



## Chemotherapy (gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) in inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma: a clinical practice guideline

*A.A. Gupta MD MSc,\* X. Yao MSc,† S. Verma MD,‡ H. Mackay MD,§ and L. Hopkins MD MSc|| on behalf of the Sarcoma Disease Site Group and the Gynecology Cancer Disease Site Group*

### ABSTRACT

#### Questions

Does chemotherapy—that is, gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin—improve clinical outcomes in women with inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma (LMS)?

Is there a difference in the tumour response rate to chemotherapy between recurrent pelvic disease and extrapelvic metastases in the target patients?

#### Methods

This guideline was developed by Cancer Care Ontario's Program in Evidence-Based Care, the Sarcoma Disease Site Group (DSG), and the Gynecologic Cancer DSG. The core methodology was the systematic review. The MEDLINE and EMBASE databases (2004 to June 2011), the Cochrane Library, main guideline Web sites, and relevant annual meeting abstracts (2005–2010) were searched. Internal and external reviews were conducted, with final approval by the DSGs and the Program in Evidence-Based Care.

#### Clinical Practice Guideline

Based on currently available evidence from the medical literature (four single-arm phase II studies, one arm of a randomized controlled trial, and one abstract), doxorubicin alone, gemcitabine alone, or gemcitabine plus docetaxel may be treatment options in first- or second-line therapy (or both) for women with inoperable, locally advanced, recurrent, or metastatic uterine LMS.

Hematologic toxicity is common and should be monitored, and granulocyte colony-stimulating factor should be considered when gemcitabine plus docetaxel is used. Other toxicities, such as neurotoxicity, pulmonary toxicity, and cardiovascular toxicity should be monitored.

No recommendation is made for or against the use of trabectedin in the targeted patients.

No data were available concerning differences in response in recurrent pelvic disease or extrapelvic metastases, or concerning quality of life.

#### KEY WORDS

Chemotherapy, clinical practice guideline, uterine leiomyosarcoma

#### 1. INTRODUCTION

Uterine sarcomas are a heterogeneous group of malignancies that include leiomyosarcoma (LMS), endometrial stromal sarcoma, adenosarcoma, and carcinosarcoma<sup>1</sup>. In 2005, the Gynecologic Cancer Disease Site Group (DSG) and the Cancer Care Ontario (CCO) Program in Evidence-Based Care (PEBC) in Ontario, Canada, developed a guideline on systemic therapy for advanced, recurrent, or metastatic uterine sarcoma (which included all types of uterine sarcoma) by searching the literature from 1980 to June 2004<sup>2</sup>. To keep the guideline relevant, current, and evidence-based for its end users, CCO's PEBC, the Sarcoma DSG, and the Gynecologic Cancer DSG decided to update the guideline. Given that the Committee on Gynecologic Oncology of the International Federation of Gynecology and Obstetrics updated the staging criteria for all four uterine sarcomas types<sup>1</sup> and that the clinical management of each type is very different, the current guideline focuses on the role of systemic chemotherapy in uterine LMS exclusively.

#### 2. QUESTIONS

What impact does chemotherapy—that is, gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin—have on clinical outcomes [that is, tumour response rate, progression-free survival (PFS), overall survival (OS), toxicity, and quality of life] in

women with inoperable, locally advanced, recurrent, or metastatic uterine LMS?

Is there a difference in the tumour response rate to chemotherapy—that is, with gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin—between recurrent pelvic disease and extrapelvic metastases in patients with uterine LMS?

### 3. METHODS

This guideline was developed by CCO's PEBC, the Sarcoma DSG, and the Gynecologic Cancer DSG using the methods of the practice guidelines development cycle<sup>3</sup>. For this project, the core methodology used to develop the evidentiary base was the systematic review. The PEBC is mandated to post its approved practice guidelines on the CCO Web site (<http://www.cancercare.on.ca/>) for dissemination to Ontario oncologists<sup>4</sup>.

#### 3.1 Literature Search

The systematic review will be published separately. Briefly, MEDLINE and EMBASE (from January 2004 to June 2011), the Cochrane Library, main guideline Web sites, and the American Society of Clinical Oncology and Connective Tissue Oncology Society annual meeting abstracts from 2005 to 2010 were searched. Pre-planned study selection criteria were used to screen the literature retrieved. The studies included in the 2005 guideline that also met the study selection criteria for this new guideline were eligible for inclusion. Evidence from the available medical literature forms the basis for the recommendations developed by the Sarcoma DSG and the Gynecologic Cancer DSG.

#### 3.2 Internal Review

Before the draft report was sent for external review, it was reviewed and approved by the PEBC Report Approval Panel, which consists of 3 members: 2 oncologists with expertise in clinical and methodology issues, and a methodologist.

#### 3.3 External Review

The PEBC external review process is two-pronged and includes

- a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts, and
- a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

##### 3.3.1 Targeted Peer Review

During the guideline development process, 10 targeted peer reviewers from Ontario and other provinces

considered to be clinical or methodology experts on the topic were identified by the Sarcoma and the Gynecologic Cancer DSGs. Several weeks before completion of the draft report, the nominees were contacted by e-mail and asked to serve as reviewers. Three nominees agreed and were sent the draft report and a questionnaire by e-mail. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and asking whether the draft recommendations should be approved as a guideline. Written comments were invited. Follow-up reminders were sent at 2 weeks (e-mail) and at 4 weeks (telephone call).

##### 3.3.2 Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of this guideline in Ontario. The 65 clinicians in the PEBC database located in a search using the terms "sarcoma" or "uterus" were contacted by e-mail about the availability of the survey. They were directed to the survey Web site; were provided with access to the survey, the guideline recommendations, and the evidentiary base; and were asked to rate the overall quality of the guideline and whether they would use and recommend it. Written comments were invited.

## 4. RESULTS

### 4.1 Literature Search Results

The MEDLINE and EMBASE searches identified 5048 citations. A check of abstracts from the American Society of Clinical Oncology and the Connective Tissue Oncology Society annual meetings yielded one abstract that met the study selection criteria. The reference lists of the included articles were hand-searched, and no further eligible papers were found. Two eligible studies were found after checking the 2005 guideline. Five full-text articles<sup>5-9</sup> and one abstract<sup>a</sup> met the pre-planned study selection criteria. Overall, the quality of evidence was poor to moderate.

### 4.2 DSG Consensus Process

The draft guideline, based on the systematic review, was circulated for review and discussion and was approved by the Sarcoma DSG and the Gynecologic Cancer DSG in February 2012.

<sup>a</sup> Duffaud F, Pautier P, Nguyen BB, *et al.* A pooled analysis of the final results of the 2 randomized phase II studies comparing gemcitabine vs. gemcitabine+docetaxel in patients with metastatic/relapsed leiomyosarcoma [abstract 898573]. Presented at the Connective Tissue Oncology Society 16th Annual Meeting; Paris, France; November 11–13, 2010.

### 4.3 Internal Review

The PEBC Report Approval Panel raised these key issues:

- The combination of gemcitabine and docetaxel is not clearly superior to gemcitabine alone and appears to have significantly more hematologic toxicity.
- The comments about toxicity should be expanded. In particular, the degree of anemia with the gemcitabine–docetaxel combination should be commented on. Similarly, the recommendation states that pulmonary and cardiovascular toxicity should be monitored. It would be helpful to state the incidence of cardiotoxicity that has been identified in the studies and, in the toxicity section, to expand on what is meant by cardiovascular toxicity.
- Was there more evidence to support doxorubicin as the standard other than the Omura study?

Feedback received from the Report Approval Panel was addressed by the authors<sup>4</sup>.

### 4.4 External Review

After approval of the guideline at internal review, the Sarcoma and Gynecologic Cancer DSGs circulated the draft guideline (with recommendations modified as noted in the internal review) to external review participants for review and feedback.

#### 4.4.1 Targeted Peer Review

Responses were received from 3 reviewers by May 3, 2012. Table 1 summarizes key results of the

feedback survey. The written comments raised these main concerns:

- Literature is available for first- and second-line treatment, but this population of patients will likely go to at least third-line treatment. Is there a hint of trabectedin demonstrating some effectiveness in that setting?
- In regard to the second question, I'm not sure that it should be included in this set of guidelines as you have no answer because there is no evidence to speak of.
- I'm not sure why trabectedin was included when it is not readily available in North America.
- I suppose that because of the lack of studies, no cost analysis was possible, but a quick mention that the cost difference is considerable would be helpful.

#### 4.4.2 Professional Consultation

The notification message was sent by e-mail on March 23, 2012, and the consultation period ended on May 7, 2012. Of the 19 responses received (29%), 10 indicated a lack of interest in the subject or current unavailability to review the guideline. Table 11 summarizes the key results from 9 clinicians. The main written comments were these:

- It will be useful if the guideline can be used to argue for funding for a particular chemotherapy agent.
- The authors have over-interpreted the phase II data and underemphasized the Duffaud 2010 abstract that suggests a lack of advantage for docetaxel and gemcitabine over gemcitabine alone.
- Rather than recommendations to use granulocyte colony–stimulating factor, it would be more

TABLE 1 Responses to eight items on the targeted peer-reviewer questionnaire

Item	Reviewer rating (n=3)				
	Lowest quality (1)	(2)	(3)	(4)	Highest quality (5)
Rate the guideline development methods.	0	0	0	2	1
Rate the guideline presentation.	0	0	0	0	3
Rate the guideline recommendations.	0	0	0	1	2
Rate the completeness of reporting.	0	0	0	1	2
Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	2	1
Rate the overall quality of the guideline report.	0	0	0	1	2
	<i>Strongly disagree</i> (1)	(2)	<i>Neutral</i> (3)	(4)	<i>Strongly agree</i> (5)
I would make use of this guideline in my professional decisions.	0	0	0	1	2
I would recommend this guideline for use in practice.	0	0	0	1	2

TABLE II Responses to 3 items on the professional consultation survey

<i>Item</i>	<i>Response (%)</i>				
	<i>Lowest quality (1)</i>	<i>(2)</i>	<i>(3)</i>	<i>(4)</i>	<i>Highest quality (5)</i>
Rate the overall quality of the guideline report.	0	11	11	67	11
I would make use of this guideline in my professional decisions.	11	11	22	22	33
I would recommend this guideline for use in practice.	11	11	22	33	22

appropriate to suggest dose reduction for neutropenia, since this is palliative therapy with limited efficacy and no evidence of survival prolongation. Granulocyte colony-stimulating factor would not be covered in Ontario for this indication.

- Data for the indications for the use of trabectedin are not discussed at all in this document and are briefly alluded to in the evidentiary base. The Demetri paper does not appear to include uterine LMS; it was almost completely inactive in LMS from other sites (relative risk < 5%), and so it would be appropriate to recommend against its use in uterine LMS, in the absence of formal testing in uterine LMS.

## 5. PRACTICE GUIDELINE

This report reflects integration of the feedback obtained through the external review process with the final approval given by the Sarcoma DSG and the Gynecologic Cancer DSG and the Report Approval Panel of the PEBC.

### 5.1 Recommendations

The Sarcoma DSG and the Gynecologic Cancer DSG offer these recommendations:

- Based on current available evidence from the medical literature [four single-arm phase II studies, one arm of a randomized controlled trial (RCT), and one abstract], doxorubicin alone, gemcitabine alone, or gemcitabine plus docetaxel may be treatment options for first- and second-line therapy in women with inoperable, locally advanced, recurrent, or metastatic uterine LMS.
- Hematologic toxicity is common and should be monitored, and granulocyte colony-stimulating factor should be considered when gemcitabine plus docetaxel is used.
- Other toxicities, such as neurotoxicity, pulmonary toxicity, and cardiovascular toxicity should be monitored.

- No recommendation is made for or against using trabectedin in the targeted patients.
- Patients should be encouraged to participate in clinical trials testing novel or targeted approaches in this disease.

### 5.2 Qualifying Statement

The following chemotherapy agent doses were suggested from the included studies:

- Doxorubicin: 60–80 mg/m<sup>2</sup> intravenously (IV) every 3 weeks
- Gemcitabine: 1000 mg/m<sup>2</sup> IV on days 1, 8, and 15 every 4 weeks
- Gemcitabine plus docetaxel: gemcitabine 900 mg/m<sup>2</sup> IV on days 1 and 8, followed by docetaxel 100 mg/m<sup>2</sup> IV on day 8 every 3 weeks

### 5.3 Key Evidence

No trials of high methodologic quality have documented the outcomes of patients with advanced or metastatic uterine LMS when no prior systemic therapy was administered. Doxorubicin has been considered the standard of care for more than 30 years.

Table III shows survival, response rate, and toxicity for each regimen.

To date, the evidence is insufficient to support or refute the use of trabectedin in the targeted patients.

## 6. DISCUSSION

Doxorubicin alone has long been considered standard treatment for patients with inoperable, locally advanced, recurrent, or metastatic soft-tissue sarcoma, including women with uterine LMS<sup>10,11</sup>.

The studies included in this systematic review must have reported at least one relevant outcome in 20 or more targeted patients. Studies that did not perform subset analyses for uterine LMS were excluded.



TABLE III Clinical outcomes for each chemotherapy regimen in advanced uterine leiomyosarcoma

Regimen	1st- or 2nd-line therapy	Median OS (months)	Median PFS (months)	Response rate, CR+PR [% (95% CI)]	Grades 3–4 toxicity (%)
Doxorubicin <sup>5,a</sup>	1st and 2nd	12.1	NR	25 (9–41)	Leukopenia: 16 Thrombocytopenia: 4 Questionable cardiac toxicity: 3 (no detail)
Gemcitabine <sup>6,b</sup>	2nd	NR	NR	21 (7–31)	Leukopenia: 27 Thrombocytopenia: 11 Red blood cell transfusion: 9 Neurotoxicity: 5 Pulmonary toxicity: 5 Cardiovascular toxicity: 5 (no detail)
Gemcitabine plus docetaxel <sup>7–9,c</sup>	1st and 2nd	14.7–16.1	4.4–6.7	27 to 53 (15–42 to 35–70)	Leukopenia: 14–23 Thrombocytopenia: 14–40 Red blood cell transfusion: 43–50 Neurotoxicity: 0–6 Pulmonary toxicity: 0–8
Gemcitabine versus Gemcitabine plus docetaxel (abstract) <sup>d</sup>	1st and 2nd	NR	4.9	18 (2–34)	NR
	1st and 2nd	NR	6.0	23 (8–38)	NR

<sup>a</sup> Adverse effects were assessed using study-defined criteria.

<sup>b</sup> Standard Gynecologic Oncology Group response criteria were used for toxicity grading.

<sup>c</sup> The U.S. National Cancer Institute Common Toxicity Criteria were used for toxicity grading.

<sup>d</sup> Duffaud F, Pautier P, Nguyen BB, *et al.* A pooled analysis of the final results of the 2 randomized phase II studies comparing gemcitabine vs. gemcitabine+docetaxel in patients with metastatic/relapsed leiomyosarcoma [abstract 898573]. Presented at the Connective Tissue Oncology Society 16th Annual Meeting; Paris, France; November 11–13, 2010.

OS = overall survival; PFS = progression-free survival; CR = complete response; PR = partial response; CI = confidence interval; NR = not reported.

Although the 1983 Omura *et al.* study<sup>12</sup> used a doxorubicin dose of 60 mg/m<sup>2</sup> IV every 3 weeks, it was conducted 30 years ago, and a dose of 70–80 mg/m<sup>2</sup> IV every 3 weeks has been used for locally advanced or metastatic soft-tissue sarcoma since 1990. Thus, in the qualifying statement, the suggested dose of doxorubicin is 60–80 mg/m<sup>2</sup> IV every 3 weeks.

Single-arm studies of gemcitabine plus docetaxel have reported numerically longer median OS (14.7–17.9 months vs. 12.1 months) and numerically higher objective response rates (27%–53% vs. 25%) than have been reported in the study of single-agent doxorubicin. Compared with doxorubicin, the combination of gemcitabine–docetaxel resulted in more toxicity. Given that no randomized comparisons of these regimens have been conducted, no conclusions can be drawn about the superiority of gemcitabine–docetaxel compared with doxorubicin. It is unlikely that such a comparative study will be undertaken, and

the recommendations about gemcitabine–docetaxel are therefore derived from phase II trial data.

The only available study for single-agent gemcitabine reported a tumour response rate of 21%<sup>6</sup>, which is not superior to the 25% response rate with single-agent doxorubicin<sup>5</sup>. Furthermore, the trial did not report OS or PFS. Thus, it is unclear from that study whether gemcitabine alone can improve survival or PFS for the targeted patients. The only available randomized data came from an abstract<sup>b</sup> that considered pooled data from two RCTs and that failed to demonstrate the superiority of gemcitabine–docetaxel over gemcitabine alone in terms of tumour response rate and PFS or to provide information about OS. However, recommendations cannot be made based on published abstracts. Without published RCTs or good-quality comparative studies, and after considering the balance between the benefits and harms from these chemotherapeutic agents, one treatment option cannot be recommended over another.

Hematologic toxicity is common for all the treatment options. The use of granulocyte colony-stimulating factor should be considered when gemcitabine–docetaxel is used, if the patient has private drug insurance to cover the cost of that drug. However, in the absence of private insurance, clinicians may consider chemotherapy dose reductions or the addition of prophylactic oral antibiotics.

## 7. FUTURE RESEARCH

A search of the U.S. National Cancer Institute clinical trials database ([http://www.cancer.gov/clinical\\_trials](http://www.cancer.gov/clinical_trials)) on August 19, 2011, for ongoing trials found only one arm of an ongoing RCT investigating the effect of gemcitabine–docetaxel that met the selection criteria for the present systematic review. The other eight studies that might have been included focused on patients with advanced soft-tissue sarcoma, and confirmation about whether a subgroup analysis for 20 or more patients with advanced or recurrent uterine LMS will be included in those studies is required. No eligible studies addressed differences in tumour response rates between pelvic and extrapelvic metastases in patients with uterine LMS. Thus, well-designed and good-quality RCTs are needed to investigate the efficacy of chemotherapy in patients with inoperable, locally advanced, recurrent, or metastatic uterine LMS.

## 8. NOTE

The Duffaud *et al.* study was fully published in a peer-reviewed journal in August 2012<sup>13</sup>. That publication, a phase II RCT lacking a sufficient sample size calculation, showed no significant difference between gemcitabine alone and gemcitabine–docetaxel (as in the 2010 abstract<sup>b</sup>), and therefore it remains unclear whether the lack of difference is a result of the study being underpowered or whether there truly was no difference. Thus, the working group members stand by their current recommendations. This guideline will follow the CCO PEBC update policy as described in the next subsection.

## 9. UPDATES

This document will be reviewed in 3 years' time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review

<sup>b</sup> Duffaud F, Pautier P, Nguyen BB, *et al.* A pooled analysis of the final results of the 2 randomized phase II studies comparing gemcitabine vs. gemcitabine+docetaxel in patients with metastatic/relapsed leiomyosarcoma [abstract 898573]. Presented at the Connective Tissue Oncology Society 16th Annual Meeting; Paris, France; November 11–13, 2010.

will be posted on the CCO Web site. If new evidence that will result in changes to these recommendations becomes available before 3 years have elapsed, an update will be initiated as soon as possible.

## 10. ACKNOWLEDGMENTS

The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through CCO. All work produced by the PEBC is editorially independent from its funding source.

## 11. CONFLICT OF INTEREST DISCLOSURES

The guideline authors declared they have no financial conflicts of interest. One Sarcoma DSG member declared conflicts and reported receiving \$10,000 or less as honoraria for speaking at annual meetings and \$10,000 for mutational analysis for gastrointestinal stromal tumour from Novartis Oncology; other Sarcoma DSG members had no financial conflicts of interest. The Gynecologic Cancer DSG members declared they had no financial conflicts of interest. The Report Approval Panel members and the targeted external reviewers declared that they had no financial conflicts of interest.

## 12. REFERENCES

- FIGO Committee on Gynecologic Oncology. FIGO staging for uterine sarcomas. *Int J Gynaecol Obstet* 2009;104:179.
- Kanjeekal S, Chambers A, Fung MF, Verma S. Systemic therapy for advanced uterine sarcoma: a systematic review of the literature. *Gynecol Oncol* 2005;97:624–37.
- Browman GP, Levine MN, Mohide EA, *et al.* The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502–12.
- Gupta A, Yao X, Verma S, Mackay H, Hopkins L on behalf of the Sarcoma Disease Site Group (DSG), and the Gynecology Cancer DSG. *Chemotherapy (i.e., Gemcitabine, Docetaxel Plus Gemcitabine, Doxorubicin, or Trabectedin) for Inoperable, Locally Advanced, Recurrent, or Metastatic Uterine Leiomyosarcoma*. Evidence-based series 11-11. Toronto, ON: Cancer Care Ontario, Program in Evidence-Based Care; 2012.
- Omura GA, Major FJ, Blessing JA, *et al.* A randomized study of Adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. *Cancer* 1983;52:626–32.
- Look KY, Sandler A, Blessing JA, Lucci JA 3rd, Rose PG on behalf of the Gynecologic Oncology Group (GOG) Study. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) study. *Gynecol Oncol* 2004;92:644–7.
- Hensley ML, Maki R, Venkatraman E, *et al.* Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol* 2002;20:2824–31.
- Hensley ML, Blessing JA, Degeest K, Abulafia O, Rose PG, Homesley HD. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a

- Gynecologic Oncology Group phase II study. *Gynecol Oncol* 2008;109:323–8.
9. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol* 2008;109:329–34.
  10. Sleijfer S, Seynaeve C, Verweij J. Using single-agent therapy in adult patients with advanced soft tissue sarcoma can still be considered standard care. *Oncologist* 2005;10:833–41.
  11. Sarcoma Disease Site Group. *Doxorubicin-Based Chemotherapy for the Palliative Treatment of Adult Patients with Locally Advanced or Metastatic Soft Tissue Sarcoma*. Evidence-based series 11-1. Ver. 2. Toronto, ON: Cancer Care Ontario, Program in Evidence-Based Care; 2011.
  12. Bramwell VH, Anderson D, Charette ML on behalf of the Sarcoma Disease Site Group. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. *Cochrane Database Syst Rev* 2003;:CD003293.
  13. Pautier P, Floquet A, Penel N, *et al*. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed

leiomyosarcomas: a Fédération nationale des centres de lutte contre le cancer (FNCLCC) French Sarcoma Group Study (TAXO-GEM study). *Oncologist* 2012;17:1213–20.

**Correspondence to:** Abha Gupta, c/o Xiaomei Yao, 60 (G) Wing, 2nd Floor, Room 222, McMaster University, Henderson Site, 711 Concession Street, Hamilton, Ontario L8V 1C3.

**E-mail:** yaoxia@mcmaster.ca, ccopgi@mcmaster.ca

\* Department of Hematology/Oncology, The Hospital for Sick Children, Toronto, ON.

† Cancer Care Ontario, Program in Evidence-Based Care, Department of Oncology, McMaster University, Hamilton, ON.

‡ Department of Medical Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, ON.

§ Department of Medical Oncology, University Health Network, Princess Margaret Hospital, Toronto, ON.

|| Department of Obstetrics and Gynecology, The Ottawa Hospital, Ottawa, ON.