

# Singapore Cancer Network (SCAN) Guidelines for Front-Line Systemic Therapy of Newly Diagnosed Advanced Epithelial Ovarian Cancer

The Singapore Cancer Network (SCAN) Gynaecological Cancers Systemic Therapy Workgroup

## Abstract

**Introduction:** The SCAN gynaecological cancers systemic therapy workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for front-line systemic therapy of advanced epithelial ovarian cancer. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2013), the European Society of Medical Oncology (2013), the National Institute of Health and Clinical Excellence (2011), the Scottish Intercollegiate Guidelines Network (2011) and the Greater Metropolitan Clinical Taskforce (2009). Recommendations on the role of systemic therapy with intravenous chemotherapy, intraperitoneal chemotherapy, anti-angiogenic agents and neoadjuvant chemotherapy in newly diagnosed advanced epithelial ovarian cancer were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for front-line systemic therapy of advanced epithelial ovarian cancer.

Ann Acad Med Singapore 2015;44:421-33

**Key words:** Clinical practice guidelines, Chemotherapy, Anti-angiogenics

## Introduction

Epithelial ovary cancer (EOC) is one of the most challenging cancers to treat and remains the most lethal of all gynaecological cancers worldwide.

Ovarian cancer is the fifth most common cancer and the seventh most common cause of cancer mortality amongst females in Singapore. Over the last 40 years, the incidence of ovarian cancer has climbed continuously from 6.2 per 100,000 (1973 to 1977) to 12.4 per 100,000 (2008 to 2012). A total of 1587 new cases of ovarian cancer were diagnosed between 2008 and 2012. The majority of women (70%) present with advanced disease (International Federation of Gynecology and Obstetrics (FIGO) stage III or IV) due to the lack of effective screening and “silent presentation”. Prognosis for advanced stage disease is poor—the 5-year age-standardised overall survival (OS) was 30.5% and 11.5% for stage III and stage IV disease, respectively.<sup>1</sup>

Treatment of advanced EOC involves a 2-pronged

approach, with cytoreductive surgery and chemotherapy as the mainstays of primary therapy.

Cytoreductive surgery aims to remove all macroscopic disease as resection has consistently been shown by retrospective studies to be associated with improved progression-free survival (PFS) and OS.<sup>2,3</sup> However, prospective randomised studies are lacking and whether or not diseases amenable to complete resection are biologically different from those which cannot be completely resected remains a controversial question.

For the last 15 years, the gold standard of care has been to administer platinum-taxane chemotherapy intravenously every 3 weeks postdebulking surgery. However, the optimal method of administering platinum-taxane chemotherapy remains to be determined. In recent years, variables such as the scheduling (dose-dense vs 3-weekly), route of drug administration (intraperitoneal (IP) vs intravenous (IV)) and the timing of chemotherapy (neoadjuvant vs frontline)

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have challenged the conventional platinum-taxane regimen. Targeted therapy is also making inroads into the front-line treatment of advanced EOC.

### **The SCAN Guidelines for Front-line Systemic Therapy of Advanced EOC**

The SCAN Guidelines are clinical practice guidelines for the front-line systemic treatment of newly diagnosed advanced EOC. It includes guidelines for the treatment of FIGO stage II, III or IV EOC (based on the 1997 FIGO staging for ovary cancer) but excludes carcinosarcoma and non-epithelial cancer of the ovary.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of advanced EOC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

### **Target Users of the Guidelines**

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with ovarian cancer.

### **Guideline Recommendations/Development**

The SCAN Gynaecological Cancers Workgroup comprises a panel of 8 medical oncologists and 1 oncology pharmacist from Singapore with special interests in the management of gynaecological cancers. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework<sup>4</sup> was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the

extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to answer the following questions pertaining to front-line systemic therapy for women with newly diagnosed advanced EOC:

1. What is the optimal IV chemotherapy regimen for advanced EOC following primary cytoreductive surgery?
2. What is the role of IP chemotherapy in women with optimally debulked advanced EOC?
3. What is the role of front-line bevacizumab?
4. What is the role of neoadjuvant chemotherapy in advanced EOC?

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Guidelines for Ovarian Cancer Version 2.2013” by the National Cancer Comprehensive Network (NCCN, USA)<sup>5</sup>
- “Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society of Medical Oncology (ESMO), 2013<sup>6</sup>
- “SIGN 135. Management of Epithelial Ovarian Cancer. A National Clinical Guideline” by the Scottish Intercollegiate Guidelines Network (SIGN, UK), November 2013<sup>7</sup>
- “Ovarian Cancer: the Recognition and Initial Management of Ovarian Cancer (CG122)” by the National Institute of Health and Clinical Excellence (NICE, UK), 2011<sup>8</sup>
- “Best Clinical Practice. Gynaecological Cancer Guidelines 2009” by the Greater Metropolitan Clinical Taskforce (GMCT, Australasia)<sup>9</sup>

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of advanced EOC, it will be reviewed earlier.

## 1. What is the Optimal IV Chemotherapy Regimen for Advanced EOC Following Primary Cytoreductive Surgery?

### *Platinum-taxane Chemotherapy*

As advanced EOC has a high risk of recurrence when treated with debulking surgery alone, chemotherapy following surgery is recommended. Platinum-paclitaxel has been the standard of care for the last 15 years, a consequence of 2 high quality landmark phase III randomised controlled trials (RCTs), the GOG 111 and EORTC-NCIC OV10. These trials demonstrated that cisplatin-paclitaxel combinations yield significant improvements in PFS and OS in women with advanced EOC following primary cytoreductive surgery as compared to cisplatin-cyclophosphamide chemotherapy.<sup>10,11</sup>

### *Cisplatin versus Carboplatin*

The combination carboplatin-paclitaxel has demonstrated similar efficacy as cisplatin-paclitaxel but has advantages such as a more favourable toxicity profile and added convenience due to it being administered in an outpatient setting. These advantages have been demonstrated in 2 non-inferiority phase III RCTs.<sup>12,13</sup>

Carboplatin-paclitaxel has since become the worldwide standard of care in front-line treatment of EOC. The most commonly used schedule is carboplatin (AUC 5-6) in combination with paclitaxel (175 mg/m<sup>2</sup>), both administered intravenously every 3 weeks. Typically, 6 cycles of chemotherapy are given. There is no evidence to suggest that improved outcomes will be obtained with more than 6 cycles of chemotherapy.

### *Paclitaxel Intolerance*

For women who are allergic to or intolerant of paclitaxel, carboplatin-pegylated liposomal doxorubicin (PLD) can be considered as an alternative, based on a single phase III RCT, the MITO-2 study.<sup>14</sup> PLD (30 mg/m<sup>2</sup>) in combination with carboplatin (AUC 5) given every 3 weeks yielded similar PFS and OS as the paclitaxel (175 mg/m<sup>2</sup>) and carboplatin (AUC 5) combination.

### *Patients Unfit for Combination Chemotherapy*

Women who are unfit for combination chemotherapy can be given single-agent carboplatin, as indicated by the International Collaborative Ovarian Neoplasm (ICON) 3 findings.<sup>15</sup>

### *Adding in a Third Cytotoxic Drug*

To date, there have been at least 5 good quality phase III RCTs involving more than 6000 patients that investigate the

addition of a third cytotoxic drug to the standard platinum and paclitaxel combination, either as triplet therapy<sup>16-19</sup> or as sequential doublets.<sup>20</sup> Not only did the addition of a third drug not improve survival outcomes, it also enhanced toxicities, in particular haematological toxicities.

### *Chemotherapy Scheduling: Dose-dense Chemotherapy*

The rationale for dose-dense chemotherapy comes from the Norton-Simon hypothesis, which states that increasing the dose density of chemotherapy reduces the chance of emergence of resistant clones and improves efficacy by reducing the regrowth of tumour cells between treatment cycles.<sup>21</sup>

This concept was tested in a single large phase III RCT in Japan (NOVEL-JGOG 3062). In this trial, IV paclitaxel (80 mg/m<sup>2</sup>) given weekly in combination with IV carboplatin (AUC 6) given every 3 weeks resulted in significant improvement in PFS and OS in women with advanced EOC as compared to those of the standard IV carboplatin and paclitaxel regimen.<sup>22</sup> Long-term follow-up results showed that at a median follow-up of 76.8 months, the median PFS was 28.2 months in the dose-dense arm (vs 17.5 months in the conventional group; HR = 0.76; 95% CI, 0.61 to 0.91; *P* = 0.0037) and the median OS was 100.5 months (vs 62.2 months in the conventional group; HR = 0.79; 95% CI, 0.63 to 0.99; *P* = 0.039). However, the dose-dense carboplatin-paclitaxel combination was associated with greater haematological toxicities leading to greater dose-delays and lower completion rates. Less than half of the patients completed treatment according to study protocol and 38% of patients stopped this regimen prematurely (vs 21% in the conventional group). Incidence of grade III or IV anaemia was significantly higher in the dose-dense arm (69% vs 44%; *P* < 0.001). Dose-dense chemotherapy is also more inconvenient due to the weekly treatment schedule. The overall quality of life (QoL) did not differ significantly between the 2 treatment groups.<sup>23</sup> However, according to the taxane subscale, QoL was significantly lower in the dose-dense group, a consequence of the increased neurotoxicity (*P* = 0.02).

A second dose-dense study, the MITO-7, was a recently published<sup>24</sup> phase III RCT that used a different chemotherapy schedule from the JGOG 3062. It administered IV carboplatin (AUC 2) in combination with paclitaxel (80 mg/m<sup>2</sup>) weekly in the treatment of EOC following primary debulking surgery. Although the weekly regimen has a more favourable toxicity profile compared with the conventional 3-weekly chemotherapy, contrary to the JGOG 3062, there was no difference in PFS between the 2 treatment arms. The OS data was immature. The findings of 2 other dose-dense studies, the GOG 262 (NCT 00951496) and the ICON 8 (NCT 01654146), are yet to be published.<sup>25,26</sup>

*Cost-effectiveness Analyses for Dose-dense Chemotherapy*

An actual cost data collection was not performed by the JGOG 3062. However, a cost-effectiveness analysis using the Markov economic decision model found that dose-dense paclitaxel administered weekly is a cost-effective treatment option for advanced ovarian cancer.<sup>27</sup> The incremental cost-effectiveness ratio was USD \$4859 per progression-free life-year saved for the dose-dense weekly regimen as compared to the conventional 3-weekly regimen.

**Recommendations for Front-line IV Chemotherapy Following Primary Cytoreductive Surgery**

The SCAN workgroup has voted 6 to 2 in favour of the adoption of the SIGN guidelines<sup>7</sup> for front-line IV chemotherapy following cytoreductive surgery (Table 1 and Supplementary Table 1) due to its comprehensive nature. The workgroup also recommends the discussion of dose-dense chemotherapy as a treatment option with patients.

There is unanimous agreement amongst the working

Table 1. Singapore Cancer Network (SCAN) Guidelines for Front-line Systemic Treatment for Advanced Epithelial Ovary Cancer

	<b>Guideline Recommendations</b>
What is the Optimal IV Chemotherapy Postprimary Cytoreductive Surgery?	<p>SIGN Guidelines: Carboplatin is the platinum drug of choice in both single and combination therapy (A).</p> <p>Paclitaxel is recommended in combination therapy with platinum in the first-line postsurgery treatment of EOC where the potential benefits justify the toxicity of the therapy.</p> <p>In those unable to tolerate paclitaxel, pegylated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative (A).</p> <p>Patients who are unfit for combination therapy should be offered single-agent carboplatin (A).</p> <p>A third cytotoxic agent should not be added to carboplatin and paclitaxel (A).</p> <p>Dose-dense chemotherapy: Carboplatin AUC 6 (day 1 q21) and paclitaxel 80 mg/m<sup>2</sup> (days 1, 8, 15 q21) may be considered for the treatment of first-line ovarian cancer. The increased toxicity and frequency of visits need to be discussed with the patient (B).</p>
What is the Role of IP Chemotherapy in Optimally Debulked Advanced EOC?	<p>ESMO Guidelines: IP treatment has not been adopted as standard of care in view of its greater toxicity and difficulty delivering all the planned treatment.</p> <p>Lack of current standard intravenous chemotherapy in the standard arms of the IP trials has made the interpretation of the results difficult.</p> <p>Recommends IP chemotherapy in the context of clinical trial.</p>
What is the Role of Upfront Bevacizumab in Advanced EOC?	<p>ESMO Guidelines: Bevacizumab is recommended for patients with poor prognostic features (as defined in ICON7 Trial):</p> <ul style="list-style-type: none"> <li>• stage IV</li> <li>• suboptimal debulking (I,B)</li> </ul> <p>Bevacizumab should be given with paclitaxel and carboplatin with a treatment duration of 1 year.</p> <p>Bevacizumab has been licensed by the EMA at 15 mg/kg for use with carboplatin and paclitaxel for ≤15 months or until progression.</p>
What is the Role of Neoadjuvant Chemotherapy in Advanced EOC?	<p>NCCN Guidelines: Consider neoadjuvant chemotherapy/primary interval cytoreduction (diagnosis by fine needle aspiration, biopsy or paracentesis) for patients with bulky stage III/IV who are poor surgical candidates due to high-risk comorbidity conditions or disease factors (Category I).</p> <p>Published data demonstrates that primary assessments and debulking by a gynaecologic oncologist results in a survival advantage. Patients being evaluated for neoadjuvant chemotherapy should be seen by a fellowship-trained gynaecologic oncologist prior to being considered a poor surgical candidate.</p>

EMA: European Medicines Agency; EOC: Epithelial ovary cancer; ESMO: European Society for Medical Oncology; IP: Intraperitoneal; IV: Intravenous; NCCN: National Comprehensive Cancer Network; SIGN: Scottish Intercollegiate Guidelines Network

group members that platinum-taxane is the standard of care for front-line chemotherapy and that the SIGN guidelines are the most comprehensive of all guidelines reviewed as it recommends:

- Single-agent carboplatin in patients who are unable to tolerate combination chemotherapy.
- Carboplatin-pegylated liposomal doxorubicin in cases of taxane-intolerance.
- Against the addition of a third cytotoxic agent to platinum-taxane.

The role of dose-dense chemotherapy was more contentious. Two working group members felt that based on the JGOG 3062 data,<sup>22</sup> there is sufficient evidence to support the use of dose-dense chemotherapy as a standard treatment. They therefore voted for the NCCN guidelines<sup>5</sup> (Table 1) which endorses this mode of treatment as a Category 1 treatment. Six working group members felt that although the JGOG 3062 is a potentially practice-changing study, there exists a possibility that the results may be a chance finding or could be due to pharmacogenomics differences between the Japanese and Caucasian populations. In the absence of confirmatory trial data and in view of the increased toxicities and increased hospital visits associated with dose-dense treatment, they opined that pending the results of other dose-dense studies, dose-dense chemotherapy can only be considered an option and not a standard of care. Hence, they endorsed the SIGN guidelines which recommend dose-dense chemotherapy as a treatment option to be discussed with patients.

The workgroup acknowledges that there is no local data regarding front-line IV chemotherapy for advanced EOC.

## 2. What is the Role of IP Chemotherapy in Optimally Debulked Advanced EOC?

The natural history of ovarian cancer is transcoelomic spread and the disease is frequently confined to the peritoneal compartment at diagnosis and relapse. The benefit of administering chemotherapy directly into the peritoneal compartment is supported by pharmacokinetic data showing a multifold higher concentration of drug in the abdominal cavity. In 2006, the National Cancer Institute (NCI) published a meta-analysis of 8 randomised studies evaluating the benefit of IP chemotherapy. In the combined analysis of 6 of the 8 randomised studies, the hazard ratio (HR) for OS for IP versus IV therapy was 0.79 (95% CI, 0.70 to 0.89). The latest study by Armstrong et al comparing IP cisplatin and IP paclitaxel with the standard IV cisplatin and IV paclitaxel (GOG 172) was included. Although only 42% of patients on the IP chemotherapy arm completed all 6 cycles of therapy, on an intention-to-treat analysis, IP chemotherapy extended median OS by 16 months (66 months vs 50 months) in a

comparison with standard IV paclitaxel and IV cisplatin.<sup>28</sup> The most common toxicities were related to port catheter complications, increased nausea, vomiting and abdominal pain, and higher haematologic, metabolic and neurotoxicity.

Consequently, the NCI issued a clinical announcement in January 2006 regarding their position on the preferred treatment for optimally debulked stage III ovarian cancer.<sup>29</sup> This stated that, “Based on the results of 8 phase III clinical trials, the NCI is encouraging doctors to follow surgery with a combination of 2-drug delivery methods: IV and IP. The combined approach, though more toxic, extends OS for women with advanced ovarian cancer by about a year compared to IV drip alone.”

The NCCN guideline,<sup>5</sup> in line with NCI, has recommended that stage II and III optimally debulked (<1 cm) patients with ovarian cancer who are eligible for chemotherapy should be informed of the option of IP chemotherapy versus IV chemotherapy (or be considered for participation in a clinical trial). The guideline recommends for all women to be counselled about the benefit of IP chemotherapy prior to surgery.

In contrast, the 2011 NICE guidelines<sup>8</sup> were explicit in their recommendation against the use of IP chemotherapy except in the context of a clinical trial. While the NICE guideline development group placed importance on the improvements in disease-free survival (DFS) and OS associated with IP chemotherapy, they also recognised that IP chemotherapy was more toxic, complex to administer and expensive. The ESMO 2013 guidelines has also highlighted that IP chemotherapy has not been adopted as a standard of care in the majority of institutions and countries due to its greater toxicity and the difficulty in delivering the entirety of the planned treatment.<sup>6</sup> The guidelines further recognise that much of the IV chemotherapy used in the control arms of reported IP chemotherapy trials are no longer considered current IV treatment standards.

In 2013, SIGN emphasised that IP chemotherapy may be considered as a first-line therapy for eligible women with advanced ovarian cancer, provided that it is delivered in a centre with appropriate expertise and that the potential for toxicities is fully explained.<sup>7</sup> In contrast, the Australian 2009 GMCT guidelines indicate that IP chemotherapy is not recommended for patients who have significant intra-abdominal adhesions at the conclusion of their surgery as these adhesions may limit the distribution of the chemotherapy drug within the abdomen.<sup>9</sup>

Ongoing trials such as PETROC/OV21 (NCT00993655),<sup>30</sup> JGOG 3109 (NCT01506856)<sup>31</sup> and GOG 252 (NCT00951496)<sup>32</sup> are seeking to evaluate the benefit of IP chemotherapy against standard arms that incorporate weekly IV paclitaxel, bevacizumab and the use of IP carboplatin vis-à-vis cisplatin for the reduction of toxicity.

### *Cost-effectiveness Analyses*

No cost-effectiveness analyses using local cost data and societal norms in Singapore have been performed. An analysis performed by the GOG based on an American perspective showed that compared to the IV paclitaxel and carboplatin regimen, the IP paclitaxel and cisplatin combination has an incremental cost-effectiveness ratio of USD \$180,022 per quality-adjusted life year (QALY) saved (using a 7-year time horizon).<sup>33</sup>

### **Recommendations for IP Chemotherapy in Optimally Debulked Advanced EOC**

The SCAN workgroup has voted 5 to 3 in favour of the adoption of the 2013 ESMO guidelines.<sup>6</sup> The workgroup recognises that there exists no local efficacy and toxicity data on IP chemotherapy. The workgroup agreed that the current evidence-based schedule for IP chemotherapy as described in GOG 172 is associated with excess toxicity, more complex to administer and also that there is a lack of experience and familiarity with the procedure locally. In Singapore, the most commonly used regimen is the JGOG dose-dense chemotherapy which has been shown to be superior to the standard 3-weekly IV paclitaxel and carboplatin regimen.<sup>22</sup> As such, the SCAN workgroup has voted in support of the adoption of the 2013 ESMO guidelines<sup>6</sup> for local patients (Supplementary Table 1).

### **3. What is the Role of Front-line Bevacizumab in Advanced EOC?**

Bevacizumab is a humanised monoclonal antibody that binds vascular endothelial growth factor (VEGF) and prevents it from binding to its receptor. This blocks the growth and maintenance of tumour-associated blood vessels. In women with newly diagnosed EOC, postsurgical chemotherapy is given with a curative intent. Unfortunately, the vast majority of women still relapse. The incorporation of bevacizumab as part of the upfront treatment programme was evaluated in 2 randomised studies.

The first study conducted by GOG 0218 was a phase III randomised placebo-controlled study involving 1873 women with stage III or IV EOC who had undergone surgical cytoreduction.<sup>34</sup> At a median follow-up of 17 months, there was a significant increase in the median PFS in patients receiving upfront followed by maintenance bevacizumab as compared to when chemotherapy-alone is administered (14.1 vs 10.3 months,  $P < 0.001$ ). This translates into a significant reduction in the risk of disease progression or death (HR = 0.72, 95% CI, 0.63 to 0.82). There was no improvement in OS (39.7 vs 39.3 months for the maintenance bevacizumab and chemotherapy-alone group respectively). PFS was not significantly increased

in patients who did not receive maintenance bevacizumab (they received upfront with placebo maintenance) when compared with the chemotherapy-alone group.

The second study by the ICON7 randomly assigned 1528 previously untreated women with high-risk early stage (I or IIA, clear cell or grade III) or advanced EOC to standard chemotherapy for 6 cycles with or without bevacizumab during chemotherapy, followed by maintenance treatment for 12 additional cycles.<sup>35</sup> Compared to standard chemotherapy, the incorporation of bevacizumab resulted in a significant improvement of the median PFS by 1.7 months at a follow-up of 42 months. For women with a high risk of progression (stage III with >1.0 cm residual disease at the end of surgery or stage IV), bevacizumab was associated with significant improvement in PFS (18.1 vs 14.5 months) and OS (36.6 vs 28.8 months). However, this analysis was a posthoc subgroup analysis. In the final survival analysis at a median follow-up of 49 months, there was no difference in median OS (58 months for both arms using restricted means analysis). Women with high risk of progression experienced a lengthening of survival by 4.8 months from 34.5 months to 39.3 months.

In both studies, bevacizumab-containing treatments were associated with greater toxicities. There were higher incidences of grade III and IV adverse events (66% vs 56% in control group),<sup>35</sup> hypertension and gastrointestinal-wall disruption.<sup>34-35</sup> Global QoL was not improved by the addition of bevacizumab.<sup>34-37</sup>

### *Cost-effectiveness Analyses*

Actual cost data was not collected in GOG 0218 or ICON 7. However, independent modelled cost-effectiveness analyses using available data on PFS and OS report that without improvement in OS, the use of bevacizumab as part of the front-line therapy for ovarian cancer is not cost effective.<sup>8,38-41</sup> These analyses include an analysis by the UK NICE appraisal committee which reported a range of incremental cost-effectiveness ratios from £128,000 to £161,000 per QALY for the use of bevacizumab at its licensed dose of 15 mg/kg body weight with a treatment duration of 15 months or time horizon of 25 years or both.<sup>8</sup> Treatment with maintenance bevacizumab leads to improved PFS but is associated with both direct and indirect costs.

### **Recommendations for Front-line Bevacizumab**

The SCAN workgroup has voted in favour of the adoption of the ESMO guidelines. ESMO guidelines recommend the use of upfront bevacizumab with chemotherapy followed by maintenance bevacizumab for patients with poor prognostic features as defined in the ICON 7 trial.<sup>6</sup> Bevacizumab is currently licensed by the European Medicines Agency

(EMA) at a dosage of 15 mg/kg for use with carboplatin and paclitaxel for less than 15 months or until progression.

The NCCN guidelines listed upfront bevacizumab with chemotherapy followed by maintenance therapy as a Category III recommendation as there were major disagreements within the NCCN Panel. Less than 50% of panel members agreed with the recommendation. It was felt that data from GOG 0218 and ICON 7 had not shown a statistically significant increase in OS and/or improved QoL.

Four out of 8 SCAN workgroup members concurred with the ESMO guidelines as it defined the role of bevacizumab comprehensively. However, while bevacizumab is licensed at a dose of 15 mg/kg in the European Union, SCAN workgroup members unanimously agreed that a dose of 7.5 mg/kg based on the ICON7 regimen is preferable due to the lower toxicities and cost involved. Three members expressed disagreement with regard to the NCCN guidelines, endorsing the widely differing opinions regarding the use of bevacizumab. One member agreed with the recommendation by the SIGN guidelines against upfront bevacizumab as cost-effectiveness analyses have shown that the treatment's cost does not justify its health benefits.

The workgroup acknowledges that there is currently no local data on upfront bevacizumab. The diverse views of the SCAN workgroup are reflected in the NCCN guidelines. The workgroup has voted in favour of the ESMO guidelines (Supplementary Table 1) but recommends the careful selection of patients when considering the use of upfront bevacizumab. Only patients with poor prognostic features as defined in ICON7 should be considered for upfront bevacizumab. The preferred dose of bevacizumab is 7.5 mg/kg as defined by the ICON7 regimen.

#### 4. What is the Role of Neoadjuvant Chemotherapy in Advanced EOC?

There are 2 phase III trials on neoadjuvant chemotherapy in advanced EOC. The EORTC 55971<sup>42</sup> randomised 718 women with stage III or IV ovarian cancer to neoadjuvant chemotherapy followed by interval debulking surgery or primary debulking surgery. There were no significant differences between the study groups with regards to OS (HR = 0.98; 95% CI, 0.82 to 1.18) or PFS (HR = 1.01; 95% CI, 0.86 to 1.17). In the EORTC 55971 study, there was increased debulking rate and reduced surgical complications in the neoadjuvant chemotherapy group. In the CHORUS study, a phase III randomised trial to investigate the timing of initial surgery in ovarian cancer,<sup>43</sup> patients with clinical stage III or IV ovarian cancer were randomised to primary surgery followed by 6 cycles of platinum-based chemotherapy or 3 cycles of neoadjuvant chemotherapy followed by surgery before another 3 cycles of platinum-based chemotherapy.

CHORUS was designed to demonstrate non-inferiority of neoadjuvant chemotherapy based on a 3-year survival of 50% with primary debulking surgery. A total of 550 women were randomised. Median tumour size was 8 cm, 25% FIGO IV and 19% World Health Organization (WHO) performance status 2. At a median follow-up of 3 years, the OS is superior for the neoadjuvant chemotherapy group (24.5 months vs 22.8 months; HR = 0.87; 80% CI, 0.76 to 0.98).

No cost-effectiveness analysis was done.

With regard to the EORTC trial, we are mindful of the fact that the accrued patients have very extensive and bulky disease as 73% had tumours of >5 cm and 47% had tumours of >10 cm at randomisation. Similarly, the median size of tumour in the CHORUS trial was 8 cm. Hence, the results of the trials on the role of neoadjuvant chemotherapy cannot be extrapolated to patients with less bulky disease. Furthermore, in a posthoc analysis in the EORTC trial, amongst patients with metastatic disease <5 cm in diameter at randomisation, the OS was slightly longer in the primary surgery group than in the neoadjuvant chemotherapy group (HR = 0.64; 95% CI, 0.45 to 0.93). Hence, rather than recommending neoadjuvant chemotherapy as an alternative for ovarian cancer patients with any stage or disease bulk, it is preferable to reserve neoadjuvant chemotherapy for selected patients with bulky stage III or IV disease, at the same time taking into account the resectability, age, stage, histology and performance status.<sup>44</sup>

#### SCAN Workgroup Recommendations for Neoadjuvant Chemotherapy in Advanced EOC

All members of the workgroup unanimously voted for the NCCN guidelines as it endorses the use of neoadjuvant chemotherapy in patients who are poor surgical candidates due to comorbidities and disease factors. The NCCN recommends the involvement of gynaecologic oncologists in deciding if neoadjuvant chemotherapy should be given. As it does not specify the neoadjuvant chemotherapy regimen, it accommodates for the treating oncologist to make the judgement that best suits the patient's interests as some patients may not be able to tolerate standard combination chemotherapy.

#### Conflicts of Interest

*Dr Chia reports receiving advisory board fees from GSK, Astra Zeneca and Bayer; Dr Lim, receiving travel support from Roche; Dr See, receiving accommodation and travel grants from GSK, conference support from GSK and Sirtex and advisory fees from Roche; Ms Foo, Dr Lim, Dr Lim, Dr Ngo, Dr Soh and Dr Tan have nothing to disclose.*

### Workgroup Members

The Members of the SCAN Gynaecological Cancers Systemic Therapy Workgroup are Section Lead and Workgroup Chairperson: Sheow Lei Lim, MBBS (Hons, Aust), MRCP (UK), MD (UK), Department of Gynaecological Oncology, KK Women's and Children's Hospital, Singapore; Workgroup Members (Voting): John WK Chia, MBBS, MRCP (UK), FAM (S'pore), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Siew Eng Lim, MBBCh, Medl Onco (ABIM), Med Onco (FAMS), Department of Haematology-Oncology, National University Cancer Institute, Singapore; Yi Wan Lim, MBBChir, MRCP (UK), Department of Haematology-Oncology, National University Cancer Institute, Singapore; Lynette Ngo, MBBS (S'pore), MMed (Int Med), MRCP (UK), Department of Medical Oncology, Raffles Cancer Centre, Singapore; Hui Ti See, MB ChB (Leicester), MRCP, FAMS (Med Oncology), Department of Medical Oncology, Parkway Cancer Centre, Singapore; Lay Tin Soh, MBBS (S'pore), FRCP (UK), FAMS, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; David SP Tan, MRCP (UK) (Medical Oncology), PhD, Department of Haematology-Oncology, National University Cancer Institute, Singapore; Non-Voting Member: Koon Mian Foo, BSc (Pharmacy), BCOP, Department of Pharmacy, KK Women's and Children's Hospital, Singapore.

### Reviewers

Invited reviewers were Peter Ang, MBBS (S'pore), MRCP (UK), M Med (Int Med), OncoCare Cancer Centre, Singapore; Xiaohua Wu, MD, PhD, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, People's Republic of China. An additional invited reviewer chose to be anonymous.

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Supplementary Table 1. International Guidelines for the Systemic Treatment of Advanced Epithelial Ovarian Cancer

Guidelines Title	NCCN Clinical Practice Guidelines in Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 2.2013	Newly Diagnosed and Relapsed Epithelial Ovarian Carcinomas: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	SIGN - Management of Epithelial Ovarian Cancer. A National Clinical Guideline. SIGN Publication No. 135	Ovarian Cancer: The Recognition and Initial Management of Ovarian Cancer (CG122)	Best Clinical Practice Gynaecological Cancer Guidelines 2009, GMCT
Date Released	13 June 2013	July 2013	November 2013	May 2013	2009
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	Scottish Intercollegiate Guidelines Network (SIGN), United Kingdom	National Institute of Health and Clinical Excellence (NICE), United Kingdom	Greater Metropolitan Clinical Taskforce (GMCT)
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Recommendations developed from discussion at consensus conferences. Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines are endorsed by the JSMO.	SIGN is a collaborative network of clinicians, healthcare professionals and patient organisations that develops guidelines using a standard methodology based on a systematic review of the evidence for the NHS in Scotland. Recommendations are explicitly linked to the supporting evidence. NHS evidence has accredited the process used by SIGN to develop guidelines.	Guideline development group made up of health professionals, representatives of patient and carer groups and technical experts assesses the available evidence and makes recommendations. After the guideline development group finalises the recommendations, the collaborating centre produces the final guideline. NICE formally approves the final guideline and issues its guidance to the NHS.	Guidelines development working group that consists of gynaecological oncologists, radiation oncologists, medical oncologists, gynaecological pathologists, palliative medicine consultants, nurse oncologists from Australia's New South Wales, Queensland, Tasmania and New Zealand. The workgroup was tasked by the GMCT to review the Gynaecological Oncology Clinical Practice Guidelines that were originally published in 2004, using updated references and are intended to be evidence-based wherever possible.
Target Population	Advanced epithelial ovarian cancer.	Advanced epithelial ovarian cancer.	Advanced epithelial ovarian cancer.	Advanced epithelial ovarian cancer.	Advanced epithelial ovarian cancer.
Front-line Postoperative Chemotherapy	Carboplatin (AUC 5 – 7.5)/ paclitaxel 175 mg/m <sup>2</sup> q3wk 6 cycles (Category I)  Carboplatin (AUC 5 – 6)/ docetaxel 60 – 75 mg/m <sup>2</sup> q3wk 6 cycles (Category I)  <u>Dose-dense Chemotherapy:</u> Carboplatin AUC 6 (Day 1)/ paclitaxel 80 mg/m <sup>2</sup> (Days 1, 8, 15); q3wk 6 cycles (Category I)	<u>Standard Chemotherapy:</u> Paclitaxel 175 mg/m <sup>2</sup> and carboplatin AUC 5 – 6, administered intravenously q3wks (I,A)  Patients who develop an allergy to or do not tolerate paclitaxel – alternative regimen: <ul style="list-style-type: none"> <li>• Carboplatin/docetaxel or</li> <li>• Carboplatin/pegylated liposomal doxorubicin (II,A)</li> </ul>	Carboplatin is the platinum drug of choice in both single and combination therapy (A).  Paclitaxel is recommended in combination therapy with platinum in the first line posturgery treatment of epithelial ovarian cancer where the potential benefits justify the toxicity of the therapy.  In those unable to tolerate paclitaxel, pegylated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative (A).	Paclitaxel in combination with a platinum-based therapy (cisplatin or carboplatin) should be the standard chemotherapy: <ul style="list-style-type: none"> <li>• Paclitaxel 175 mg/m<sup>2</sup> in a 3-hour intravenous infusion, followed by a platinum every 3 weeks</li> </ul>	Current recommendation is carboplatin/paclitaxel q3wks for 6 cycles.

EMA: European Medicines Agency; IP: Intraperitoneal; JSMO: Japanese Society of Medical Oncology; NHS: National Health Service; QOL: Quality of life; RCT: Randomised controlled trial

Supplementary Table 1. International Guidelines for the Systemic Treatment of Advanced Epithelial Ovarian Cancer (Con't)

Guidelines Title	NCCN Clinical Practice Guidelines in Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 2.2013	Newly Diagnosed and Relapsed Epithelial Ovarian Carcinomas: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	SIGN - Management of Epithelial Ovarian Cancer. A National Clinical Guideline. SIGN Publication No. 135	Ovarian Cancer: The Recognition and Initial Management of Ovarian Cancer (CG122)	Best Clinical Practice Gynaecological Cancer Guidelines 2009, GMCT
Front-line Bevacizumab – Chemotherapy	Option to use bevacizumab-containing regimens per ICON-7 and GOG-218: Carboplatin AUC 6 /paclitaxel 175 mg/m <sup>2</sup> /bevacizumab 7.5 mg/kg q3wk x 5 – 6 cycles → continue bevacizumab for up to 12 additional cycles (Category III).	<u>Dose-dense chemotherapy:</u> In the absence of confirmatory data, dose-dense administration of paclitaxel currently can only be considered an option, and not as a standard of care (1,B).	Patients who are unfit for combination therapy should be offered single-agent carboplatin (A).  A third cytotoxic agent should not be added to carboplatin and paclitaxel (A).  <u>Dose-dense chemotherapy:</u> Carboplatin AUC 6 (day 1) and paclitaxel 80 mg/m <sup>2</sup> (days 1, 8, 15) q3wk may be considered for the treatment of first-line ovarian cancer. The increased toxicity and frequency of visits need to be discussed with the patient (B). Recommendation: Where possible, patients should be enrolled in ongoing clinical trials in order to establish if this regime should become the standard of care. There are several ongoing studies that assess the efficacy of dose-dense paclitaxel (ICON8, GOG262, MITO7) and results are awaited.	Patients who are unfit for combination therapy should be offered single-agent carboplatin (A).  A third cytotoxic agent should not be added to carboplatin and paclitaxel (A).  <u>Dose-dense chemotherapy:</u> Carboplatin AUC 6 (day 1) and paclitaxel 80 mg/m <sup>2</sup> (days 1, 8, 15) q3wk may be considered for the treatment of first-line ovarian cancer. The increased toxicity and frequency of visits need to be discussed with the patient (B). Recommendation: Where possible, patients should be enrolled in ongoing clinical trials in order to establish if this regime should become the standard of care. There are several ongoing studies that assess the efficacy of dose-dense paclitaxel (ICON8, GOG262, MITO7) and results are awaited.	6 of 8 votes
Member Votes	Recommended for patients with poor prognostic features:	<ul style="list-style-type: none"> <li>stage IV,</li> <li>suboptimal debulking (as defined in ICON7 trial) (1,B).</li> </ul>	Not recommended – cost-effectiveness analysis has shown that the treatment's cost in relation to its health benefits is not sufficient.	Not recommended – bevacizumab does not provide benefit to justify its high cost.	Nil

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Supplementary Table 1. International Guidelines for the Systemic Treatment of Advanced Epithelial Ovarian Cancer (Cont'd)

Guidelines Title	NCCN Clinical Practice Guidelines in Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 2.2013	Newly Diagnosed and Relapsed Epithelial Ovarian Carcinomas: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	SIGN – Management of Epithelial Ovarian Cancer. A National Clinical Guideline. SIGN Publication No. 135	Ovarian Cancer: The Recognition and Initial Management of Ovarian Cancer (CG122)	Best Clinical Practice Gynaecological Cancer Guidelines 2009, GMCT
Carboplatin AUC 6/paclitaxel 175 mg/m <sup>2</sup> /bevacizumab 15 mg/kg q3wk x 6 cycles. Bevacizumab started on Day 1 of cycle 2 q3wk for up to 22 cycles (Category III).	Major disagreements among panel members, therefore Category 3. Recommendation: (data from the 2 phase III RCTs have not shown a statistically significant increase in overall survival and/or improved QOL)	Bevacizumab has been licensed by the EMA at 15 mg/kg for use with carboplatin and paclitaxel for ≤15 months or until progression.			
Encourage participation in ongoing clinical trials involving anti-angiogenesis agents.	4 of 8 votes (majority)				
Front-line IP Chemotherapy	<p>Stage II and III optimally debulked to &lt;1 cm:</p> <ul style="list-style-type: none"> <li>All women should be counselled regarding benefit of IP chemotherapy prior to surgery.</li> <li>Day 1: IV paclitaxel 135 mg/m<sup>2</sup> over 3 or 24 hours; Day 2: IP cisplatin 75 – 100 mg/m<sup>2</sup>; Day 8: IP paclitaxel 60 mg/m<sup>2</sup>, q3wk 6 cycles. (Category I for stage III)</li> </ul>	<p>IP treatment has not been adopted as standard of care in view of its greater toxicity and difficulty delivering all the planned treatment. Lack of current standard intravenous chemotherapy in the standard arms of the IP trials has made the interpretation of the results difficult. Recommends IP chemotherapy in the context of clinical trial.</p>	<p>Chemotherapy which includes an IP element can be considered for women with a new diagnosis of epithelial ovarian cancer and residual disease ≤1 cm after primary surgery provided a regimen of proven benefit in a clinical trial compared to intravenous therapy is used, it is delivered in a centre with appropriate expertise and the potential toxicities are fully explained (B).</p> <p>Where possible, women receiving IP chemotherapy should be enrolled into ongoing clinical trials.</p>	<p>IP chemotherapy is an option supported by Phase III trials for patients with low volume residual disease following surgery. However the reported benefits need to be balanced against the drawbacks of catheter-related morbidity, infection, and discomfort associated with treatment.</p> <p>Toxicity +++, complex and expensive.</p> <p>Do not offer IP chemotherapy except in clinical trial.</p> <p>IP chemotherapy is not recommended for patients who have significant intra-abdominal adhesions at the conclusion of their surgery as the adhesions may limit the distribution of chemotherapy within the abdomen.</p>	
Member Votes	5 of 8 votes				

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Supplementary Table 1. International Guidelines for the Systemic Treatment of Advanced Epithelial Ovarian Cancer (Cont)

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Front-line Neoadjuvant Chemotherapy	<p>Consider neoadjuvant chemotherapy/primary interval cytoreduction (diagnosis by fine needle aspiration, biopsy or paracentesis) for patients with bulky stage III/IV who are poor surgical candidates due to high-risk comorbidity conditions or disease factors (Category I).</p> <p>Published data demonstrate that primary assessment and debulking by a gynaecologic oncologist results in a survival advantage. Patients being evaluated for neoadjuvant chemotherapy should be seen by a fellowship-trained gynaecologic oncologist prior to being considered a poor surgical candidate.</p>	<p>The use of chemotherapy with interval surgery is becoming more widely accepted and is offered to patients with poor performance status, low albumin levels and in those with very extensive tumour dissemination.</p> <p>Validation of this approach may come from further trials that are ongoing.</p>	<p>The use of neoadjuvant chemotherapy in women with stage IIIc or IV ovarian cancer may be considered as an alternative to primary debulking surgery (A).</p> <p>Good practice points: With regard to selecting who will benefit from neoadjuvant chemotherapy, treatment should be individualised to the patient taking into account resectability, age, histology, performance status and after ruling out the possibility of other primary tumours and full discussion at multidisciplinary meetings.</p>	<p>If performing surgery for women with ovarian cancer, whether before chemotherapy or after neoadjuvant chemotherapy, the objective should be complete resection of all macroscopic disease.</p> <p>NIL</p>	

Member Votes 8 of 8 votes

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