BKM120	Phase 2 Multicenter Study to Assess the Safety and Efficacy of BKM120 as Monotherapy in Treatment of Initial or Recurrent Metastatic Endometrial Cancer After 1st Line Therapy in Patients Who Cannot Undergo Local Surgery and/or Radiotherapy.	Recruiting	NCT01397877	December 2014	January 9, 2014
paclitaxel + carboplatin + trastuzumab vs. paclitaxel + carboplatin	Randomized Phase II Evaluation of Carboplatin/Paclitaxel With and Without Trastuzumab (Herceptin) in HER2/Neu+ Patients With Advance/Recurrent Uterine Serous Papillary Carcinoma.	Recruiting	NCT01367002	July 2015	January 28, 2014
TKI258 (dovitinib)	A Phase II, Open-label, Single-arm, Non-randomized, Multi-center Study to Evaluate the Efficacy of Oral TKI258 as Second-line Therapy in Patients With Either FGFR2 Mutated or Wild-type Advanced and/or Metastatic Endometrial Cancer.	Recruiting	NCT01379534	June 2014	March 13, 2014

Abstracts

Interventions	Population	N	Outcomes	Brief results	References
paclitaxel + carboplatin + megesterol acetate	Patients with stage III-IV or recurrent endometrial cancer.	28	• OS • PFS • Toxicity	• The median OS was 36.3 months. • The median progression-free interval was 31.9 months. • Thirteen (48%) patients experienced grade 3/4 neutropenia and nine (33%) patients developed grade 3/4 anemia.	Bevis et al., 2010
paclitaxel + carboplatin	Patients with advanced or recurrent endometrial	40	• OS • DFS	• The 2-year OS was 71.8%. • The 2-year DFS was 77.6%.	Shan et al., 2011

	cancer.		• ORR • Toxicity	• The ORR was 70% • Hematological toxicities included grade 3/4 neutropenia (52.5%), anemia (15%) and thrombocytopenia (12.5%). The rate of grade 3 reversible hypersensitivity was 5%.	
ridaforolimus	Patients with metastatic and/or locally advanced recurrent endometrial cancer.	34	• ORR • Toxicity	• The ORR was 7.7%. • The most common adverse events of any grade were mucositis (64%), fatigue (64%), anorexia (48%), diarrhea (45%), nausea (42%), taste alteration (42%) and rash (36%). Seven (21%) and two (6%) patients had grade 3 lymphopenia and anemia, respectively.	Mackay et al., 2011
sunitinib	Patients with recurrent or metastatic endometrial cancer who have been treated with up to one prior chemotherapy regimen. Median age=66 years	34	• OS • TTP • ORR • Toxicity	• The median OS was 19 months. • The median TTP was 2.53 months. • The ORR was 15%. • The most common grade 3/4 adverse events were fatigue (40%) and hypertension (20%).	Correa et al., 2010
ridaforolimus vs. (medroxyprogesterone or megestrol) or chemotherapy	Patients with unresectable stage III or IVA or metastatic endometrial cancer previously treated with one or two lines of chemotherapy.	130	• OS • PFS • ORR • Toxicity	• The median OS was 10.0 months for ridaforolimus and 8.9 months for the comparator arm. The difference was not significant. HR=0.93 (95% CI: 0.55-1.58; p=0.4). • The median PFS was significantly prolonged in the ridaforolimus group (3.6 months) compared with the comparator group (1.9 months). HR=0.53 (p=0.008). • The ORR for ridaforolimus and comparator were 0% and 4.3%, respectively. • Common grade 3/4 toxicities for ridaforolimus were hyperglycemia (19%), anemia (9%), back pain (8%), asthenia (8%), diarrhea (6%), stomatitis (6%), and anorexia, mucosal inflammation, fatigue, cough, hypokalemia, elevated ALT, elevated GGT, and hypertriglyceridemia (each at 5%). Common grade 3/4 toxicities for the comparator arm were abdominal pain and anemia (each at 5%).	Oza et al., 2011b
pegylated liposomal doxorubicin + paclitaxel or docetaxel	Patients (PS of 0-1) with metastatic endometrial cancer and 0-1 prior treatment for metastatic disease. Median age=65 years (PlDx + P) and 63 years (PlDx + D)	22	• TTP • ORR • Toxicity	• The median TTP was 26.6 weeks for PlDx + P and 15.5 weeks for PlDx + D. • The ORR was 20% for PlDx + P and 30% for PlDx + D. • Grade 3/4 toxicities in patients treated with PlDx + P included ANC with febrile neutropenia (2 cases), hemoglobin (1), skin (3), platelets (1), neuropathy (1) and edema (1). Grade 3/4 toxicities seen in patients treated with PlDx + D were ANC (4 cases), skin/nails (3), nausea/vomiting (2), hemoglobin (1), mucositis (1) and sepsis (1).	Szmulewitz et al., 2005

Abbreviations: SOGC=Society of Obstetricians and Gynaecologists of Canada; GOC=Gynecologic Oncology of Canada; GOG=Gynecologic Oncology Group; RCT=randomized clinical trial; PFS=progression-free survival; OS=overall survival; ORR=objective response rate; RR=relative risk; CI:confidence interval; Dx=doxorubicin; QOL=quality of life; P=paclitaxel; Cb=carboplatin; C=cisplatin; PS=performance status; BSC=best supportive care; ECOG=Eastern Cooperative Oncology Group; F=filgrastim; E=epirubicin; D=docetaxel; RFS=recurrence-free survival; FACT/GOG-Ntx=Functional Assessment of Cancer Therapy/Gynecologic Oncology Group — Neurotoxicity; TTP=time to progression; ICH=immunohistochemistry; FISH=fluorescence in situ hybridization; M=methotrexate; V=vinblastine; SWOG=Southwest Oncology Group; DFS=disease-free survival; PlDx=pegylated liposomal doxorubicin; ANC=absolute neutrophil count

Clinical Expert Interest Declaration: None	
Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.	
1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	No
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	a) Yes. Homesley data suggests no benefit to 3 drugs vs. 2 Dox/cis vs. Dox/cis/pacl. b) Yes **Note:** A statement should be made to indicate more recent data suggesting no benefit to the 3 drug combination for recurrence free survival.
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	No. Carbo/taxol vs. carbo/taxol/bev **Note:** The estimated primary completion date for this ongoing trial is December 2017.
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a	Yes

	full update of this document within the next year?	
Review Outcome	ENDORSE	
DSG/GDG Approval Date	March 6, 2014	
DSG/GDG Commentary	N/A	

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Literature Search Strategy:

Medline

1. exp endometrial neoplasms/
2. exp uterine neoplasms/
3. (endometri$ and (cancer$ or neoplas$ or carcin$ or malig$ or tumo$)).tw.
4. uterine papillary serous carcinoma.tw.
5. or/ 1-4
6. (advance$ or recur$).tw.
7. 5 and 6
8. exp drug therapy/
9. exp drug therapy combination/
10. exp chemotherapy/
11. exp hormone/
12. exp antineoplastic agents/
13. chemothera$.tw.
14. (hormon$ adj3 thera$).tw.
15. or/ 8-14
16. 7 and 15
17. meta-analysis as topic/
18. meta analysis.pt.
19. (meta analy$ or metaanaly$).tw.
20. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
21. (systematic adj (review$ or overview?)).tw.
22. (exp Review Literature as topic/or review.pt or exp review/) and systematic.tw.
23. or/ 17-22
24. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or chinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.

25. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
26. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
27. (study adj selection).ab.
28. 26 or 27
29. review.pt.
30. 28 and 29
31. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
32. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
33. random allocation/ or double blind method/ or single blind method/
34. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
35. or/ 31-34
36. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
37. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
38. (clinic$ adj trial$1).tw.
39. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
40. placebos/
41. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
42. (allocated adj2 random).tw.
43. or/ 36-42
44. 23 or 24 or 25 or 30 or 35 or 43
45. 16 and 44
46. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
47. 45 not 46
48. limit 47 to English
49. Animal/
50. Human/
51. 49 not 50
52. 48 not 51
53. (200404$ or 200405$ or 200406$ or 200407$ or 200408$ or 200409$ or 200410$ or 200411$ or 200412$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).ed.
54. 52 and 53

Embase

1. exp endometrial neoplasms/
2. exp uterine neoplasms/
3. (endometri$ and (cancer$ or neoplas$ or carcin$ or malig$ or tumo$)).tw.
4. uterine papillary serous carcinoma.tw.
5. or/ 1-4
6. (advance$ or recur$).tw.
7. 5 and 6
8. exp drug therapy/
9. exp drug therapy combination/
10. exp chemotherapy/
11. exp hormone/
12. exp antineoplastic agents/
13. chemothera$.tw.
14. (hormon$ adj3 thera$).tw.

15. or/ 8-14
16. 7 and 15
17. exp Meta Analysis/ or exp “Systematic Review”/
18. (meta analy$ or metaanaly$).tw.
19. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
20. (systematic adj (review$ or overview?)).tw.
21. exp “Review”/ or review.pt.
22. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
23. (study adj selection).ab.
24. 21 and (22 or 23)
25. or/ 17-20, 24
26. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or chinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
27. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
28. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
29. randomization / or single blind procedure/ or double blind procedure/
30. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
31. or/ 28-30
32. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
33. (clinic$ adj trial$1).tw.
34. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
35. placebo/
36. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
37. (allocated adj2 random).tw.
38. or/ 32-37
39. 25 or 26 or 27 or 31 or 38
40. 16 and 39
41. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
42. 40 not 41
43. limit 42 to English
44. Animal/
45. Human/
46. 44 not 45
47. 43 not 46
48. (200404$ or 200405$ or 200406$ or 200407$ or 200408$ or 200409$ or 200410$ or 200411$ or 200412$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).dd.
49. 47 and 48

Clinicaltrials.gov
Searched http://clinicaltrials.gov/ct2/search/advanced with keywords: (“advanced” OR “recurrent”) AND (“endometrial” OR “uterine papillary serous carcinoma”) AND “chemotherapy”. Filter was used to limit results to Phase II-IV trials.

The Canadian Medical Association Infobase
Searched http://www.cma.ca/index.php?ci_id=54293&la_id=1 by conditions: cancer, endometrial.

Searched http://onlinelibrary.wiley.com/cochranelibrary/search/ (the Cochrane Library), http://www.guideline.gov/ (the National Guidelines Clearinghouse), and http://www.ascopubs.org/serach (ASCO Meeting Abstracts) with keywords: ("advanced" OR "recurrent") AND ("endometrial" OR "uterine papillary serous carcinoma") AND "chemotherapy".

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 4-8 Version 3: Section 2

Systemic Therapy for Advanced or Recurrent Endometrial Cancer, and Advanced or Recurrent Uterine Papillary Serous Carcinoma

Guideline Review Summary

A. Covens, D. Sivajohanathan, and Members of the Gynecologic Cancer Disease Site Group

June 6, 2017

The 2004 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2004. In 2013, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (RP) conducted an updated search of the literature from 2004 to 2013 and the data supported the 2004 recommendations. Please see Appendix A for this document summary and review table.

In 2016, this document was assessed again and in accordance with the PEBC Document Assessment and Review Protocol, was determined to require a review. An updated search of the literature from 2013 to 2017 was performed by a PEBC methodologist (DS) and a clinical expert (AC) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Gynecologic Cancer Disease Site Group (DSG) endorsed the recommendations found in Section 1 (Practice Guideline Report) on June 6, 2017.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

3. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?

4. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma?

Literature Search and New Evidence
The new search (December 2013 to May 2017) yielded 1 practice guideline, 8 RCTs (4 publications and 4 abstracts), and 6 non-randomized phase II trials. An additional search for ongoing studies on clinicaltrials.gov yielded 16 potentially relevant ongoing trials. Brief results of these publications are shown in the Document Summary and Review Tool.

Impact on the Guideline and Its Recommendations
The new data support existing recommendations. The Expert Panel has noted that current practice has changed in the treatment of advanced or recurrent endometrial cancer with a preference for a taxane-platinum drug combination although the three-drug combination is still an option. There are data suggesting that a taxane-platinum drug combination has similar efficacy with better toxicity when compared with the three-drug paclitaxel/cisplatin/doxorubicin combination (Miller, 2012). The Expert Panel recognizes that this evidence comes from an abstract of an interim analysis of a phase III RCT with no full publication and does not meet the criteria for inclusion in this review. However, since this abstract has caused a change in practice, a statement regarding this will be included in the qualifying statements of the recommendations.

The Gynecology DSG ENDORSED the 2004 recommendations on the chemotherapeutic and hormonal therapy options for advanced or recurrent endometrial cancer and advanced or recurrent uterine papillary serous carcinoma.

Number and Title of Document under Review	Guideline 4-8 Version 2: Systemic therapy for advanced or recurrent endometrial cancer and advanced or recurrent uterine papillary serous carcinoma
Current Report Date	March 6, 2014
Clinical Expert	Dr. Allan Covens
Research Coordinator	Duvaraga Sivajohanathan
Date Assessed	November 29, 2016
Approval Date and Review Outcome (once completed)	June 6, 2017 ENDORSE

Original Question(s):

3. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?
4. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma?

Target Population:

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Study Selection Criteria:

Inclusion Criteria
Evidence-based clinical practice guidelines or systematic reviews regarding systemic therapy for advanced disease from other guideline-development groups were eligible for inclusion.

To address the question regarding the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer, full articles or abstracts of randomized controlled trials (RCTs) were selected for inclusion if they met the following criteria:

4. RCTs or meta-analyses comparing regimens of systemic chemotherapy or hormonal therapy to the standard treatment for advanced or recurrent endometrial cancer reporting at least one of the following outcomes: survival, quality of life, response rate, or toxicity.
5. RCTs that reported on heterogeneous populations (e.g., included women with a range of disease stages) were eligible if results were given separately for the group with advanced or recurrent endometrial cancer.
6. When RCTs were not available, phase II trials of chemotherapy and hormonal therapy agents were included.

To address the question regarding the chemotherapeutic options for women with advanced or recurrent UPSC, full articles or abstracts of RCTs were selected for inclusion if they met the following criteria:

3. RCTs comparing systemic therapy regimens that included women with stage IIIc or IV UPSC with measurable or evaluable disease at the start of systemic therapy, and reported at least one of the following outcomes: survival, quality of life, response rate, or toxicity.
4. When RCTs were not available, phase II trials of chemotherapy agents were included.

Exclusion Criteria

3. Non-English language publications were excluded.
4. Studies evaluating the role of radiotherapy, administered with chemotherapy or hormonal therapy, were excluded.

Search Details:

- December 2013 to March 8, 2017 (MEDLINE, EMBASE)
- December 2013 to May 5, 2017 (ASCO annual meetings, the Cochrane library, clinicaltrials.gov, the National Guidelines Clearinghouse, and the Canadian Medical Association Infobase)

Summary of New Evidence:

Of 578 total hits from MEDLINE and EMBASE + 173 hits from ASCO + 98 hits from clinicaltrials.gov + 4 hits from the Cochrane Library + 26 hits from the National Guidelines Clearinghouse + 6 hits from the Canadian Medical Association Infobase, 15 references representing 1 practice guideline, 8 RCTs (4 publications and 4 abstracts), and 6 non-randomized phase II trials. There were 16 ongoing trials identified.

Details from the included trials are summarized in the tables below.

Clinical Expert Interest Declaration:

None

5. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
6. Does the newly identified evidence support the existing recommendations?	Yes
7. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes

Review Outcome as recommended by the Clinical Expert	ENDORSED
If outcome is UPDATE, are you aware of trials now underway (not yet published) that will impact recommendations?	N/A
DSG/GDG Commentary	N/A

Guidelines

Reference	Recommendations
Singapore Cancer Network (SCAN) Guidelines for the Systemic Therapy of Endometrial (Uterine) Cancers (2015)	1. What are the chemotherapeutic options for women with advanced or recurrent endometrial cancers? • The group unanimously endorsed the ESMO guidelines 2013 on the treatment of advanced endometrial cancer as it was felt to be the most comprehensive among the 3 chosen guidelines. The use of taxane - platinum-based chemotherapy should be considered as standard of care (in comparison to platinum-non-taxane combination); while the use of hormones can be considered. There is data to support the role of mTOR inhibitors in patients with metastatic/recurrent endometrioid endometrial cancer following failure of first-line chemotherapy. 2. What is the role of chemotherapy in women with uterine papillary serous carcinoma or clear cell carcinoma? • The group unanimously endorsed the NCCN guidelines version 2.2015 on the treatment of uterine papillary serous carcinoma or clear cell carcinoma. All the members agree that chemotherapy should be recommended for all stages of UPSC/clear cell, including stage I disease. NCCN recommendations were considered to be the most comprehensive and to best represent the current evidence.

Published Randomized Controlled Trials

Author, year	Population	N	Median Follow-up	Intervention/ Comparison	Outcomes of interest	Brief results

Fleming GF (2014) Phase II	Patients with measurable endometrial carcinoma that was either stage III or IV or persistent or recurrent after treatment for earlier stage disease.	50 21	NR	Temsirolimus Vs. Temsirolimus + megestrol acetate alternating with tamoxifen	Toxicity Tumour response PFS OS	• The trial was suspended and the combination arm was closed to accrual due to an excess of venous thrombosis. No thrombotic events were reported in the single temsirolimus arm. • 22% of patients in the temsirolimus arm and 28.6% in the combination arm discontinued study treatment for toxicity. • The response rate for temsirolimus was 22% and 14.3% for the combination arm. • The median PFS for temsirolimus was 5.6 mths and 4.2 mths for the combination arm. • The median OS for temsirolimus was 13.3 mths and 9.6 mths for the combination arm.
Oza A (2015) Phase II	Patients (ECOG PS ≤1) with documented unresectable stage III or IVa, metastatic, or recurrent histologically confirmed endometrial cancer. Median age: 66 yrs	64 66	NR	Ridaforolimus Vs Comparator (progestin or chemotherapy)	PFS OS ORR Safety and tolerability of oral ridaforolimus	• The median PFS for ridaforolimus was 3.6 mths and 1.9 mths for the comparator. The difference was significant (HR, 0.53; 95% CI, 0.31-0.90; p=0.008). • The median OS for ridaforolimus was 10.0 mths and 9.6 mths for the comparator. The difference was not significant (HR, 1.06; 95% CI, 0.7-1.59; p=0.604). • The ORR for ridaforolimus was 0% and 4% for the comparator. The difference was not significant (p=0.925). • Most common grade 3-5 treatment-emergent adverse events in ridaforolimus arm: diarrhea (11.1%), asthenia (7.9%), hyperglycemia (19.0%), anemia (12.7%), and stomatitis (6.3%). • Treatment discontinuation as a result of adverse events in in the treatment arm was 33% versus 6% in the comparator arm.
Pautier P (2017) Phase II	Post-menopausal women (ECOG PS 0-2) with confirmed, advanced, or recurrent endometrial carcinoma not eligible for treatment with surgery or radiotherapy alone; documented estrogen receptor positivity, at least one measurable target lesion, life expectancy ≥6 mths. Median age: 68.1 yrs for irosustat; 67.4 yrs for megestrol acetate	36 37	NR	Irosustat Vs. Megestrol acetate	Percentage of pts alive without progression after 6 mths Clinical benefit ORR PFS TTP OS Duration of response Safety & tolerability	• Percentage of pts alive without progression after 6 mths was 36.1% for irosustat and 54.1% for megestrol acetate. The difference was not significant. • Study was prematurely stopped after futlilty analysis. • The clinical benefit was reached in 57.1% for irosustat-treated patients and 70.6% for megestrol acetate-treated patients. The p-value was not reported. • The ORR was 8.6% for irosustat and 35.3% for megestrol acetate. The p-value was not reported. • The median PFS was 16.1 wks for irosustat and 40.1 wks for megestrol acetate. The difference was not significant. • The median TTP was 16.3 wks for irosustat and 40.1 wks for megestrol acetate. The difference was significant (p=0.04). • The median OS was 63.4 wks for irosustat and not reached for megestrol acetate. The p-value was not reported. • The mean duration of response was not calculable for irosustat and 105.1 wks for megestrol acetate. • Treatment-related toxicities (grade 3-4) were symptomatic hyponatremia, asthenia, dry skin and worsening of hypertension for irosustat (each n=1) and pulmonary embolism (n=2) and

						hyperglycemia (n=1) for megestrol acetate.
McMeekin S (2015) Phase III	Patients (Karnofsky PS ≥70) with histologic or cytologic diagnosis of advanced, recurrent, or metastatic endometrial carcinoma, not curable by local measures. Median age: 64.0 yrs	248 248	NR	Ixabepilone Vs. Control chemotherapy (paclitaxel or doxorubicin)	OS PFS ORR Toxicity Duration of response Time to response	• Interim analysis for futility for OS favoured the control chemotherapy arm (HR, 1.3; 95% CI, 1.0-1.7; p=0.0397). Study was discontinued based on these results. • The median PFS for ixabepilone was 3.4 mths and 4.0 mths for the control chemotherapy arm. The difference was not significant (HR, 1.0; 95% CI, 0.8-1.3; p=0.8011) • The ORR for ixabepilone was 15.2% and 15.7% for the control chemotherapy arm. The difference was not significant. • Study drug-related serious adverse events in the ixabepilone arm were 17% and 12% in the control chemotherapy arm. Two patients in the ixabepilone arm died from study drug toxicity.

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; mths = months; n= sample size; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; TTP = time to progression; vs = versus; wks = weeks; yrs = years

Published Non-Randomized Controlled Trials

Author, year, reference	Population	N	Median Follow-up	Intervention/ Comparison	Outcomes of interest	Brief results
Simpkins F	Patients (GOG PS 0-2) histologically	15	36 mths	Paclitaxel + carboplatin +	6-month PFS	• PFS at 6 months, 93% (95% CI, 82-100)

(2015)	confirmed primary stage III or IV or recurrent endometrial carcinoma. Median age: 63 yrs			bevacizumab	RR OS Toxicity	• Median PFS, 18mths (95% CI, 11-25) • ORR, 73% (95% CI, 45-91) • Median OS, 58 mths (95% CI, 48-68) • Most common grade 3-4 adverse events included neutropenia (66.7%), leukopenia (46.7%), thrombocytopenia (20%)
Konecny GE (2015)	Patients (ECOG PS 0-2) with advanced or metastatic endometrial cancer with progressive disease after first-line antineoplastic treatment, with tissue specimen for FGFR2 assessment and at least one measurable lesion. Median age: 64.5 yrs (FGFR2 –mutated) 65.0 yrs (FGFR2-non-mutated)	22 Vs 31	2.7 mths (1.3-5.5) *for PFS	Dovitinib (FGFR2 –mutated) Dovitinib (FGFR2-non-mutated)	PFS at 18 weeks ORR Duration of response PFS OS Safety & tolerability	• PFS at 18 weeks for FGFR2 –mutated, 31.8% (95% CI, 13.9-54.9); FGFR2-non-mutated , 29.0% (95% CI, 14.2-48.0) • At planned interim analysis, neither group of patients were continued to stage two of the study. • Median PFS for FGFR2 –mutated, 4.1 mths (95% CI, 2.6-5.5); FGFR2-non-mutated , 2.7 mths (95% CI, 1.4-6.8). • Median OS for FGFR2 –mutated, 20.2 mths (95% CI, 8.2-20.2); FGFR2-non-mutated , 9.3 mths (95% CI, 6.0-15.2). • ORR for FGFR2 –mutated, 5%; FGFR2-non-mutated, 16% • Most common grade 3-4 adverse events included hypertension (17%), diarrhea (9%), fatigue (8%) and skin rash (8%).
Slomovitz BM (2015)	Patients (Zubrod PS 0-2) with histologically confirmed progressive or reccurent endometrial cancer who had received up to two prior chemotherapeutic regimens and no history of an invasive malignancy other than endometrial cancer. Median age: 62 yrs	38	14 mths (1.4-46.8)	Everolimus + letrozole	CBR ORR OS PFS	• CBR at 16 weeks, 40% • ORR, 32% (95% CI, 17-49) • Median OS, 14 mths (95% CI, 9.5-24.4) • Median PFS, 3.0 mths (95% CI, 1.9-15.7) • Twelve patients required a dose reduction of everolimus to 5mg. Some of the common grade 3-4 adverse events included diarrhea (5%), headaches (5%), dry mouth (3%), dyspnea (3%), enteritis (3%), and fatigue (11%).
Makker V (2016)	Patients (ECOG PS 0-1) with recurrent or persistent endometrial cancer that was refractory to curative therapy or established treatments.	56	NR	Apitolisib	ORR PFS at 6 mths	• ORR, 6% • Kaplan-Meier estimate at 6 mths, 20% (95% CI, 7-33%)

	Median age: 65.5 yrs				PFS OS Toxicity	• Median PFS, 3.5 mths (95% CI, 2.7-3.7) • Median OS, 15.7 mths (95% CI, 9.2-17.0) • 95% of patients experienced treatment-related adverse events. • Most common treatment-related AEs (grade >=3): hyperglycemia (41%), diarrhea (20%), and rash (30%)
Lindemann K (2014)	Patients (WHO PS 0-2) with histologically confirmed advanced (FIGO stage III-IV) or relapsed endometrial cancer of endometrioid type not considered for curative treatment. Median age: 69.5 yrs	Estrogen-receptor +, 40 Estrogen-receptor -, 12	NR	Examestane	ORR PFS OS Toxicity	• Trial was stopped prematurely in the estrogen-receptor negative patients due to lack of recruitment. • ORR in estrogen-receptor positive patients , 10% • Median PFS in estrogen-receptor positive patients, 3.8 mths (95% CI, 0.7-6.9); estrogen-receptor negative patients, 2.6 mths (95% CI, 2.1-3.1) • Median OS in estrogen-receptor positive patients, 13.3 mths (95% CI, 7.8-18.9); estrogen-receptor negative patients, 6.1 mths (95% CI, 4.1-8.2) • Common grade 3-4 included anorexia (3.8%), venous thrombosis (5.8%), fatigue (3.8%), nausea, vomiting, abdominal pain, and dizziness (1.9% each).
Martin L (2013)	Patients (ECOG PS ≤1) with histologically confirmed advanced and/or metastatic endometrial or cervical cancer with disease progression with at least one measurable lesion, and had failed one prior line of systemic chemotherapy. Median age: 61.5 yrs	12 (EC)	20.1 mths	PM00104 (Zalypsis®)	ORR PFS at 4 mths PFS OS Toxicity	• No objective responses – protocol criteria for further recruitment were not met and recruitment was closed. • Median PFS, 1.8 mths • Median OS, 5.5 mths • Asthenia (47.4%), nasueas (42.1%), vomiting (21.1%), diarrhea (21.2%), anorexia, constipation, night sweats and purexia (15.8% each) were the most common drug-related adverse events. Two patients had grade 3-4 adverse events.

Abbreviations: AE = adverse event; CBR = clinical benefit rates; CI = confidence interval; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; mths = months; n = sample size; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; RR = response rate; vs = versus; WHO = World Health Organization; yrs = years

Abstracts

Author, year, reference	Population	N	Median Follow-up	Intervention/ Comparison	Outcomes of interest	Brief results
Lorusso D (2015) MITO END-2 Randomized, phase II	Patients with advanced (stage III-IV) or recurrent (progression > 6 months after completion of previous platinum chemotherapy) endometrial cancer, and ≤ 1 prior CT lines.	54 54	13 mths	Carboplatin + paclitaxel Vs. Carboplatin + paclitaxel + bevacizumab	PFS ORR Toxicity	• The median PFS was 8.7 mths for carboplatin + paclitaxel and 13.0 mths for carboplatin + paclitaxel + bevacizumab. The difference was significant (HR, 0.57; 95% CI, 0.34-0.96; p = 0.036) • The ORR was 54.3% for carboplatin + paclitaxel and 72.7% for carboplatin + paclitaxel + bevacizumab. A p-value was not reported. • Cardiac toxicity (grade 3) was documented in 4 cases in the carboplatin + paclitaxel + bevacizumab arm and in no cases in the carboplatin + paclitaxel arm.
Miller DS (2014) Randomized, phase III	Patients with endometrial cancer progressing after prior therapy with platinum-taxane-based chemotherapy.	NR	NR	Zoptarelin doxorubicin (AEZS-108) Vs. Doxorubicin	Survival PFS ORR CBR QoL	NR
Aghajanian C (2015) Randomized, phase II	Patients with measurable stage III or IVA, stage IVB or recurrent endometrial cancer	NR	NR	Carboplatin + paclitaxel + bevacizumab Vs. Carboplatin + paclitaxel + temsirolimus Vs. Ixabepilone + carboplatin + bevacizumab	PFS	• PFS was not significantly increased in any experimental arm when compared to historical control (GOG 209). • OS is significantly increased in the carboplatin + paclitaxel + bevacizumab arm (p<0.039) compared with the historical control but not in any of the other arms. • Hypertension (grade 3-4) was more common in the bevacizumab arms (16%) than in the temsirolimus arm (3%) (p=0.001). • Pneumonitis (p=0.004) and oral mucositis (p<0.001) were more common the in temsirolimus arm.
Glasspool RM (2016) Randomized, phase II	Patients with recurrent clear-cell carcinoma of the ovary or endometrium.	NR	NR	Nintedanib Vs. Physicians choice of chemotherapy	PFS	NR

Abbreviations: CBR = clinical benefit rate; CI = confidence interval; mths = months; HR = hazard ratio; NR = not reported; ORR = objective response rate; PFS = progression-free survival; QoL = quality of life; vs = versus

Ongoing Trials

Protocol ID	Official Title	Intervention/ Comparison	Status	Estimated Study Completion Date	Last Updated
NCT02684227	A Phase II Study With a Limited Safety Lead-In of Enzalutamide in Combination With Carboplatin and Paclitaxel in Advanced Stage or Recurrent Endometrioid Endometrial Cancer	Enzalutamide + Carboplatin + Paclitaxel	Recruiting	Aug 2019	March 31, 2017
NCT02064725	A Phase II Study of Sodium Cridanimod in Conjunction With Progestin Therapy in Patients With Progesterone Receptor Negative Recurrent or Persistent Endometrial Carcinoma	Sodium cridanimod + progestin therapy	Active, not recruiting	July 2018	January 23, 2017
NCT02730416	ENGOT-EN1/FANDANGO: A Randomized Phase II Trial of First-line Combination Chemotherapy With Nintedanib / Placebo for Patients With Advanced or Recurrent Endometrial Cancer	Nintedanib + carboplatin + paclitaxel Vs Placebo + carboplatin + paclitaxel	Recruiting	July 2022	March 29, 2017
NCT02866370	A Randomised Phase II Study Of Nintedanib (BIBF1120) Compared To Chemotherapy in Patients With Recurrent Clear Cell Carcinoma Of The Ovary Or Endometrium	For EC Nintedanib Vs. Carboplatin + paclitaxel + doxorubicin	Recruiting	March 2021	August 10, 2016
NCT02549209	Phase II Study of Pembrolizumab in Combination With Carboplatin and Paclitaxel for Advanced or Recurrent Endometrial Adenocarcinoma	Pembrolizumab + paclitaxel + carboplatin	Not open yet	Nov 2019	April 13, 2017
NCT02584478	A Phase 1/2A Evaluation of the Safety and Efficacy of Adding AL3818, a Dual Receptor Tyrosine Kinase Inhibitor, to Standard Platinum-Based Chemotherapy, in Subjects With Recurrent or Metastatic Endometrial, Ovarian, Fallopian, Primary Peritoneal or Cervical Carcinoma (AL3818-US-002)	AL3818 + carboplatin + paclitaxel	Recruiting	Jan 2018	July 11, 2016
NCT01770171	A Randomized Phase II Trial of Carboplatin-Paclitaxel Compared to Carboplatin-Paclitaxel-Bevacizumab in Advanced (Stage III-IV) or Recurrent Endometrial Cancer	Carboplatin + paclitaxel Vs. Carboplatin + paclitaxel + bevacizumab	Recruiting	Dec 2017	January 15, 2013

NCT02725268	A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3Kα Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer	Paclitaxel Vs. Paclitaxel + MLN0128 Vs. MLN0128 Vs. MLN0128 + MLN1117	Recruiting	Aug 2018	May 11, 2017
NCT02755844	A Phase I/II Trial to Assess the Safety and Efficacy of Metronomic Cyclophosphamide, Metformin and Olaparib in Recurrent Advanced/Metastatic Endometrial Cancer Patients	Olaparib + metformin + metronomic cyclophosphamide	Not yet open	Nov 2019	April 26, 2016
NCT02065687	A Randomized Phase II/III Study of Paclitaxel/Carboplatin/Metformin (NSC#91485) Versus Paclitaxel/Carboplatin/Placebo as Initial Therapy for Measurable Stage III or IVA, Stage IVB, or Recurrent Endometrial Cancer	Paclitaxel + carboplatin + metformin Vs. Paclitaxel + carboplatin + placebo	Recruiting	Sept 2019	May 2, 2017
NCT01367002	Randomized Phase II Evaluation of Carboplatin/Paclitaxel With and Without Trastuzumab (Herceptin) in HER2/Neu+ Patients With Advance/Recurrent Uterine Serous Papillary Carcinoma	Carboplatin + paclitaxel + trastuzumab Vs. Carboplatin + paclitaxel	Recruiting	July 2019	January 23, 2017
NCT02423954	A Phase IB/II Study of Nivolumab Plus Chemotherapy in Patients With Advanced Cancer (NivoPlus)	Temsirolimus Vs. Irinotecan Vs. XELIRI Irinotecan + capecitabine	Recruiting	April 2017	December 10, 2015

NCT00063999	Randomized Phase III Trial of Doxorubicin/Cisplatin/Paclitaxel and G-CSF Versus Carboplatin/Paclitaxel in Patients With Stage III & IV or Recurrent Endometrial Cancer	Doxorubicin + cisplatin + paclitaxel + G-CSF Vs. Carboplatin + paclitaxel	Active, not recruiting	June 2013	October 26, 2016
NCT00977574	A Three Arm Randomized Phase II Study of Paclitaxel/Carboplatin/Bevacizumab, Paclitaxel/Carboplatin/Temsirolimus and Ixabepilone/Carboplatin/Bevacizumab as Initial Therapy for Measurable Stage III or IVA, Stage IVB, or Recurrent Endometrial Cancer	Paclitaxel + carboplatin + bevacizumab Vs. Paclitaxel + carboplatin + temsirolimus Vs. Ixabepilone + carboplatin + bevacizumab	Active, not recruiting	Jan 2017	April 25, 2017
NCT01100359	Phase II Multicenter Trial of the Austrian AGO With the Combination of Liposomal Doxorubicin (Myocet®) and Carboplatin in Primary Advanced or Metastatic and Recurrent Endometrial Cancer	Carboplatin + liposome-encapsulated doxorubicin citrate	Unknown	Oct 2010	August 6, 2013
NCT00006903	Phase II Study of Faslodex In Recurrent/Metastatic Endometrial Cancer	Fulvestrant	Unknown	Nov 2010	May 29, 2015

Abbreivations: EC = endometrial cancer; G-CSF = filgrastim

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