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Appendices

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Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation

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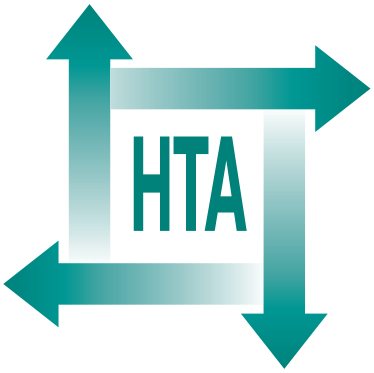
NHS R&D HTA Programme



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Appendix 1

Details of FIGO cancer staging

Stage I: Growth limited to the ovaries.
Ia One ovary involved.
Ib Both ovaries involved.
Ic Ascites; an accumulation of fluid in the abdominal (peritoneal) cavity present or positive peritoneal washings.

Stage II: Growth limited to pelvis.
IIa Extension to gynaecological adnexae (on or in a structure associated with the uterus such as on ovary, fallopian tube or uterine ligament).
IIb Extension to other pelvic tissues.
IIc Ascites or positive washings.

Stage III: Extra pelvic tumour present – limited to true pelvis but with superficial liver metastases, peritoneal surface seedlings, or histologic-proven malignant extension to the omentum.
IIIa Limited to true pelvis with negative nodes, but seeding of abdominal peritoneal surfaces or histologic-proven extension to small bowel or mesentery.
IIIb Peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes negative.
IIIc Peritoneal metastasis beyond pelvis >2 cm in diameter and/or positive retroperitoneal or inguinal nodes.

Stage IV: Metastases to distant sites (including hepatic parenchymal disease).

Appendix 2

Summary of current manufacturers' information provided for health professionals

Intervention	Indications for treatment in UK	Warnings or cautions	Side-effects	Dosagein adults	Cost
Topotecan is available in a 4-mg vial of powder	Topotecan is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy	*Contraindications:* A history of severe hypersensitivity to topotecan or to any of the excipients Pregnant or breast-feeding Severe bone marrow depression prior to starting first course (baseline neutrophils $<1.5 \times 10^9$/l and/or a platelet count of $\leq 100 \times 10^9$/l) *Special warnings and special indications for use:* Haematological toxicity is dose-related and full blood count including platelets should be monitored regularly. As expected, patients with poor performance status have a lower response rate and an increased incidence of complications such as fever and infection. There is no experience of the use of topotecan in patients with severely impaired renal function (creatinine clearance <20 ml/min) or severely impaired hepatic function (serum bilirubin ≥ 10 mg/dl) due to cirrhosis. Topotecan is not recommended to be used in these patient groups A small number of hepatically impaired patients (serum bilirubin between 1.5 and 10 mg/dl) were able to tolerate 1.5 mg/m^2 for 5 days every 3 weeks although a reduction in topotecan clearance was observed. There are insufficient data available to make a dose recommendation for this patient group	*General side-effects of cytotoxic drugs:* Extravasation of intravenous drugs, oral mucositis, nausea and vomiting, bone-marrow suppression, alopecia and reproductive function adverse effects *Specific to topotecan:* Gastrointestinal effects, asthenia, alopecia and anorexia	The recommended dose of topotecan is 1.5 mg/m^2 body surface area/day administered by intravenous infusion over 30 minutes daily for five consecutive days with a 3-week interval between the start of each course. Prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of $\geq 1.5 \times 10^9$/l, and a platelet count of $\geq 100 \times 10^9$/l. Routine premedication for non-haematological adverse events is not required with topotecan	Topotecan (as hydrochloride) net price 1-mg vial = £105; 4-mg vial = £312.50

continued

Intervention	Indications for treatment in UK	Warnings or cautions	Side-effects	Dosage in adults	Cost
Pegylated liposomal doxorubicin hydrochloride (Caelyx) Caelyx is available in a 2 mg/ml concentrate for solution for infusion	Pegylated liposomal doxorubicin hydrochloride is indicated as a treatment for advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen. The drug is also indicated as a monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk and for treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD_4 counts (<200 CD_4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease	*Contraindications:* Hypersensitivity to the active substance or to any of the excipients Breast-feeding Caelyx must not be used to treat AIDS-KS that may be treated effectively with local therapy or systemic interferon alfa *Special warnings and special indications for use:* *Cardiac toxicity*: it is recommended that all patients receiving Caelyx routinely undergo frequent ECG monitoring. Transient ECG changes such as T-wave flattening, S–T segment depression and benign arrhythmias are not considered mandatory indications for the suspension of Caelyx therapy. However, reduction of the QRS complex is considered more indicative of cardiac toxicity. If this change occurs, the most definitive test for anthracycline myocardial injury, i.e. endomyocardial biopsy, must be considered. The evaluation of left ventricular function is considered to be mandatory before each additional administration of Caelyx that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2 *Myelosuppression*: many patients treated with Caelyx have baseline myelosuppression due to such factors as their pre-existing HIV disease or numerous concomitant or previous medications or tumours involving bone marrow. In the pivotal trial in patients with ovarian cancer treated at a dose of 50 mg/m^2, myelosuppression was generally mild to moderate, reversible and was not associated with episodes of neutropenic infection or sepsis. However, because of the potential for bone-marrow suppression, periodic blood counts must be performed frequently during the course of Caelyx therapy, and at a minimum, prior to each dose of Caelyx. Persistent severe myelosuppression may result in superinfection or haemorrhage	*General side-effects of cytotoxic drugs:* Extravasation of intravenous drugs, oral mucositis, nausea and vomiting, bone-marrow suppression, alopecia, and reproductive function adverse effects *Specific to Caelyx:* Nausea and vomiting, myelosuppression, alopecia and mucositis	The recommended dose of Caelyx is 50 mg/m^2 administered intravenously once every 4 weeks, for as long as the disease does not progress and the patient continues to tolerate treatment	For i.v. infusion, doxorubicin hydrochloride 2 mg/ml encapsulated in liposomes. For dilution before use. Net price 10-ml vial = £411.30, 25 ml vial = £813.49

continued

Intervention	Indications for treatment in UK	Warnings or cautions	Side-effects	Dosage in adults	Cost
		Infusion-associated reactions: serious and sometimes life-threatening infusion reactions, which are characterised by allergic-like or anaphylactoid-like reactions, with symptoms including asthma, flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial oedema, chills, back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of Caelyx. Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications to treat these symptoms (e.g. antihistamines, corticosteroids and adrenaline) and emergency equipment should be available for immediate use. In most patients treatment can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle *Diabetic patients*: note that each vial of Caelyx contains sucrose and the dose is administered in 5% (50 mg/ml) glucose solution for infusion			
Paclitaxel is available in vials containing 30, 100 or 300 mg of paclitaxel as a 6 mg/ml solution	Paclitaxel is indicated for second-line chemotherapy of ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen. The drug is also indicated for the primary treatment of ovarian cancer, in combination with cisplatin, in patients with advanced	*Contraindications:* Paclitaxel is contraindicated in patients with severe hypersensitivity reactions to paclitaxel or any other component of the formulation, especially polyethoxylated castor oil Paclitaxel is contraindicated during pregnancy and lactation Paclitaxel should not be used in patients with baseline neutrophils $<1.5 \times 10^9$/l. *Special warnings and special precautions for use:* Patients must be pretreated with corticosteroids, antihistamines and H_2 antagonists. Taxol should be given **before** cisplatin when used in combination. *Hypersensitivity reactions*: significant hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angiodema and generalised urticaria have occurred in <1% of patients receiving paclitaxel after adequate	*General side-effects of cytotoxic drugs:* Extravasation of intravenous drugs, oral mucositis, nausea and vomiting, bone-marrow suppression, alopecia and reproductive function adverse effects *Specific to paclitaxel:* Myelosuppression, peripheral neuropathy and cardiac conduction defects with arrhythmias (which are nearly always	The recommended dose of paclitaxel for the secondary treatment of ovarian and breast carcinomia is 175 mg/m^2 administered over a period of 3 hours with a 3-week interval between courses. Subsequent doses of paclitaxel should be administered according to individual patient tolerance. Paclitaxel should not be	Paclitaxel 6 mg/ml, net price 5-ml vial = £124.79, 16.7-ml vial = £374.00, 50 ml-vial = £1122.00 (hosp. only)

continued

Intervention	Indications for treatment in UK	Warnings or cautions	Side-effects	Dosage in adults	Cost
	disease or residual disease (>1 cm) after initial surgery. Paclitaxel is also indicated for the treatment of metastatic carcinoma of the breast in patients who have failed or are not candidates for standard anthracycline-containing therapy and also for the treatment of non-small-cell lung cancer	premedication. These reactions are probably histamine mediated. In the case of severe hypersensitivity reactions, paclitaxel should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with the drug *Haematological*: bone-marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to a level $\geq 1.5 \times 10^9$/l and the platelets recover to a level $\geq 100 \times 10^9$/l *Cardiovascular*: severe cardiac conduction abnormalities have been reported rarely. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel *Nervous system*: although the occurrence of peripheral neuropathy is frequent, the development of severe symptoms is unusual. In severe cases, a dose reduction of 20% is recommended for all subsequent courses of paclitaxel *Patients with liver impairment*: there is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment Paclitaxel is not recommended for patients with severely impaired hepatic function *Other*: Since paclitaxel contains dehydrated alcohol (396 mg/ml), consideration should be given to possible central nervous system and other effects Special care should be taken to avoid intra-arterial administration of paclitaxel. In animal trials investigating local tolerance, severe tissue reactions occurred following intra-arterial administration	asymptomatic). It also causes muscle pain and alopecia; nausea and vomiting are mild to moderate	readministered until the neutrophil count is $\geq 1.5 \times 10^9$/l and the platelet count is $\geq 100 \times 10^9$/l. Patients who experience severe neutropenia (neutrophil count $<0.5 \times 10^9$/l for ≥ 7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses All patients must be premedicated with corticosteroids, antihistamines and H_2 antagonists prior to paclitaxel	

Appendix 3

Search strategies

Search strategies

Limits:

- Date limits applied to update searches run for previous NICE TARs (by publication date) for topotecan (2000–4), Caelyx (2001–4) and paclitaxel (2001–4).
- Animal-only studies were excluded where possible.
- Study design: no limits.
- Language: no limits.

MEDLINE

(Ovid host)
2000/2001 – April 2004

1. exp Ovarian Neoplasms/
2. (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3. (adenexa$ adj4 mass$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4. or/1-3
5. Topotecan/
6. topotecan.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7. (hycamtin or hycamptamine).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8. or/5-7
9. exp Doxorubicin/
10. doxil.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
11. (doxorubicin hydrochloride or doxorubicin hcl).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
12. liposomal doxorubicin.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
13. (caelyx or adriamycin or rubex).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
14. liposome encapsulated doxorubicin.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
15. or/9-14
16. Paclitaxel/
17. paclitaxel.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
18. docetaxel.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
19. taxol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
20. taxotere.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
21. or/16-20
22. 8
23. limit 22 to yr=2000-2004
24. 15
25. limit 24 to yr=2001-2004
26. 21
27. limit 26 to yr=2001-2004
28. 23 or 25 or 27
29. 4 and 28
30. animal/ not (animal/ and human/)
31. 29 not 30

PREMEDLINE

(Ovid host)
2000/2001 – April 2004

1. (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, abstract]
2. (adenexa$ adj4 mass$).mp. [mp=title, abstract]
3. 1 or 2
4. topotecan.mp. [mp=title, abstract]
5. (hycamtin or hycamptamine).mp. [mp=title, abstract]
6. 4 or 5
7. doxil.mp. [mp=title, abstract]
8. (doxorubicin hydrochloride or doxorubicin hcl).mp. [mp=title, abstract]
9. liposomal doxorubicin.mp. [mp=title, abstract]
10. (caelyx or adriamycin or rubex).mp. [mp=title, abstract]
11. liposome encapsulated doxorubicin.mp. [mp=title, abstract]
12. or/7-11
13. paclitaxel.mp. [mp=title, abstract]

14. docetaxel.mp. [mp=title, abstract]
15. taxol.mp. [mp=title, abstract]
16. taxotere.mp. [mp=title, abstract]
17. or/13-16

EMBASE

(Ovid host)
2000/2001 – April 2004

1. exp Ovary Cancer/
2. (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
3. (adenexa$ adj4 mass$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. or/1-3
5. Topotecan/
6. topotecan.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (hycamtin or hycamptamine).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
8. or/5-7
9. Doxorubicin/
10. doxil.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
11. (doxorubicin hydrochloride or doxorubicin hcl).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
12. liposomal doxorubicin.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
13. (caelyx or adriamycin or rubex).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
14. liposome encapsulated doxorubicin.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
15. or/9-14
16. Paclitaxel/
17. paclitaxel.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
18. docetaxel.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
19. taxol.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
20. taxotere.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
21. or/16-20
22. 8
23. limit 22 to yr=2000-2004
24. 15
25. limit 24 to yr=2001-2004
26. 21
27. limit 26 to yr=2001-2004
28. 23 or 25 or 27
29. 4 and 28
30. animal/ or non-human/
31. human/
32. 30 not (30 and 31)
33. 29 not 32

CINAHL

(Ovid host)
2000/2001 – April 2004

1. exp Ovarian Neoplasms/
2. (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
3. (adenexa$ adj4 mass$).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
4. or/1-3
5. topotecan.mp. [mp=title, cinahl subject headings, abstract, instrumentation]
6. (hycamtin or hycamptamine).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
7. or/5-6
8. exp Doxorubicin/
9. doxil.mp. [mp=title, cinahl subject headings, abstract, instrumentation]
10. (doxorubicin hydrochloride or doxorubicin hcl).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
11. liposomal doxorubicin.mp. [mp=title, cinahl subject headings, abstract, instrumentation]

12. (caelyx or adriamycin or rubex).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
13. liposome encapsulated doxorubicin.mp. [mp=title, cinahl subject headings, abstract, instrumentation]
14. or/8-13
15. Paclitaxel/
16. paclitaxel.mp. [mp=title, cinahl subject headings, abstract, instrumentation]
17. docetaxel.mp. [mp=title, cinahl subject headings, abstract, instrumentation]
18. taxol.mp. [mp=title, cinahl subject headings, abstract, instrumentation]
19. taxotere.mp. [mp=title, cinahl subject headings, abstract, instrumentation]
20. or/15-19
21. 7
22. limit 21 to yr=2000-2004
23. 14
24. limit 23 to yr=2001-2004
25. 20
26. limit 25 to yr=2001-2004
27. 22 or 24 or 26
28. 4 and 27

DARE
NHS EED
HTA Database

(http://www.york.ac.uk/inst/crd/crddatabases.htm)
2000/2001 – April 2004

s ovar$(4w)(cancer$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)
s adenexa$(4w)mass$
s s1 or s2
s topotecan
s hycamtin or hycamptamine
s s4 or s5
s s6 and ((2000 or 2001 or 2002 or 2003 or 2004)/xyr)
s doxil
s doxorubicin hydrochloride or doxorubicin(w)hcl
s liposomal(w)doxorubicin
s caelyx or adriamycin or rubex
s liposome(w)encapsulated(w)doxorubicin
s s8 or s9 or s10 or s11 or s12
s s13 and ((2001 or 2002 or 2003 or 2004)/xyr)
s paclitaxel
s docetaxel
s taxol
s taxotere
s s15 or s16 or s17 or s18
s s19 and ((2001 or 2002 or 2003 or 2004)/xyr)
s s7 or s14 or s20
s s3 and s21

Cochrane Controlled Trials Register
Cochrane Database of Systematic Reviews
(The Cochrane Library)

2000/2001 – Issue 2, 2004

#1. OVARIAN NEOPLASMS explode all trees (MeSH)
#2. (ovar* near cancer*)
#3. (ovar* near tumor*)
#4. (ovar* near tumour*)
#5. (ovar* near malignan*)
#6. (ovar* near oncolog*)
#7. (ovar* near carcinoma)
#8. (ovar* near neoplas*)
#9. (ovar* near mass*)
#10. (ovar* near growth*)
#11. (ovar* near cyst*)
#12. (adenexa* near mass*)
#13. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
#14. TOPOTECAN single term (MeSH)
#15. (topotecan or hycamtin or hycamptamine)
#16. (#14 or #15)
#17. (#14 or #15) (2000 to current date)
#18. DOXORUBICIN explode tree 1 (MeSH)
#19. (doxil or (doxorubicin next hydrochloride) or (doxorubicin next hcl))
#20. (liposomal next doxorubicin)
#21. (caelyx or adriamycin or rubex)
#22. (liposome next encapsulated next doxorubicin)
#23. (#18 or #19 or #20 or #21 or #22)
#24. #23 (2001 to current date)
#25. PACLITAXEL single term (MeSH)
#26. (paclitaxel or docetaxel or taxol or taxotere)
#27. (#25 or #26)
#28. (#25 or #26) (2001 to current date)
#29. (#17 or #24 or #28)
#30. (#13 and #29)

Science Citation Index
Index to Scientific and Technical Proceedings
(Web of Knowledge)

2000/2001 – April 2004

((ovar* same (cancer* or tumo?r* or malignan* or oncolog* or carcinoma* or neoplas* or mass* or growth* or cyst*)) or (adenexa* same mass*)) and (topotecan or hycamtin or hycamptamine)
[limit: 2000-2004]

((ovar* same (cancer* or tumo?r* or malignan* or oncolog* or carcinoma* or neoplas* or mass* or growth* or cyst*)) or (adenexa* same mass*)) and (doxil or doxorubicin hydrochloride or

doxorubicin hcl or liposomal doxorubicin or caelyx or adriamycin or rubex or liposome encapsulated doxorubicin)
[limit: 2001-2004]

((ovar* same (cancer* or tumo?r* or malignan* or oncolog* or carcinoma* or neoplas* or mass* or growth* or cyst*)) or (adenexa* same mass*)) and (paclitaxel or docetaxel or taxol or taxotere)
[limit: 2001-2004]

Biosis

(Edina host)
2000/2001 – April 2004

ovar* w4 cancer*
ovar* w4 tumo*r*
ovar* w4 malignan*
ovar* w4 oncolog*
ovar* w4 carcinoma*
ovar* w4 neoplas*
ovar* w4 mass*
ovar* w4 growth*
ovar* w4 cyst*
adenexa* w4 mass*

and

topotecan or hycamtin or hycamptamine (2000-2004)
or
doxil or "doxorubicin hydrochloride" or "doxorubicin hcl" (2001-2004)
or
"liposomal doxorubicin" or caelyx or adriamycin (2001-2004)
or
rubex or "liposome encapsulated doxorubicin" (2001-2004)
or
paclitaxel or docetaxel or taxol or taxotere (2001-2004)

OHE HEED (CD-ROM)

2000/2001 – April 2004

ovarian or ovary or ovaries

and

topotecan or hycamtin or hycamptamine or doxil or doxorubicin or caelyx or adriamycin or rubex or paclitaxel or docetaxel or taxol or taxotere

Controlled Trials.com – *m*RCT / ISRCTN
(http://controlled-trials.com/)
2000/2001 – April 2004

ovarian and (topotecan or hycamtin or hycamptamine or doxorubicin or doxil or caelyx or adriamycin or rubex or paclitaxel or docetaxel or taxol or taxotere)

Cancer Portfolio.org
(http://www.cancerportfolio.org/)
2000/2001 – April 2004

Year = 2004; 2003; 2002; 2001; 2000
Type of Research = Causes of Cancer/Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment; Cancer Control, Survivorship and Outcomes Research
Type of Cancer = Ovarian Cancer
Any of these words = topotecan or hycamtin or hycamptamine or doxorubicin or doxil or caelyx or adriamycin or rubex or paclitaxel or docetaxel or taxol or taxotere

Clinical Trials,gov

(http://www.clinicaltrials.gov/)
2000/2001 – April 2004

topotecan or hycamtin or hycamptamine or doxorubicin or doxil or caelyx or adriamycin or rubex or paclitaxel or docetaxel or taxol or taxotere [ALL-FIELDS] AND "ovarian cancer" [CONDITION]

Appendix 4

Excluded studies

Study details	Reason for exclusion
Anonymous, 2002[79]	Discussion article
Piccart, 2003[80]	First-line therapy
Villella, 2002[81]	Retrospective analysis
Gore, 2000[82]	Review not SR
Soriano, 2000[83]	Phase II study, not RCT
Glimelius, 2001[84]	Background on treatment pathway in ovarian cancer
Hogberg, 2001[85]	Review, not systematic
Karlsson, 2001[86]	Included as relevant related SR
Vermoken, 2000[87]	Background discussion on treatment in ovarian cancer
Mobus, 2000[88]	Retrospective survival analysis of patients treated with topotecan
Fracasso, 2003[89]	Phase II trial on oxaliplatin
Gronlund, 2002[90]	Information on prognostic factors
Anonymous, 2002[91]	Discussion article
Cannistra, 2002[92]	Background article on CAP versus paclitaxel trial
du Bois, 2001[93]	Dose-finding study of carboplatin gemcitabine combination
Chan, 2001[94]	Longitudinal study on QoL after treatment
Slimane, 2003[95]	Commentary on first-line treatment trials
Anonymous, 2000[96]	Commentary on GOG111
Bernardi, 2003[97]	Phase II study, not RCT
Markham, 2002[98]	Abstract on the results of GOG/SWOG
Conte, 2000[99]	Discussion on chemotherapy in second-line disease
Muggia, 2001[100]	Background: commentary on PLDH versus topotecan trial
Gonzalez-Martin, 2003[101]	Background: single versus combination therapy
Ross, 2001[46]	Background: review article on treatment options for second-line therapy
Zeimet, 2002[102]	Commentary paper in German
Covens, 2000[40]	Relevant SR on topotecan
Johnston, 2001[103]	Background
Mayer, 2001[104]	Not an RCT; Phase II study
Markman, 2001[105]	General background on second-line therapy
Costa, 2001[106]	First-line therapy
Sun, 2002[107]	Background
Health Technology Board for Scotland, 2002[108]	Same as the NICE Guidance on the use of PLDH (Caelyx) for the treatment of advanced ovarian cancer
Harper, 2002[109]	Review
Le, 2003[110]	Review of QoL issues
Kaye, 2002[111]	Review
Bookman, 2002[112]	Information on considerations in trial design
Anonymous, 2001[113]	Not data
Ohara, 2002[114]	Case report
Lehoczky, 2002[115]	Case report
Topuz, 2001[116]	Not an RCT; Phase II study
Markman, 2003[117]	Study on the impact of the sequence of delivery on neutropenia
Anonymous, 2001[118]	Background references for economics
Anonymous, 2001[119]	Background on oxaliplatin
Bilgin, 2003[120]	Treatment with second-line gemcitabine therapy
Wojciechowska-Lacka, 2003[121]	Study on disease progression after first-line paclitaxel and cisplatin or carboplatin treatment
Castellano, 2002[122]	Phase II non-RCT
Alvarez, 2003[123]	Background on second-line treatment options
Armstrong, 2004[124]	Commentary on use of topotecan dosing
Armstrong, 2002[125]	Commentary on the use of topotecan

continued

Study details	Reason for exclusion
Lakusta, 2001[126]	Cohort study on QoL measures
Hahn, 2003[127]	Study on QoL in patients treated with doxil as second-line therapy
Patel, 2001[128]	Background on the use of PLDH
Gold, 2003[129]	Topotecan combined with amifostine as second-line therapy
Hensley, 2001[130]	Background on AE of PLDH
Stebbing, 2002[131]	Commentary on trial 30-49
Holzner, 2002[132]	Background on QoL
Toffoli, 2002[133]	Correspondence article
Armstrong, 2003[134]	Bryostatin1 as the intervention
Chiara, 2004[135]	Non-RCT Phase II study
Latorre, 2002[136]	Background
Markman, 2000[137]	Background on choices for second-line therapy
Yasuda, 2002[138]	Phase II study not an RCT
Gorbunova, 2002[139]	Paper in Polish
Piccart, 2002[140]	Long-term follow-up results of GOG111
Pignata, 2001[141]	Background on QoL issues in gynaecological cancers
Goldwasser, 2001[142]	Commentary on oxaliplatin in cancers
Boruta, 2002[143]	Retrospective study; not an RCT
Ozols, 2002[144]	Commentary on the management of ovarian cancer
Mielcarek, 2002[145]	QoL of patients treated with paclitaxel as first-line therapy
Breidenbach, 2003[146]	Discussion article on side-effect profiles of different chemotherapy regimens
Woronoff-Lemsc, 2001[147]	Background: economics
Favalli, 2002[148]	Protocol for the After-6 study
Beshara, 2002[149]	Retrospective analysis of the use of topotecan as a second-line therapy
Markman, 2003[150]	Background on disease stage measurement in ovarian cancer
Markman, 2003[151]	First-line therapy
Bolis, 2004[152]	First-line therapy
Slater, 2001[153]	Commentary on non-curative chemotherapy
Boehnke Michaud, 2000[154]	Background on paclitaxel
Baron-Hay, 2001[155]	Commentary on the use of oxaliplatin
Doyle, 2001[156]	Background: economics
Wagner, 2001[157]	Background on the use of paclitaxel–cisplatin
Le, 2003[158]	Background
Boos, 2003[159]	Discussion on off-label use of treatments
Fireman, 2000[160]	Cost of care for patients in cancer trials
Lendermann, 2003[161]	Correction on letter to the editor
Bodurka-Bevers, 2000[162]	Background: economics
Bolis, 2001[75]	Intervention is epidoxorubicin
Chan, 2003[163]	Background: QoL during chemotherapy
Donato, 2003[164]	Background: editorial
Flynn, 2002[165]	Background on optimum time interval between surgery and chemotherapy
Gadducci, 2001[166]	Background
Anonymous, 2001[167]	Economic background
Neymark, 2002[168]	Background: economics
Geldblom, 2000[169]	Phase I study
Szucs, 2003[170]	Background: cost-effectiveness
Van Den Bosch, 2001[171]	Not an RCT and not second-line therapy
ICON1 Collaborators, 2003[172]	Background: ICON 1
Piccart, 2000[173]	Commentary
Chan, 2003[174]	Commentary on the NICE guidance on PLDH
Anonymous, 2003[175]	Commentary on the NICE guidance on paclitaxel
Anonymous, 2002[176]	Commentary on NICE guidance for PLDH
Anonymous, 2002[177]	Commentary on single agent carboplatin as first-line treatment choice
Young, 2001[178]	Background: economics
Copeland, 2003[179]	Protocol and rationale for ICON 5 (useful background)
Wenzel, 2004[180]	Abstract only: not clear that intervention is after failure of first-line platinum-based therapy

continued

Scarfone, 2001[181]	Abstract only: not clear that this is second-line therapy after failure of first-line platinum-based therapy
Gennatas, 2000[182]	Abstract only: not clear that this is second-line after failure of first-line platinum-based therapy
Muggia, 2000[183]	First-line therapy
Piccart, 2000[184]	First-line therapy
Einhorn, 2003[185]	Background on radiation therapy
Nicholls, 2001[186]	Background: economics
de Haes, 1987[187]	Background: QoL
Bolis, 1999[188]	Excluded: research update date of 2000
Dranitsaris, 2004[189]	Background: economics
ICON Group, 2002[190]	Background: ICON 3 (first-line therapy)
Fiorica, 2003[191]	Background: use of topotecan for advanced treatment (useful specific background)
Mutch, 2003[192]	Background: gemcitabine combination chemotherapy (general)
Stuart, 2003[193]	Background: first-line treatment regimens (general)
Fabbro, 2001[194]	Non-randomised Phase II study
Bankhead, 2004[195]	Useful general background article
Wang, 2003[196]	Commentary on ICON 4 (not useful as background)
ICON 1 & EOTTC – ACTION, 2003[197]	Platinum-based first-line therapy
Calhoun, 2001[198]	Background: economics
Moe, 2003[199]	Background: economics
Wu, 2001[200]	Reports on first-line therapy
Calhoun, 2003[201]	Impact of chemotherapy delays on QoL in patients undergoing first-line chemotherapy (not specific to ovarian cancer)
Biamonte, 2000[202]	Topotecan versus nihil as maintenance therapy after first-line treatment
Moss, 2002[203]	Background: management of advanced ovarian cancer patients (general)
Adams, 2004[204]	Article on use of erythropoietin in USA
Guastalla, 2003[205]	Background on adverse events associated with paclitaxel
Katsumata, 2003[206]	Background on docetaxel
Kose, 2003[207]	Phase II study of gemcitabine + carboplatin
Maenpaa, 2003[208]	Background article on docetaxel
Gronlund, 2001[209]	Retrospective study of results of patients receiving paclitaxel/carboplatin first-line therapy
Calhoun, 2003[210]	Psychometric properties of scale evaluating neuropathy
Piccart, 2003[211]	Does not have PLDH, topotecan or paclitaxel as an intervention
Bookman, 2003[212]	Background to GOG158 and ICON 5
Malik, 2000[213]	Commentary on single institution's experience of participating in topotecan trials
Vermorken, 2001[214]	Background on drug actions of oxaliplatin and paclitaxel
Bookman, 1998[215]	Not an RCT; preupdated searches
Kavanagh, 2002[216]	Not an RCT
Ojeda, 2003[51]	Background: economics
Jasas, 2003[217]	Phase II study of second-line use of oral topotecan + cisplain (i.v.)
Sehouli, 2001[218]	Abstract only: Phase II study (not randomised)
Lalisang, 2003[219]	First-line therapy with docetaxel, epirubicin and cisplatin
Wheatley, 2003[220]	Letter to the editor (useful commentary on ICON 4)
Mielke, 2003[221]	Study of different infusion times for paclitaxel in patients with different types of cancer
Green, 2003[222]	Reply to letter to the editor (useful background on ICON 4)
Anonymous, 2003[223]	Commentary on the results of ICON 4
Vorobiof, 2003[224]	Phase II study of Caelyx + carboplatin (not randomised)
Newman, 2003[225]	Letter to the editor (useful commentary on ICON4)

AE, adverse events; GOG, Gynaecologic Oncology Group; SR, systematic review; SWOG, Southwark Oncology Group.

Appendix 5

Details of quality assessment

Clinical effectiveness studies were assessed using the following criteria based on CRD Report 4

1. Was the method used to assign participants to the treatment groups really random? (Computer-generated random numbers and random number tables were accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week).
2. Was the allocation of treatment concealed? (Concealment was deemed adequate where randomisation is centralised or pharmacy controlled, or where the following are used: serially numbered identical containers, on-site computer-based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented in terms of myocardial infarction, stroke, heart failure, hypertension, diabetes and current or former smoker?
5. Was baseline comparability achieved in terms of myocardial infarction, stroke, heart failure, hypertension, diabetes and current or former smoker?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may influence the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
13. Were the reasons for withdrawals stated?
14. Was an intention to treat analysis included?

Items were graded in terms of 'yes' (item properly addressed); 'no' (item not properly addressed); 'partially addressed' (item partially addressed); 'unclear or not enough information'; or 'NA' (not applicable).

Studies of cost-effectiveness were assessed using the following criteria; this is an updated version of the checklist developed by Drummond

Study question

1. Costs and effects examined.
2. Alternatives compared.
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society).

Selection of alternatives

4. All relevant alternatives are compared (including do nothing if applicable).
5. The alternatives being compared are clearly described (who did what, to whom, where and how often).
6. The rationale for choosing the alternative programmes or interventions compared is stated.

Form of evaluation

7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?

Effectiveness data

9. The source(s) of effectiveness estimates used are stated (*e.g. single study, selection of studies, systematic review, expert opinion*).
10. Effectiveness data from RCT or review of RCTs.

11. Potential biases identified (especially if data not from RCTs).
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).

Costs

13. All the important and relevant resource use are included.
14. All the important and relevant resource use are measured accurately (with methodology).
15. Appropriate unit costs are estimated (with methodology).
16. Unit costs are reported separately from resource use data.
17. Productivity costs are treated separately from other costs.
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.

Benefit measurement and valuation

19. The primary outcome measure(s) for the economic evaluation are clearly stated (*cases detected, life-years, QALYs, etc*.).
20. Methods to value health states and other benefits are stated (*e.g. time trade-off*).
21. Details of the individuals from whom valuations were obtained are given (*patients, members of the public, health care professionals, etc*.).

Decision modelling

22. Details of any decision model used are given (*e.g. decision tree, Markov model*).
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified.
24. All model outputs are described adequately.

Discounting

25. Discount rate used for both costs and benefits given.
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?

Allowance for uncertainty

Stochastic analysis of patient-level data

27. Details of statistical tests and confidence intervals are given for stochastic data.
28. Uncertainty around cost-effectiveness expressed (*e.g. CI around ICER, CEACs*).
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (*e.g. unit costs, discount rates*) and analytical decisions (*e.g. methods to handle missing data*).

Stochastic analysis of decision models

30. Are all appropriate input parameters included with uncertainty?
31. Is second-order uncertainty (uncertainty in means) included rather than first-order uncertainty (uncertainty between patients)?
32. Are the probability distributions adequately detailed and appropriate?
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytical decisions (e.g. methods to handle missing data).

Deterministic analysis

34. The approach to sensitivity analysis is given (*e.g. univariate, threshold analysis*).
35. The choice of variables for sensitivity analysis is justified.
36. The ranges over which the variables are varied are stated.

Presentation of results

37. Incremental analysis is reported using appropriate decision rules.
38. Major outcomes are presented in both a disaggregated and an aggregated form.
39. Applicable to the NHS setting.

All items were graded as either 'yes' (item adequately addressed); 'x', no (item not adequately addressed); '?', unclear or not enough information; 'NA', not applicable; or 'NS', not stated.

Appendix 6

Data extraction tables

Trial: 30-49[22]

In the following tables and data, sources are indicated by the following symbols preceding entries. †, Extracted from Shering-Plough Ltd. *Data on File. A Phase III randomised, open-label comparative study of Doxil/Caelyx versus topotecan HCL in patients with epithelial ovarian carcinoma following failure of first-line, platinum-based chemotherapy. Final Report 2004*. Kenilworth, NJ: Schering-Plough Research Institute; 2004.

±, Extracted from Schering-Plough Ltd. *Caelyx (pegylated liposomal doxorubicin hydrocholoride) in the treatment of recurrent ovarian cancer in the United Kingdom. A submission to the National Institute for Clinical Excellence, 29 August 2001*. Kenilworth, NJ: Schering-Plough; 2001. ‡, Extracted from Schering-Plough Ltd. *Caelyx (pegylated liposomal doxorubicin hydrocholoride) in the treatment of recurrent ovarian cancer in the United Kingdom. A submission to the National Institute for Clinical Excellence, 6 June 2004*. Kenilworth, NJ: Schering-Plough: 2004.

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
Author: Gordon, 2001[22] **Objective** To compare the efficacy and safety of PLDH and topotecan in patients with epithelial ovarian carcinoma that recurred after or did not respond to platinum-based first-line chemotherapy **Trial ID:** 30-49 **Phase:** Phase III **Method of randomisation** Centrally randomised and stratified for platinum sensitivity and bulky disease **Length of follow-up:** Up to 1 year, or less if disease progression occurred	**Number randomised** 481 randomised; 474 in ITT **Disease type:** Epithelial **Disease stage:** Advanced **Occurrence of secondary spread:** Yes, in the majority of cases, but not all **Therapy stage:** Second-line **Previous treatments** Chemotherapy (platinum-based first-line regimen); radiotherapy (but only if involved less than one-third of haemopoietic sites) **Disease present after first-line treatment?** Residual: yes Refractory: yes **Age/age range of participants** PLDH: median 60.0 years (range 27–87 years) Topotecan: median 60.0 years (range 25–85 years) **Characteristics** **PLDH (I)** Mean (SD) 59.2 (11.3) Median age: 60.0 years (range: 27–87 years) <65: 156 (65.3%) ≥ 65: 83 (34.7%) **± Race (*n* = 239)** White: 217/239 (90.8%) Black: 14/239 (5.9%) Hispanic: 2/239 (0.8%) Asian: 3/239 (1.3%) Other: 3/239 (1.3%)	**Intervention (I)** **Type:** PDLH **No. randomised:** Not reported. 239 were treated **Route of administration:** i.v. **Dose:** 50 mg/m^2 as a 1-h infusion **No. of cycles:** Not stated (protocol up to 6) Length per cycle: 28 days **Control (C)** **Type:** Topotecan **No. randomised:** Not reported. 235 were treated **Route of administration:** i.v. **Dose:** 1.5 mg/m^2/d as a 30-minute infusion for 5 days **No. of cycles:** Not stated (protocol up to 8) **Length per cycle:** 21 days **Comments about intervention/control:** In the absence of disease progression, treatment with both agents was continued for up to 1 year. Treatment could also continue if the patient demonstrated sustained clinical benefit. Patients who discontinued treatment after 6 months	**Withdrawals from intervention (I)** Overall seven participants were lost to follow-up prior to the first dose. The study group assignment and reason for these withdrawals is not stated. No other reasons for lost to follow-up are reported **Withdrawals from control (C)** Overall seven participants were lost to follow-up prior to the first dose. The study group assignment and reason for these withdrawals is not stated. No other reasons for lost to follow-up are reported **Adverse events** **PLDH** PLDH: 43 participants in the group withdrew from the study due to adverse events, but there were no treatment-related deaths in the group PLDH (*n* = 239) † All grades Body as a whole: Asthenia: 96 (40.2%) Abdominal pain: 80 (33.5%) Fever: 51 (21.3%) Pain: 50 (20.9%) Mucous membrane disorder: 34 (14.2%) Back pain: 28 (11.7%) Infection: 28 (11.7%) Headache: 25 (10.5%) Digestive system: Nausea: 110 (46.0%) Stomatitis: 99 (41.4%) Vomiting: 78 (32.6%) Constipation: 72 (30.1%) Diarrhoea: 50 (20.9%) Anorexia: 48 (20.1%) Dyspepsia: 29 (12.1%) Intestinal obstruction: 27 (11.3%)	**Authors' conclusions** The comparable efficacy, favourable safety profile and convenient dosing support the role of PLDH as a valuable treatment option in this patient population **Comments** This was designed as an equivalence study with 80% power to detect statistical equivalence of the two drugs A sample size calculation was performed prior to recruitment which suggested a total of 360 participants, 175 in each treatment group, were required to ensure with a probability of 80% that the lower 95% one-sided CI of the HR of topotecan to PLDH could not fall below 0.757. However, the sample size was increased to 460 to cover anticipated losses to follow-up Karnofsky performance status data are not provided in terms of the individual study groups The analysis is not an ITT analysis as reported by the trialists. 481 participants were originally randomised but the analysis performed was based on only 474 participants

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	± CA-125 at baseline (U/ml) (*n* = 224) Mean (SD): 900.26 (1933.342) Median: 198.50 Range: 3.0–18801.0 **Initial FIGO stage** I 11/239 (5%) II 13/239 (5%) II 175/239 (73%) IV 40/239 (17%) **± Prestudy chemotherapy regimens** Combination platinum and taxane: 176/239 (73.6%) Combination platinum and non-taxane: 6/239 (2.5%) Platinum alone: 57/239 (23.9%) Type of prior platinum therapy: Carboplatin only: 145/239 (60.7%) Cisplatin only: 68/239 (28.5%) Both: 26/239 (10.9%) **Prior anthracycline therapy** Yes: 11/239 (4.6%) No: 228/239 (95.4%) **Drug-free interval** Mean (SD): 10.2 (11.98) months Median: 7.0 months (range: 0.9–82.1 months) Median CA-125: 199 U/ml (range: 3.0–18801.0 U/ml) **Sum of lesions at baseline** Mean (SD): 38.7 (54) cm^2 Median: 20 cm^2 (range: 1–441 cm^2) **Platinum sensitivity** Sensitive: 109/239 (46%) Refractory: 130/239 (54%)	(six cycles of PLDH, eight cycles of topotecan) were considered protocol completed. Response to study drug was based on objective tumour assessments. A complete response (CR) was defined as complete disappearance of all measurable and assessable disease, no new lesions, and no disease-related symptoms. A partial response (PR) was documented in patients with ≥ 50% decrease in the sum of the products of bidimensional perpendicular diameters of all measurable lesions; progression of assessable disease and new lesions were not allowed. Progressive disease (PD) was classified in patients with a ≥ 50% increase in the sum of products of bidimensionally measured lesions over the smallest sum obtained as the best response, or reappearance of any lesion that had disappeared, or clear worsening of any assessable disease, or failure to return for evaluation because of	Haemic and lymphatic system: Anaemia: 96 (40.2%) Leukopenia: 88 (36.8%) Neutropenia: 84 (35.1%) Thrombocytopenia: 31 (13.0%) Metabolic/nutritional disorder: Peripheral oedema: 27 (11.3%) Nervous system: Paresthesia: 24 (10.0%) Dizziness: 10 (4.2%) Respiratory system: Pharyngitis: 38 (15.9%) Dyspnoea: 36 (15.1%) Cough increased: 23 (9.6%) Skin and appendages: Hand–foot syndrome: 121 (50.6%) Rash: 68 (28.5%) Alopecia: 46 (19.2%) Grade 3 Body as a whole: Asthenia: 17 (7.1%) Abdominal pain: 24 (10.0%) Fever: 2 (0.8%) Pain: 4 (1.7%) Mucous membrane disorder: 9 (3.8%) Back pain: 4 (1.7%) Infection: 5 (2.1%) Headache: 2 (0.8%) Digestive system: Nausea: 12 (5.0%) Stomatitis: 19 (7.9%) Vomiting: 17 (7.1%) Constipation: 6 (2.5%) Diarrhoea: 5 (2.1%) Anorexia: 6 (2.5%) Dyspepia: 2 (0.8%) Intestinal obstruction: 19 (7.9%) Haemic and lymphatic system: Anaemia: 13 (5.4%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Presence of bulky disease Present: 111/239 (46%) Absent: 128/239 (54%) **± Platinum sensitivity/bulky disease** Refractory/present: 64 (26.8%) Refractory/absent: 66 (27.6%) Sensitive/present: 44 (18.4%) Sensitive/absent: 65 (27.2%) **± KPS at baseline:** 50: 1 (0.4%) 60: 7 (2.9%) 65: 1 (0.4%) 70: 30 (12.6%) 75: 0 80: 53 (22.2%) 85: 0 90: 96 (40.2%) 100: 50 (20.9%) Total <80: 39 (16.3%) Total ⩾80: 199 (83.3%) Not available: 1 (0.4%) **± Histological tumour type** Serous papillary: 145 (60.7%) Mucinous: 6 (2.5%) Endometrioid: 11 (4.6%) Clear cell: 9 (3.8%) Transitional cell: 1 (0.4%) Undifferentiated: 55 (23.0%) Unspecified adenocarcinoma: 11 (4.6%) Not specified: 1 (0.4%) Histological tumour grade: Well differentiated: 4 (1.7%) Moderately differentiated: 16 (6.7%) Poorly differentiated: 53 (22.2%) Unspecified differentiated: 125 (52.3%)	death or deteriorating condition, or the appearance of any new lesion or site. Patients were classified as having stable disease if they did not qualify for CR, PR or PD. **Actual study treatment administration:** **PLDH (*n* = 239):** Total number of dosing cycles: 1164 Cumulative dose, mg/m^2: Median: 200 Range: 47–1301 Mean cycle dose, mg/m^2: Median: 50 Range: 34–58 Mean cycle length, days: Median: 30 Range: 27–56 (*n* = 212) ± Most patients received 4–5 cycles of study drug (estimated by dividing cumulative dose by the cycle dose) **Topotecan (*n* = 235)** Total number of dosing cycles: 1249 Cumulative dose, mg/m^2: Median: 36 Range: 3–165 Mean cycle dose, mg/m^2: Median: 7 Range: 3–10 Mean cycle length, days: Median: 24	Leukopenia: 21 (8.8%) Neutropenia: 19 (7.9%) Thrombocytopenia: 3 (1.3%) Metabolic/nutritional disorder: Peripheral oedema: 5 (2.1%) Nervous system: Paresthesia: 0 Dizziness: 0 Respiratory system: Pharyngitis: 0 Dyspnoea: 8 (3.3%) Cough increased: 0 Skin and appendages: Hand–foot syndrome: 55 (23.0%) Rash: 10 (4.2%) Alopecia: 3 (1.3%) Grade 4 Body as a whole: Asthenia: 0 Abdominal pain: 1 (0.4%) Fever: 0 Pain: 1 (0.4%) Mucous membrane disorder: 0 Back pain: 0 Infection: 0 Headache: 0 Digestive system: Nausea: 1 (0.4%) Stomatitis: 1 (0.4%) Vomiting: 2 (0.8%) Constipation: 0 Diarrhoea: 1 (0.4%) Anorexia: 0 Dyspepia: 0 Intestinal obstruction: 4 (1.7%) Haemic and lymphatic system: Anaemia: 1 (0.4%) Leukopenia: 3 (1.3%) Neutropenia: 10 (4.2%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Not specified: 41 (17.2%) **± Ascites at baseline** Absent: 162 (67.8%) Present: 77 (32.2%) Not available: 0 **Topotecan (C)** Median age: 60.0 years (range: 25–85 years) <65: 138 (58.7%) ⩾65: 97 (41.3%) **± Race (*n* = 235)** White: 226/235 (96.2%) Black: 7/235 (3.0%) Hispanic: 2/235 (0.9%) Asian: 0 Other: 0 **Initial FIGO stage** I 15/235 (6%) II 8/235 (3%) II 164/235 (70%) IV 48/235 (20%) **± Prestudy chemotherapy regimens (*n* = 235)** Combination platinum and taxane: 170/235 (72.3%) Combination platinum and non-taxane: 13/235 (5.5%) Platinum alone: 52/235 (22.1%) Type of prior platinum therapy: Carboplatin alone: 145/235 (61.7%) Cisplatin alone: 61/235 (26.0%) Both: 29/235 (12.3%) **Prior anthracycline therapy:** Yes: 19/235 (8.1%) No: 216/235 (91.9%)	Range: 20–38 (*n* = 211) ± Most patients received 4–5 cycles of study drug (estimated by dividing cumulative dose by the cycle dose) **Protocol deviations** Protocol deviations included: (1) failure to meet entry criteria (7 receiving PLDH, 2 receiving topotecan; (2) patients who continued in study after first clinically significant change in left ventricular ejection fraction (LVEF) (13 receiving PLDH); (3) patients who continued treatment after documented disease progression (40 receiving PLDH, 42 receiving topotecan); (4) patients who completed <8 cycles of treatment but were deemed protocol-completed by the investigator (20 receiving topotecan)	Thrombocytopenia: 0 Metabolic/nutritional disorder: Peripheral oedema: 0 Nervous system: Paresthesia: 0 Dizziness: 0 Respiratory system: Pharyngitis: 0 Dyspnoea: 2 (0.8%) Cough increased: 0 Skin and appendages: Hand–foot syndrome: 2 (0.8%) Rash: 0 Alopecia: 0 **Topotecan (*n* = 235)** Topotecan: 37 participants withdrew due to treatment-related adverse events and three participants died (all from complications of neutropenia and sepsis) † All grades: Body as a whole: Asthenia: 121 (51.5%) Abdominal pain: 89 (37.9%) Fever: 72 (30.6%) Pain: 40 (17.0%) Mucous membrane disorder: 8 (3.4%) Back pain: 24 (10.2%) Infection: 15 (6.4%) Headache: 35 (14.9%) Digestive system: Nausea: 148 (63.0%) Stomatitis: 36 (15.3%) Vomiting: 103 (43.8%) Constipation: 107 (45.5%) Diarrhoea: 82 (34.9%) Anorexia: 51 (21.7%) Dyspepia: 33 (14.0%) Intestinal obstruction: 26 (11.1%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Drug-free interval Mean (SD): 10.1 (13.81) months Median: 6.7 months (range: 0.5–9.6 months) **± CA-125 at baseline (U/ml)** Mean (SD): 931.80 (2454.587) Median: 178.00 (range: 3.0–29,330.0) **Sum of lesions at baseline** Mean (SD) : 33.5 (38.67) Median: 20 cm^2 (range: 1–296 cm^2) **Platinum sensitivity** Sensitive: 111/235 (47%) Refractory: 124/235 (53%) **Presence of bulky disease** Present: 111/235 (47%) Absent: 124/235 (53%) **± Platinum sensitivity/bulky disease** Refractory/present: 60 (25.5%) Refractory/absent: 65 (27.7%) Sensitive/present: 45 (19.1%) Sensitive/absent: 65 (27.7%) **± KPS at baseline** 50: 0 60: 7 (3.0%) 65: 0 70: 29 (12.3%) 75: 1 (0.4%) 80: 56 (23.8%) 85: 1 (0.4%) 90: 85 (36.2%) 100: 53 (22.6%) Total <80: 37 (15.7%) Total ≥80: 195 (83.0%) Not available: 3 (1.3%)		Haemic and lymphatic system: Anaemia: 177 (75.3%) Leukopenia: 151 (64.3%) , Neutropenia: 193 (82.1%) Thrombocytopenia: 153 (65.1%) Metabolic/nutritional disorder: Peripheral oedema: 41 (17.4%) Nervous system: Paresthesia: 21 (8.9%) Dizziness: 24 (10.2%) Respiratory system: Pharyngitis: 42 (17.9%) Dyspnoea: 55 (23.4%) Cough increased: 27 (11.5%) Skin and appendages: Hand–foot syndrome: 2 (0.9%) Rash: 29 (12.3%) Alopecia: 123 (52.3%) Grade 3: Body as a whole: Asthenia: 19 (8.1%) Abdominal pain: 19 (8.1%) Fever: 8 (3.4%) Pain: 4 (1.7%) Mucous membrane disorder: 0 Back pain: 2 (0.9%) Infection: 2 (0.9%) Headache: 0 Digestive system: Nausea: 16 (6.8%) Stomatitis: 1 (0.4%) Vomiting: 18 (7.7%) Constipation:11 (4.7%) Diarrhoea: 9 (3.8%) Anorexia: 3 (1.3%) Dyspepia: 0 Intestinal obstruction: 14 (6.0%) Haemic and lymphatic system: Anaemia: 59 (25.1%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	± Histological tumour type Serous papillary: 130 (55.3%) Mucinous: 9 (3.8%) Endometrioid: 15 (6.4%) Clear cell: 10 (4.3%) Transitional cell: 0 Undifferentiated: 53 (22.6%) Unspecified adenocarcinoma: 18 (7.7%) Not specified: 0 **± Histological tumour grade** Well differentiated: 3 (1.3%) Moderately differentiated: 13 (5.5%) Poorly differentiated: 72 (30.6%) Unspecified differentiated: 110 (46.8%) Not specified: 37 (15.7%) **± Ascites at baseline** Absent: 168 (71.5%) Present: 65 (27.7%) Not available: 2 (0.9%) **Inclusion/exclusion criteria** Women >18 years of age with measurable or measurable and assessable disease that had recurred or failed first-line platinum-based chemotherapy. Measurable disease was defined as bidimensionally measurable lesions(s) with clearly defined margins by plain X-ray with at least one diameter ≥ 0.5 cm (excluding bone lesions) or by CT, MRI or another imaging scan with both diameters greater than the distance between cuts of the imaging study or palpation with both diameters ≥2 cm. Assessable disease included unidimensionally measurable		Leukopenia: 83 (35.3%) Neutropenia: 33 (14.0%) Thrombocytopenia: 40 (17.0%) Metabolic/nutritional disorder: Peripheral oedema: 6 (2.6%) Nervous system: Paresthesia: 0 Dizziness: 0 Respiratory system: Pharyngitis: 1 (0.4%) Dyspnoea: 7 (3.0%) Cough increased: 0 Skin and appendages: Hand–foot syndrome: 0 Rash: 1 (0.4%) Alopecia: 15 (6.4%) Grade 4: Body as a whole: Asthenia: 0 Abdominal pain: 4 (1.7%) Fever: 5 (2.1%) Pain: 0 Mucous membrane disorder: 0 Back pain: 0 Infection: 0 Headache: 0 Digestive system: Nausea: 3 (1.3%) Stomatitis: 0 Vomiting: 5 (2.1%) Constipation: 2 (0.9%) Diarrhoea: 1 (0.4%) Anorexia: 0 Dyspepia: 0 Intestinal obstruction: 7 (3.0%) Haemic and lymphatic system: Anaemia: 10 (4.3%) Leukopenia: 36 (15.3%) Neutropenia: 146 (62.1%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	lesion(s), mass(es) with margins not clearly defined, lesion(s) with both diameters ≥ 0.5 cm, lesion(s) on scan with either diameter ≥ 2 cm and malignant ascites or pleural effusion in conjunction with serum CA-125 levels >100 U/ml in the absence of cirrhosis. Additional criteria included adequate bone-marrow function (platelets ⩾100,000/mm^3, haemoglobin ⩾9 g/dl, absolute neutrophil count ⩾1500 cells/mm^3) renal function (serum creatinine ⩽2.5 mg/dl), liver function [alanine aminotransferase (AST) ⩽ two times the upper limit of normal, alkaline phosphate ⩽ two times the upper limits of normal, bilirubin ⩽ upper limit of normal)], cardiac function (left ventricular ejection fraction (LVEF) ⩾ 50% or the institutional normal), Karnofsky performance status ⩾ 60%, and a disease-free period of >5 years from prior malignancies (except curatively treated basal cell carcinoma, squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix). Patients were excluded if they were pregnant or breast-feeding, expected to live ≤ 3 months, had received prior radiation therapy to greater than one-third of haematopoietic sites, had a history of cardiac disease that met the New York State Heart Association Classification class 2 or greater, had an uncontrolled systemic infection, had received an investigational agent within 30 days of the first dose of study drug, had		Thrombocytopenia: 40 (17.0%) Metabolic/nutritional disorder: Peripheral oedema: 0 Nervous system: Paresthesia: 0 Dizziness: 0 Respiratory system: Pharyngitis: 0 Dyspnoea: 3 (1.3%) Cough increased: 0 Skin and appendages: Hand–foot syndrome: 0 Rash: 0 Alopecia: 0 **Dosing adjustments** **PLDH** Total dosing adjustments: 137 (57.3%); 25.2% doses were reduced due to PPE Delayed doses: 124 (51.9%) Interrupted doses: 23 (9.6%) Reduced doses: 65 (27.2%) ± Reason for delay, interruption or reduction: Hand–foot syndrome: 105/415 (25.3%) Stomatitis: 105/415 (25.3%) Haematological toxicity: 46/415 (11.1%) Other laboratory toxicity: 3/415 (0.7%) Infusion reaction: 17/415 (4.1%) Intercurrent illness: 20/415 (4.8%) Scheduling problem: 36/415 (8.7%) Other: 204/415 (49.2%) Granulocyte/granulocyte-macrophage colony-stimulating factor: 11 (4.6%) **Topotecan** Total dosing adjustments: 184 (78.3%); 43.3% doses reduced due to haematological toxicity. Delayed doses: 151 (64.3%) Interrupted doses: 34 (14.5%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	received prior PLDH or topotecan therapy, had received chemotherapy within 29 days of the first dose of study drug (or within 42 days if patient had received a nitrosourea or mitomycin). Additionally no concurrent investigational or antineoplastic agents were permitted during the study **Comments about participants** Patients were prospectively stratified based on platinum sensitivity and the presence or absence of bulky disease. Patients were categorised as platinum sensitive if they had a PFS interval of >6 months after first-line platinum-based chemotherapy. Patients were considered platinum refractory if they progressed during initial platinum-based chemotherapy, demonstrated stable disease or relapsed within 6 months after completing platinum-based chemotherapy. Bulky disease was defined as the presence of a tumuor mass >5 cm		Reduced doses: 122 (51.9%) ± Reason for delay, interruption or reduction: Hand–foot syndrome: 0 Stomatitis: 1/684 (0.1%) Haematological toxicity: 295/684 (43.1%) Other laboratory toxicity: 1/684 (0.1%) Infusion reaction: 3/684 (0.4%) Intercurrent illness: 29/684 (4.2%) Scheduling problem: 72/684 (10.5%) Other: 397/684 (58.0%) Granulocyte/granulocyte macrophage colony-stimulating factor: 68 (29.1%) **Discontinuations:** ± 48% of PLDH group and 47% of topotecan discontinued the study owing to disease progression **± Reasons for discontinuation** **PLDH (*n* = 239)** Disease progression: 114/239 (48%) Adverse event: 43/239 (18%) Death: 15/239 (6%) Non-compliance: 1/239 (<1%) Inappropriate enrolment: 0 Other/unknown: 31/239 (13%) Protocol completed: 34/239 (14%) Ongoing: 5/239 (2%) **± Topotecan (*n* = 235)** Disease progression: 110/235 (47%) Adverse events: 37/245 (15%) Death: 18/235 (8%) Non-compliance: 1/235 (<1%) Inappropriate enrolment: 1/235 (<1%) Other/unknown: 35/235 (15%) Protocol completed: 39/235 (17%) Ongoing: 2/235 (1%)	

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome: PFS (time from the start of study drug dosing to documented disease progression or death due to any cause) **PLDH group (I)** All participants (n = 239) Median PFS = 16.1 weeks (p = 0.095) Median survival = 60 weeks (p = 0.341) ± Time to progression: HR = 1.176 (90% CI: 1.002 to 1.381) p = 0.095 **Platinum-sensitive participants (n = 109)** Median PFS = 28.9 weeks (p = 0.37) Median survival = 108 weeks ± PFS: HR = 1.72 (95% CI: 1.145 to 2.585) Test for interaction between platinum sensitivity/resistance and survival = 0.256 (95% CI: 0.151 to 1.155) p = 0.011 **Platinum-resistant participants (n = 130)** Median PFS = 9.1 weeks (p = 733) Median survival = 35.6 weeks (p = 0.455) **Topotecan group (C)** All participants (n = 235) Median PFS = 17.0 weeks (p = 0.095) Median survival = 56.7 weeks (p = 0.341) ± Time to progression: HR = 1.176 (90% CI: 1.002 to 1.381) p = 0.095 **Platinum-sensitive participants (n = 111)** Median PFS = 23.3 weeks (p = 0.37) Median survival= 71.1 weeks (p = 0.008) **Platinum-resistant participants (n = 124)** Median PFS = 13.6 weeks (p = 0.733) Median survival = 41.3 weeks (p = 0.455)	**Outcome: Response** **PLDH group (I) (n = 239)** Overall response: 47/239 (19.7%) (p = 0.390) Complete response: 9/239 (3.8%) Partial response: 38/239 (15.9%) Stable disease: 77/239 (32.2%) **Platinum-sensitive participants (n = 109)** Overall response: 31/109 (28.4%) (p = 0.964) Complete response: 8/109 (7.3%) Partial response: 23/109 (21.1%) Stable disease: 41/109 (37.6%) **Platinum-resistant participants (n = 130)** Overall response: 16/130 (12.3%) (n = 130) Complete response: 1/130 (0.8%) Partial response: 15/130 (11.5%) Stable disease: 36/130 (27.7%) **Topotecan group (C) (n = 235)** Overall response: 40/235 (17%) Complete response: 11/235 (4.7%) Partial response: 29/235 (12.3%) Stable disease: 95/235 (40.4%) **Platinum-sensitive participants (n = 111)** Overall response: 32/111 (28.8%) (p = 0.964) Complete response: 10/111 (9.0%) Partial response: 22/111 (19.8%) Stable disease: 42/111 (37.8%) **Platinum-resistant participants (n = 124)** Overall response: 8/124 (6.5%) (p = 0.118) Complete response: 1/124 (0.8%) Partial response: 7/124 (5.6%) Stable disease: 53/124 (42.7%)	**Outcome: QoL** Baseline data: For both the PLDH and topotecan groups: not reported; questionnaire only completed by 82% of participants. However, function and symptom scale scores were similar between the two treatment groups **Follow-up data:** For both the PLDH and topotecan groups: No significant differences between the intervention and control groups at 12 weeks follow-up. **Comments** QoL (assessed by QLQ-C30: 82% of participants completed QoL measure at baseline, at 12 weeks, <50% of participants in either treatment arm were still in the QoL study

± Time to progression for subgroups based on baseline characteristics

Variable	Subgroup	Treatment	*n*	Median TTP (days)	HR	95% CI for HR[a]
Overall response	ITT	PLDH	239	113	1.176	0.972 to 1.423
		Topotecan	235	119		
Age	<65 years	PLDH	156	121	1.190	0.932 to 1.520
		Topotecan	138	113		
	≥ 65 years	PLDH	83	103	1.147	0.835 to 1.575
		Topotecan	97	128		
KPS at baseline	<80	PLDH	39	53	0.867	0.523 to 1.438
		Topotecan	37	71		
	≥ 80	PLDH	200	131	1.157	0.939 to 1.426
		Topotecan	194	134		
Drug-free interval after last dose of first-line therapy	≤ 6 months	PLDH	102	57	1.095	0.815 to 1.470
		Topotecan	109	94		
	>6 to ≤ 18 months	PLDH	107	148	1.170	0.874 to 1.566
		Topotecan	94	131		
	>18 months	PLDH	30	290	1.530	0.832 to 2.812
		Topotecan	32	228		
Bulky disease	Present	PLDH	111	92	1.143	0.863 to 1.151
		Topotecan	111	110		
	Absent	PLDH	128	131	1.206	0.929 to 1.565
		Topotecan	124	128		
Platinum sensitivity	Sensitive	PLDH	109	202	1.349	1.018 to 1.788
		Topotecan	111	163		
	Refractory	PLDH	130	66	1.046	0.807 to 1.356
		Topotecan	124	95		
Ascites	Present	PLDH	77	63	0.930	0.653 to 1.325
		Topotecan	65	102		
	Absent	PLDH	162	157	1.295	1.026 to 1.635
		Topotecan	168	134		

[a] 95% CIs were estimated from the original 90% CI reported using the following equations:
ln 95% CI, lower CI = ln HR – [1.96 × (ln of HR – ln lower 90% CI)/1.645].
ln 95% CI, upper CI = ln HR + [1.96 × (ln HR – ln upper 90% CI)/1.645].

† Long-term follow-up efficacy analysis

Objective: To compare the efficacy of PLDH versus topotecan in terms of survival and PFS when 90% of participants had died or were lost to follow-up.

Length of follow-up: 3 years.

† **Outcome 1:** overall survival

PLDH (n = 239)
% censored: 16.7
Median survival (weeks): 62.7 (range: 1.7–258.3)

Topotecan (n = 235)
% censored: 8.9
Median survival (weeks): 59.7 (range: 1.6–247.1)
HR = 1.216 (95% CI: 1.00 to 1.478) p = 0.050

Overall survival rates

	PLDH					Topotecan				
Overall survival[a]	**Alive**	**Dead**	**Censored**	**Rate (%)**	**95% CI**	**Alive**	**Dead**	**Censored**	**Rate (%)**	**95% CI**
1	132	104	3	56.3	50.0 to 62.6	126	108	1	54.0	47.6 to 60.3
2	80	154	5	34.7	28.6 to 40.8	54	178	3	23.6	18.1 to 29.1
3	38	185	16	20.2	14.9 to 25.5	24	201	10	13.2	8.8 to 17.7

[a] 1 year = 365 days; 2 years = 731 days; 3 years = 1096 days.

† Platinum sensitive disease

PLDH (*n* = 109)
% censored: 22.0
Median survival (weeks): 107.9 (range: 6.9–258.3)

Topotecan (*n* = 110)
% censored: 10.9
Median survival (weeks): 70.1 (range: 1.6–24.1+)
HR = 1.432 (95% CI: 1.066 to 1.923); $p = 0.017$

Overall survival rates – platinum-sensitive disease

	PLDH					Topotecan				
Overall survival[a]	**Alive**	**Dead**	**Censored**	**Rate (%)**	**95% CI**	**Alive**	**Dead**	**Censored**	**Rate (%)**	**95% CI**
1 year	79	28	2	74.1	65.8 to 82.4	72	37	1	66.2	57.4 to 75.1
2 years	53	52	4	51.2	41.6 to 60.7	33	75	2	31.0	22.2 to 39.7
3 years	26	75	8	28.4	19.6 to 37.1	16	89	5	17.5	10.2 to 24.7

[a] 1 year = 365 days; 2 years = 731 days; 3 years = 1096 days.

† Platinum-refractory disease

PLDH (*n* = 130)
% censored: 12.3
Median survival (weeks): 38.3 (range: 1.7–253.9+)

Topotecan (*n* = 125)
% censored: 7.2
Median survival (weeks): 42.1 (range: 1.6–239.3)
HR = 1.069 (95% CI: 0.823, 1.387); $p = 0.618$

† Overall survival rates – platinum-refractory disease

	PLDH					Topotecan				
Overall survival[a]	**Alive**	**Dead**	**Censored**	**Rate (%)**	**95% CI**	**Alive**	**Dead**	**Censored**	**Rate (%)**	**95% CI**
1	53	76	1	41.5	32.8 to 50.1	54	71	0	43.2	34.5 to 51.9
2	27	102	1	21.1	14.1 to 28.2	21	103	1	17.2	10.5 to 23.8
3	12	110	8	13.8	7.6 to 20.0	8	112	5	9.5	4.2 to 14.7

[a] 1 year = 365 days; 2 years = 731 days; 3 years = 1096 days.

† Overall survival for subgroups according to baseline disease characteristics

Variable	Group	*N*	HR	95% CI for HR
	Manufacturer's ITT	474	1.216	1.00 to 1.478
Age	<65 year	294	1.322	1.022 to 1.710
	≥ 65 years	180	1.077	0.786 to 1.477
Baseline KPS	<80	76	0.871	0.531 to 1.427
	≥ 80	394	1.242	0.999 to 1.543
Drug-free interval	≤ 6 months	211	1.103	0.826 to 1.474
	>6 to ≤ 8 months	201	1.284	0.945 to 1.744
	>18 months	62	1.191	0.663 to 2.137
Bulky disease	Present	213	1.1131	0.849 to 1.506
	Absent	261	1.294	0.991 to 1.691
Platinum sensitivity	Sensitive	219	1.432	1.066 to 1.923
	Refractory	255	1.069	0.823 to 1.387
Baseline ascites	Present	142	0.978	0.689 to 1.389
	Absent	330	1.387	1.088 to 1.768

† Outcome 2: PFS

PLDH (*n* = 239)

% censored: 2.9

Median PFS (weeks): 16.1 (range 1.3–163.4+)

Topotecan (*n* = 235)

% censored: 3.0

Median PFS (weeks): 16.9 (range: 0.4–178.6)

HR = 1.118 (95% CI: 0.928 to 1.347); $p = 0.241$

Platinum-sensitive disease

PLDH (*n* = 109)

% censored: 2.8

Median PFS (weeks): 27.3 (range: 2.4–151.9)

Topotecan (*n* = 110)

% censored: 1.8

Median PFS (weeks): 22.7 (range: 0.4 = 155.9+)

HR = 1.287 (95% CI: 0.1977 to 1.694); $p = 0.072$

Platinum-refractory disease

PLDH (*n* = 130)

% censored: 3.1

Median PFS (weeks): 9.1 (range: 1.3–162.4)

Topotecan (*n* = 125)

% censored: 4.0

Median progression free survival (weeks): 13.6 (range: 1.4–178.6)

HR = 0.992 (95% CI: 0.770 to 1.279); $p = 0.952$

† Overall survival for subgroups according to baseline disease characteristics

Variable	Group	*N*	HR	95% CI for HR
	Manufacturer's ITT	474	1.118	0.928 to 1.347
Age	<65 year	294	1.207	0.949 to 1.534
	≥ 65 years	180	1.027	0.754 to 1.398
Baseline KPS	<80	76	0.869	0.519 to 1.454
	≥ 80	394	1.104	0.900 to 1.354
Drug-free interval	≤ 6 months	211	0.994	0.747 to 1.322
	>6 to ≤ 18 months	201	1.093	0.817 to 1.461
	>18 months	62	1.371	0.789 to 2.382

± Numbers and percentages of patients with maintenance of or improvement in QoL scores at 12 weeks

Scales	Caelyx		Topotecan	
	No.	%	No.	%
Physical functioning	66/118	56	60/107	56
Role functioning	77/118	65	63/109	58
Emotional functioning	80/119	67	80/108	74
Cognitive functioning	87/119	73	79/108	73
Social functioning	82/119	69	69/108	64
Global QoL	68/117	58	54/104	52
Fatigue	67/118	57	61/109	56
Nausea/vomiting	86/119	72	77/109	71
Pain	76/119	64	88/109	81

± Number and percentages of patients with maintenance of or improvement in QoL scores at 12 weeks for platinum-sensitive and platinum-refractory subgroups

Scales	Platinum sensitive				Platinum-refractory			
	Caelyx		Topotecan		Caelyx		Topotecan	
	N.	%	No.	%	No.	%	No.	%
Physical functioning	38/65	58	30/57	53	28/53	53	30/50	60
Role functioning	36/65	55	30/59	51	41/53	77	33/50	66
Emotional functioning	38/65	58	40/58	69	42/54	78	40/50	80
Cognitive functioning	48/65	74	42/58	72	39/54	72	37/50	74
Social functioning	39/65	60	34/58	59	43/54	80	35/50	70
Global QoL	36/64	56	25/56	45	32/53	60	29/48	60
Fatigue	29/65	45	30/59	51	38/53	72	31/50	62
Nausea/vomiting	44/65	68	42/59	71	42/54	78	35/50	70
Pain	35/65	54	49/59	83	41/54	76	39/50	78

± Quality-adjusted time without symptoms or toxicity survival analysis (Q-TwiST): time (in months) spent in the three health states and their differences

Health states	Caelyx	Topotecan	Difference (95% CI)
TOX (grade 3 or higher)	0.84	1.54	–0.70 (–1.04 to –0.36)
Twist	4.65	3.51	1.14 (0.46 to 1.82)
PROG (until death or 15 months postrandomisation)	5.07	5.53	–0.46 (–1.31 to 0.39)

† Outcome 2: progression-free survival
PLDH (*n* = 239)
% censored: 2.9
Median PFS (weeks): 16.1 (range 1.3–163.4+)

Topotecan (*n* = 235)
% censored: 3.0
Median PFS (weeks): 16.9 (range: 0.4–178.6)
HR = 1.118 (95% CI: 0.928 to 1.347); $p = 0.241$

Platinum-sensitive disease
PLDH (*n* = 109)
% censored: 2.8
Median PFS (weeks): 27.3 (range: 2.4–151.9)

Topotecan (*n* = 110)
% censored: 1.8
Median PFS (weeks): 22.7 (range: 0.4–155.9+)
HR = 1.287 (95% CI: 0.l977 to 1.694); $p = 0.072$

Platinum-refractory disease
PLDH (*n* = 130)
% censored: 3.1
Median PFS (weeks): 9.1 (range: 1.3–162.4)

Platinum-sensitive disease
PLDH (*n* = 109)
Total (CR + PR): 32/109 (29.4%) (95% CI: 20.8 to 37.9%)
CR: 8/109 (7.3%)
PR: 24/109 (22.0%)

Topotecan (*n* = 110)
Total (CR + PR): 31/110 (28.2%) (95% CI: 19.8 to 36.6%)
CR: 9/110 (8.2%)
PR: 22/110 (20.0%)

PLDH (*n* = 130)
Total (CR + PR): 15/130 (11.5%) (95% CI: 6.0 to 17.0%)
CR: 1/130 (0.8%)
PR: 14/130 (10.8%)

Topotecan (*n* = 125)
Total (CR + PR): 9/125 (7.2%) (95% CI: 2.7% to 11.7%)
CR: 2/125 (1.6%)
PR: 7/125 (5.6%)

Outcome 1: Overall survival (non-stratified log-rank test)
PLDH (*n* = 240)
% censored: 16.7
Median overall survival (weeks): 63.6
(range: 1.7–258.3)

Topotecan (*n* = 241)
% censored: 9.1
Median overall survival (weeks): 57.0
(range: 0.1–247.1+)
HR = 1.246 (95% CI: 1.028 to 1.511); $p = 0.025$

Trial: 039[24-26]

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
Author: ten Bokkel Huinink, 1997[24] **Objective** To compare the efficacy and toxicity of topotecan and paclitaxel in patients with advanced epithelial ovarian cancer who have progressed during or after treatment with one platinum-based chemotherapy regimen **Trial ID:** 039 **Phase:** Phase III **Length of follow-up:** 60 weeks	**Number randomised** 235 randomised; topotcan $n = 117$; paclitaxel $n = 118$) **Disease type:** Epithelial **Disease stage:** Advanced stage III/IV **Occurrence of secondary spread:** Not reported **Therapy stage:** Second-line **Previous treatments** Radiotherapy: Topotecan: $n = 3$ Paclitaxel: $n = 4$ **Immunotherapy** Topotecan: $n = 2$ Paclitaxel: $n = 1$ Hormonal therapy: Topotecan: $n = 0$ Paclitaxel: $n = 6$ Prior chemotherapy: **Topotecan:** ($n = 112$) (%): Cyclophosphamide: 66.0 Carboplatin: 55.0 Cisplatin: 54.0 Epirubicin: 8.0 Doxorubicin hydrochloride: 4.5 Doxorubicin: 3.6 Etoposide: 1.8 Mitoxantrone: 1.8 Ifosfamide: 1.8 Epirubicin hydrochloride: 0.9 Chlorambucil: 0.9 Prednimustine: 0.9 Fluorouracil: 0.0 Pirarubicin: 0.0	**Intervention (I)** Type: Topotecan No. randomised: 117 Route of administration: i.v. Dose: 1.5 mg/m^2 as a 30-min infusion on five consecutive days No. of cycles: Dependent on response (see comments). 555 cycles in total for the whole group. Length per cycle: 21 days **Control (C)** Type: Paclitaxel No. randomised: 118 Route of administration: i.v. Dose: 175 mg/m^2 as a 3-hour infusion No. of cycles: Dependent on response to treatment (see comments). 550 cycles in total for the whole group Length per cycle: 21 days **Comments about intervention/control** Patients in the paclitaxel group were premedicated with dexamethasone, and both H_1 and H_2 receptor antagonists to prevent hypersensitivity reactions. Premedication was not given to the topotecan	**Withdrawals from intervention (I)** Five patients randomised to topotecan did not receive treatment and therefore were not included in the analysis. A further 16 were not evaluated for response: withdrawal for adverse events ($n = 7$), lost to follow-up ($n = 2$), patient refusal ($n = 2$), protocol violation – no measurable disease at baseline ($n = 2$), all lesions noted at screening were not assessed throughout study ($n = 2$) and other (pulmonary embolism) ($n = 1$). **Withdrawals from control (C)** Four patients randomised to paclitaxel did not receive treatment and therefore were not included in the analysis. A further 8 were not evaluated for response: withdrawal for adverse events ($n = 3$), patient refusal ($n = 1$), protocol violation – no measurable disease at baseline ($n = 1$), indicator lesions ($n = 1$), baseline performance status of 3 ($n = 1$), patient entered study in renal failure ($n = 1$) **Adverse events** 7% of patients in the topotecan group and 4% of patients in the paclitaxel group were withdrawn owing to adverse effects. The primary reasons for withdrawal in the topotecan group were febrile neutropenia, infection and sepsis. Neurotoxicity was the primary reason for withdrawal in the paclitaxel group. Suspected or documented infection occurred within 2 days of grade 4 neutropenia in a total of 25% of patients and 7% of courses in the topotecan group patients and in 4% of patients and 1% of courses in the paclitaxel group. In addition, 5% of patients and 1% of topotecan	**Authors' conclusions** Topotecan has efficacy at least equivalent to paclitaxel manifested by the higher response rate and significantly longer time to progression **Comments** The methods section of the report states that HRs with 95% CI were calculated. Survival curves were presented for the duration of response, time to progression and survival, but HRs were not reported. HRs are the most appropriate representation of survival or time to event data. It was also not clear from the data presented whether the median times quoted were based on Kaplan–Meier estimates

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Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Paclitaxel (*n* = 114) (%): Cyclophosphamide: 69.0 Carboplatin: 61.0 Cisplatin: 51.0 Epirubicin: 5.3 Doxorubicin hydrochloride: 6.1 Doxorubicin: 3.5 Etoposide: 0.9 Mitoxantrone: 0.9 Ifosfamide: 0.0 Epirubicin hydrochloride: 1.8 Chlorambucil: 0.9 Prednimustine: 0.0 Fluorouracil: 0.9 Pirarubicin: 0.9 **Disease present after first-line treatment?** Residual: at least 4 weeks after previous treatment Refractory: yes **Age/age range of participants** Topotecan: mean = 59.2 years (range 29–85 years) Paclitaxel: mean = 58.3 years (range 29–79 years) **Characteristics** Topotecan (*n* = 112): Mean age: 59.2 years Age range: 29–85 years Performance status: 0: 41/112 (36.6%) 1: 51/112 (45.5%) 2: 20/112 (17.9%) 3: 0/112 (0%) Weight (kg): Mean: 65.0 Range: 41–95 Body surface (m^2):	group unless nausea or vomiting occurred, in which case it was permitted in subsequent cycles. However, prophylactic recombinant G-CSF was allowed after the first course of therapy to maintain dose intensity, on day 6 of the topotecan and day 2 of the paclitaxel group, if participants had experienced any of the following: grade 4 neutropenia with fever or infection, grade 4 neutropenia lasting more than 7 days or grade 3 neutropenia that required a delay in treatment Dependent on toxicity, the doses of the two drugs could vary from 1.0 to 2.0 mg/m^2/day for topotecan and from 135 to 175 mg/m^2 for paclitaxel. Patients were withdrawn from treatment if there was a >2-week delay in treatment at the minimum dose of either medication because of toxicity The number of cycles of both the topotecan and paclitaxel interventions were determined by the	courses and 2% of patients and 0.4% of paclitaxel courses were associated with sepsis. Two patients in the topotecan group died owing to topotecan-induced sepsis. There were no deaths attributed to myelosuppression in the paclitaxel group. Prophylactic G-CSF was administered to maintain dose intensity in 23% of topotecan courses and 3% of paclitaxel courses; platelet transfusions were given in 3% and red blood cell transfusions in 27% of topotecan courses. Treatment G-CSF was given in 7% topotecan and 1% paclitaxel courses. **Haematological toxicity** Topotecan (*n* = 112) Leukopenia (grade 3): 50.9% Leukopenia (grade 4): 33.6% Neutropenia (grade 3): 15.3% Neutropenia (grade 4): 79.3% Thrombocytopenia (grade 3): 24.3% Thrombocytopenia (grade 4): 25.2% Anaemia (grade 3): 36.9% Anaemia (grade 4): 3.6% Paclitaxel (*n* = 114): Leukopenia (grade 3): 17.9% Leukopenia (grade 4): 2.7% Neutropenia (grade 3): 28.6% Neutropenia (grade 4): 23.3% Thrombocytopenia (grade 3): 0.9% Thrombocytopenia (grade 4): 1.8% Anaemia (grade 3): 3.6% Anaemia (grade 4): 2.7% **No. of courses with haematological toxicity** Topotecan (*n* = 555): Leukopenia (grade 3): 40.1% Leukopenia (grade 4): 10.4% Neutropenia (grade 3): 27.9% Neutropenia (grade 4): 37.4%	

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Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Mean: 1.7 Range: 1.3–2.3 Tumour diameter (cm): <5: 54/112 (48.2%) ≥5: 56/112 (50.0%) ND: 2/112 (1.8%) Tumour histology: Malignant serous: 58/112 (51.8%) Malignant mucinous: 6/112 (5.4%) Malignant endometrioid: 10/112 (8.9%) Undifferentiated carcinoma: 18/112 (16.1%) Other: 20/112 (17.9%) Histological grade: 0–1: 6/112 (5.4%) 2: 23/112 (20.5%) 3: 56/112 (50%) 4: 10/112 (8.9%) ND: 17/112 (15.2%) Race: White: 112 (100%) **Paclitaxel (*n* = 114)** Mean age: 58.3 years Age range: 29–79 years Performance status: 0: 42/114 (36.8%) 1: 53/114 (46.5%) 2: 17/114 (14.9%) 3: 2/114 (1.8%) Weight (kg) Mean: 67.6 Range: 46–136 Body surface (m^2): Mean: 1.7 Range: 1.4–2.4 Tumour diameter (cm): <5: 53/114 (46.5%) >5: 59/114 (51.8%)	patients' response. Patients with a CR/PR continued until progression or for 6 months after the maximal response. Patients who progressed during treatment were removed from the study. Those whose best response was stable disease after 6 courses were removed or switched to the other treatment CR was defined as the complete disappearance of all known measurable and assessable disease on two separate measurements at least 4 weeks apart. PR was defined as a 50% reduction in the sum of products of the perpendicular diameters of all measurable lesions for at least 4 weeks and with no new lesion or progression of assessable disease. PD was defined as a 25% increase in a single measurable lesion, reappearance of measurable disease, clear worsening of assessable disease or the development of new	Thrombocytopenia (grade 3): 15.3% Thrombocytopenia (grade 4): 9.6% Anaemia (grade 3): 14.9% Anaemia (grade 4): 1.1% Paclitaxel (*n* = 550): Leukopenia (grade 3): 8.8% Leukopenia (grade 4): 0.5% Neutropenia (grade 3): 21.1% Neutropenia (grade 4): 9.0% Thrombocytopenia (grade 3): 0.2% Thrombocytopenia (grade 4): 0.4% Anaemia (grade 3): 1.5% Anaemia (grade 4): 0.5% **Non-hematological toxicities occurring in >10% of treated patients** Topotecan: (*n* = not reported): Alopecia (grade 1/2): 75.9% Alopecia (grade 3/4): 0.0% Nausea (grade 1/2): 67.9% Nausea (grade 3/4): 9.8% Vomiting (grade 1/2): 53.6% Vomiting (grade 3/4): 9.9% Fatigue (grade 1/2): 33.1% Fatigue (grade 3/4): 8.0% Constipation (grade 1/2): 37.5% Constipation (grade 3/4): 5.4% Diarrhoea (grade 1/2): 33.9% Diarrhoea (grade 3/4): 6.3% Abdominal pain (grade 1/2): 21.5% Abdominal pain (grade 3/4): 5.4% Fever[b] (grade 1/2): 27.7% Fever[b] (grade 3/4): 0.9% Stomatitis (grade 1/2): 23.2% Stomatitis (grade 3/4): 0.9% Dyspnoea (grade 1/2): 17.8% Dyspnoea (grade 3/4): 6.3% Asthenia (grade 1/2): 17.0% Asthenia (grade 3/4): 5.4%	

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Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	ND: 2/114 (1.8%) Tumour histology: Malignant serous: 59/114 (51.8%) Malignant mucinous: 6/114 (5.3%) Malignant endometrioid: 15/114 (13.2%) Undifferentiated carcinoma: 8/114 (7.0%) Other: 26/114 (22.8%) Histological grade: 0–1: 8/114 (7.0%) 2: 29/114 (25.4%) 3: 50/114 (43.9%) 4: 12/114 (10.5%) ND*: 15/114 (13.2%) **Race** White: 100 Black: 5 Hispanic: 3 **Inclusion/exclusion criteria** Women with the following were included: stage III/IV disease, histological diagnosis of epithelial ovarian carcinoma, failed first-line therapy with a platinum-based chemotherapy regimen; at least one bidimensionally measurable lesion as evidence by CT or MRI scan, ultrasound, or physical examination; at least a 4-week period between prior surgery, hormonal therapy, radiotherapy or chemotherapy and treatment in the trial; an ECOG performance status of ≤ 2; adequate bone-marrow function (WBC count $\geq$ 3500, neutrophil count $\geq$ 1500 μl and platelet count $\geq$100,000/μl); normal liver function (bilirubin level	metastatic disease. SD was defined as any measurement not fulfilling the criteria for response or progression, and lasting more than 8 weeks. Non-assessable disease was defined as non-measurable lesions with an elevated CA-125 tumour marker. The duration of response was measured from the time of initial documented response to the first sign of disease progression. The time to progression was measured from the time of first study drug administration to documented progressive disease or initiation of third-line therapy. The criteria for efficacy, time to reponse and survival were measured from the time of initial drug administration to initial response and death, respectively. All responses were subject to independent review and confirmation of scans by a radiolologist who was blind to the treatment assignment **Actual study treatment administration**	Arthralgia (grade 1/2): 5.5% Arthralgia (grade 3/4): 0.9% Myalgia (grade 1/2): 3.6% Myalgia (grade 3/4): 0.0% Neuropathy (grade 1/2): 0.9% Neuropathy (grade 3/4): 0.0% Skeletal pain (grade 1/2): 4.5% Skeletal pain (grade 3/4): 0.0% Flushing (grade 1/2): 4.5% Flushing (grade 3/4): 0.0% Paresthesia (grade 1/2): 0.9% Paresthesia (grade 3/4): 0.0% Paclitaxel (n = not reported): Alopecia (grade 1/2):92.1% Alopecia (grade 3/4): 0.9% Nausea (grade 1/2): 43.0% Nausea (grade 3/4): 1.8% Vomiting (grade 1/2): 28.1% Vomiting (grade 3/4): 2.7% Fatigue (grade 1/2): 25.4% Fatigue (grade 3/4): 6.1% Constipation (grade 1/2): 30.7% Constipation (grade 3/4): 0.0% Diarrhoea (grade 1/2): 37.8% Diarrhoea (grade 3/4): 0.9% Abdominal pain (grade 1/2): 36.0% Abdominal pain (grade 3/4): 3.5% Fever[b] (grade 1/2): 17.7% Fever[b] (grade 3/4): 0.0% Stomatitis (grade 1/2): 14.0% Stomatitis (grade 3/4): 0.9% Dyspnoea (grade 1/2): 13.2% Dyspnoea (grade 3/4): 5.3% Asthenia (grade 1/2): 9.6% Asthenia (grade 3/4): 3.5% Arthralgia (grade 1/2): 28.9% Arthralgia (grade 3/4): 2.6% Myalgia (grade 1/2): 25.4% Myalgia (grade 3/4): 2.6%	

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Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	⩽ 2.0 mg/dl) and normal renal function (creatinine clearance ⩽ 1.5 mg/dl or creatinine clearance >60 ml/minute). Patients who had received more than one previous chemotherapy regimen or who had received topotecan or paclitaxel previously were excluded. **Comments about participants** Demographic and baseline disease characteristics in the ITT population were comparable between the two treatment groups Patients were stratified by age (<65 or ⩾ 65 years), ascites (present or absent) and response to prior platinum-based therapy (resistant, early, interim or late relapse) The response rates for the ITT population will be conservative as the denominator includes women who withdrew from the trial and were not evaluated for response. However, a true ITT analysis was not performed as only 226 (not the 235 randomised) were included in the analysis Patients who progressed or whose best response was stable disease after 6 courses on one regimen were eligible to be switched to the other (alternative) regimen, or were removed. 90 patients in total were entered into the alternative regimen; 53 received topotecan after failing to respond to paclitaxel and 37 received paclitaxel having failed to respond to topotecan	**Protocol deviations** Topotecan: 16/112 (14.3%) Not assessed beyond 5 days: 11 (9.8%) Did not have required measurable disease: 2 (1.8%) Indicator lesion in field of prior radiation; 1 (0.9%) Entered with second primary cancer: 1 (0.9%) >1 prior chemotherapy regimen: 1 (0.9%) Did not have required performance status: 0 Paclitaxel: 9[a] Not assessed beyond 5 days: 6 (5.3%) Did not have required measurable disease: 1 (0.9%) Indicator lesion in field of prior radiation: 1 (0.9%) Entered with second primary cancer: 0 >1 prior chemotherapy regimen: 0 Did not have required performance status: 2 (1.8%)	Neuropathy (grade 1/2): 15.8% Neuropathy (grade 3/4): 0.0% Skeletal pain (grade 1/2): 11.4% Skeletal pain (grade 3/4): 5.3% Flushing (grade 1/2): 14.1% Flushing (grade 3/4): 0.0% Paresthesia (grade 1/2): 29.0% Paresthesia (grade 3/4): 0.0% **Dosing adjustments:** Topotecan Patients receiving >1 course: 96/112 Delays after course 1: 58/112 (51.8%) patients; 100/597 courses (16.8%) Reductions after course 1: 15/112 patients (13.3%); 20/597 courses (3.3%). Escalations after course 1: 3/112 patients (2.6%); 3/597 (0.5%) **Paclitaxel** Patients receiving >1 course: 108/114 Delays after course 1: 20/114 (17.5%) patients; 26/589 courses (5.5%) Reductions after course 1: 6/114 patients (4.4%); 7/589 courses (1.2%). Escalations after course 1: 0/114 patients (0%); 0/589 (0%) **Reasons for treatment delay[c] in patients receiving >1 course: no. of courses (%)** Topotecan (n = 485) Haematologic: 56 (11.5%) Non-haematological: 11 (2.3%) Both haematologic and non-haematological: 1 (0.2%) Other: 31 (6.4%) Unassigned: 53 (10.9%) Total: 152: (31.3%) Paclitaxel (n = 475) Haematologic: 9 (1.9%) Non-hematological: 2 (0.4%)	

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Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
			Both haematologic and non-haematological: 0 (0%) Other: 19 (4.0%) Unassigned: 84 (17.7%) Total: 114 (24.0%) **Reasons for dose reductions** Topotecan (n = 485) Haematological: 21 (4.3%) Non-haematological: 1 (0.2%) Both haematologic and non-haematological: 0 (0%) Other: 0 (0%) Unassigned: 1 (0.2%) Total: 23 (4.7%) Paclitaxel (n = 475) Haematological: 7 (1.5%) Non-haematological: 0 (0%) Both haematological and non-haematological: 0 (0%) Other: 0 (0%) Unassigned: 0 (0%) Total: 7 (1.5%) **Withdrawals** Topotecan (n = 112) Adverse experience: 13 (11.6%) Protocol violation: 1 (0.9%) Lost to follow-up: 2 (1.8%) Other[d]: 11 (9.8%) Total: 27 (24.1%) Paclitaxel (n = 114) Adverse experience: 8 (7.0%) Protocol violation: 0 (0%) Lost to follow-up: 2 (1.8%) Other[d]: 5 (4.4%) Total: 15 (13.2%)	

[a] 1 patient had 2 protocol violations: performance status and lack of assessment.
[b] Excludes febrile neutropenia.
[c] Delays are not associated with course 1 of treatment.
[d] Comprised primarily of patient request or refusal.

Results

Outcome 1	Outcome 2	Outcome 3
Outcome: Response rate **Topotecan (*n* = 112)** CR: 5/112 (4.5%) PR: 18/112 (16.1%) Total (CR + PR): 23/112 (20.5%); *p* = 0.138 (95% CI: 13 to 28.3) ITT (*n* = 117) response rate = 18.8% (95% CI: 11.7 to 25.9%) **Subgroup analysis according to platinum sensitivity** **Resistant disease (*n* = 34)** CR: 0/34 (0%) PR: 3/34 (8.8%) Total (CR + PR): 3/34 (8.8%) **Early relapse (*n* = 6)** CR: 0/6 (0.0%) PR: 1/6 (16.7%) Total (CR + PR) 1/6 (16.7%) **Interim relapse (*n* = 20)** CR: 1/20 (5.0%) PR: 3/20 (15.0%) Total (CR + PR): 4/20 (20.0%) **Late relapse (*n* = 52)** C: 4/52 (7.7%) PR: 11/52 (21.2%) Total (CR + PR) 15/52 (28.8%) **Non-responders (*n* = 112)** Stable disease: 33/112 (29.5%) Progressive disease: 39/112 (34.8%) Not assessable: 17/112 (15.2%) Total: 89/112 (79.5%) **Responders** **Response in relation to baseline disease status** Age: ≤ 40 years: 0%	**Outcome: Duration of response (measured from the time of initial documented response to the first sign of disease progression)** **Topotecan** Median: 32.1 (*n* = 23) Range: 5.4–53.1 Risk ratio: 0.416; *p* = 0.2218 **Paclitaxel** Median: 19.71 (*n* = 15) Range: 6.3–24.3 Risk ratio: 0.416; *p* = 0.2218	**Outcome: Time to progression (measured from the time of first study drug administration to documented progressive disease or initiation of third-line therapy)** **Topotecan (*n* = 112)** Median: 23.1 Range: 0.7–62.1 Risk ratio: 0.578; *p* = 0.021 **Paclitaxel (*n* = 114)** Median: 14.0 Range: 0.1–30.9 Risk ratio: 0.578; *p* = 0.021

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Outcome 1	Outcome 2	Outcome 3
41–64 years: 19.7% ≥ 65 years: 23.7% Ascites: Present: 18.9% Absent: 21.3% Performance status: 0: 22.0% 1: 25.5% 2: 5.0% Tumour burden: <5 cm: 33.3% 5–≥ 10 cm: 10.9% First line response: Responder: 15.2% Non-responder: 5.4% **Paclitaxel (*n* = 114)** **Responders:** CR: 3/114 (2.6%) PR: 12/114 (10.5%) Total (CR + PR) 15/114 (13.2%); *p* = 0.138 (95% CI: 7 to 19.4) ITT (*n* = 118) response rate = 13.6% (95% CI: 7.4 to 19.7%) **Subgroup analysis according to platinum sensitivity** **Resistant disease (*n* = 33)** CR: 0/33 (0.0%) PR: 1/33 (3.0%) Total (CR + PR) 1/33 (3.0%) **Early relapse: (*n* = 10)** CR%: 0/10 (0.0%) PR: 1/10 (10%) Total (CR + PR) 1/10 (10%) **Interim relapse: (*n* = 16)** CR: 0/16 (0.0%) PR: 2/16 (12.5%) Total (CR + PR: 2/16 (12.5%)		

Outcome 1	Outcome 2	Outcome 3
Late relapse (*n* = 55) CR: 3/55 (5.5%) PR: 8/55 (14.5%) Total (CR + PR): 11/55 (20.0%) **Non-responders** Stable disease: 38/114 (33.3%) Progressive disease: 56/114 (49.1%) Not assessable: 5/114 (4.4%) Total: 99/114 (86.8%) **Responders** **Response in relation to baseline disease status** Age ≤ 40 years: 0% 41–64 years: 12.0% ≥ 65 years: 16.7% Ascites: Present: 7.5% Absent: 16.2% Performance status: 0: 14.3% 1: 13.2% 2: 11.8% Tumour burden: <5 cm: 18.0% 5–≥12.5% First-line response Responder: 10.5% Non-responder:2.6%		

continued

Outcome 4	Outcome 5	Outcome 6
Outcome: Time to response (measured from the time of initial drug administration to initial response) **Topotecan** Median: 9.0 (n = 23) Range: 3.1–19.0 Risk ratio: 0.476; p = 0.0409 **Paclitaxel** Median: 6.0 (n = 15) Range: 2.4–12.3 Risk ratio: 0.476; p = 0.0409	**Outcome: Survival (measured from the time of initial drug administration to death)** **Topotecan** Median: 61.3 (n = 112) Range: 0.7–62.1 Risk ratio: 1.210; p = 0.5153 11 patients died within 30 days of treatment, 31 after longer than 30 days of completing therapy. Death following alternate paclitaxel therapy occurred in 33 patients. Deaths were not recorded for 37 patients **Paclitaxel** Media: 42.6 (n = 114) Range: 0.1–75.3 Risk ratio: 1.210; p = 0.5153 3 patients died within 30 days of treatment, 28 after longer than 30 days of completing therapy. Death following alternate topotecan therapy occurred in 46 patients. Deaths were not recorded for 37 patients	**Outcome: Response to alternative regimen** 53 patients received topotecan after failing to respond to paclitaxel and five achieved PRs (9.4%), while 37 patients received paclitaxel after topotecan and one achieved a CR (2.7%)

Long-term follow-up from trial 039

Study details and design	Participant details	Intervention details
Author: ten Bokkel Huinink, 2004[25] **Objective** To monitor PFS and overall survival of patients randomised in a previously reported multi-centre Phase III study of topotecan versus paclitaxel in patients with advanced epithelial ovarian cancer who had failed one prior platinum-based regimen **Length of follow-up:** median 4 years	Participants: same as reported in trial 039.	Interventions: same as reported in trial 039.

Outcome 1	Outcome 2	Outcome 3
Outcome: Time to progression (definition as before) **Topotecan:** 18.9 weeks (range <1 to 92.6 weeks; 25% censored) **Paclitaxel:** 14.7 weeks (range <1 to 137.3+ weeks; 12.3% censored); $p = 0.08$	**Outcome: Survival (definition as before)** **Topotecan:** 63.0 weeks (range <1 to 238.4+ weeks; 20.5% censored) **Paclitaxel:** 53.0 weeks (range <1 to 226.3+ weeks; 12.3% censored); $p = 0.44$	**Outcome: QoL (assessed by EORTC QLQ-C30.** Questionnaire completed at baseline to end of best response. Between 75 and 85% of patients who enrolled in the study had evaluable QoL data) The QLQ-C30 results for pain, anorexia, diarrhoea, fatigue, nausea and vomiting, dyspnoea, constipation and insomnia were similar for the two groups, and treatment with either topotecan or paclitaxel was not associated with any compromise of QoL for the patients **Changes from baseline to end of best response: median (range)** **Topotecan** Appetite loss ($n = 88$): 0.0 (–100 to 67) Cognitive function ($n = 85$): 0.0 (–67 to 50) Constipation ($n = 89$): 0.0 (–100 to 67) Diarrhoea ($n = 88$): 0.0 (–67 to 100) Dyspnoea ($n = 89$): 0.0 (–67 to 67) Emotional function ($n = 85$): 8.0 (–83 to 75) Fatigue ($n = 90$) 0.0 (–78 to 89) Financial impact ($n = 89$): 0.0 (–67 to 100) Nausea/vomiting ($n = 90$): 0.0 (100 to 100) Pain ($n = 91$): 0.0 (–100 to 67) Physical function ($n = 93$): 0.0 (–100 to 80) QoL ($n = 89$): –8.0 (–58 to 83) Role function ($n = 93$): 0.0 (–100 to 100) Social function ($n = 89$): 0.0 (–83 to 67) Sleep disturbance ($n = 89$): 0.0 (–100 to 100) **Paclitaxel** Appetite loss: ($n = 89$): 0.0 (–67 to 100) Cognitive function ($n = 90$): 0.0 (–67 to 50) Constipation ($n = 91$): 0.0 (–100 to 67) Diarrhoea ($n = 94$): 0.0 (–100 to 33) Dyspnoea ($n = 94$): 0.0 (–67 to 67) Emotional function ($n = 91$): 8.0 (–100 to 75) Fatigue ($n = 94$): 0.0 (–67 to 67) Financial impact ($n = 94$): 0.0 (–100 to 67) Nausea/vomiting ($n = 94$): 0.0 (–83 to 50) Pain ($n = 93$): 0.0 (–100 to 67)

continued

Outcome 1	Outcome 2	Outcome 3
		Physical function (n = 98): 0.0 (–100 to 80) QoL (n = 95): 0.0 (–67 to 50) Role function (n = 97): 0.0 (–100 – 100) Social function (n = 95): 0.0 (–100 – 100) Sleep disturbance (n = 93): 0.0 (–100 to100) **Changes from baseline to end of best response for patients who responded to treatment: median (range)** **Topotecan** Appetite loss (n = 22): 0.0 (–100 to 67) Cognitive function (n = 21): 0.0 (–66 to 50) Constipation (n = 22): 0.0 (–67 to 67) Diarrhoea (n = 22): 0.0 (–67 to 67) Dyspnoea (n = 22): 0.0 (–67 to 67) Emotional function (n = 21): 9.0 (–42 to 75) Fatigue (n = 22) 0.0 (–78 to 56) Financial impact (n = 21): 0.0 (–33 to 34) Nausea/vomiting (n = 22): 0.0 (100 to 50) Pain (n = 22): 0.0 (–100 to 67) Physical function (n = 23): 0.0 (–80 to 80) QoL (n = 21): –8.0 (–58 to 83) Role function (n = 23): 0.0 (–100 to 100) Social function (n = 21): 0.0 (–67 to 50) Sleep disturbance (n = 22): 0.0 (–100 to 67) **Paclitaxel** Appetite loss (n = 12): 0.0 (–34 to 0) Cognitive function (n = 13): 0.0 (–17 to 33) Constipation (n = 12): 0.0 (–33 to 0) Diarrhoea (n = 13): 0.0 (–67 to 0) Dyspnoea (n = 13): 0.0 (–34 to 33) Emotional function (n = 13): 9.0 (0 to 50) Fatigue (n = 13): -11.0 (–45 to 12) Financial impact (n = 13): 0.0 (0 to 34) Nausea/vomiting (n = 13): 0.0 (–33 to 0) Pain (n = 12): –16.5 (–67 to 33) Physical function (n = 13): 0.0 (–30 to 20) QoL (n = 14): 16.0 (–50 to 34) Role function (n = 13): 0.0 (0 to 50) Social function (n = 13): 0.0 (–50 to 33) Sleep disturbance (n = 12): –33.0 (–100 to 33)

Outcome 4	Outcome 5	Outcome 6
Outcome: Long-term survival (topotecan median follow-up = 20.8 weeks, range 0–86 weeks; paclitaxel median follow-up = 23.6 weeks, range = 0–117 weeks). **Topotecan** Median survival = 63 weeks **Paclitaxel** Median survival = 53 weeks (log-rank $p = 0.44$)	**Outcome: Survial stratified by platinum sensitivity** **Topotecan** Refractory patients ($n = 34$, censored = 8): median survival = 28.4 weeks Early/interim relapse ($n = 26$, censored = 4): median survival relapse = 71.9 weeks Late relapse ($n = 52$, censored = 11): median survival = 63.4 weeks Difference between the groups: $p = 0.02$ **Paclitaxel** Refractory patients ($n = 33$, censored = 4): median survival = 39.7 weeks Early/interim relapse ($n = 26$, censored = 2): median survival = 35.0 weeks Late relapse ($n = 54$, censored = 8): median survival = 85.1 weeks Difference between the groups: $p = 0.0004$	**Outcome: Alternative regimen** **Demographic characteristics of patients crossing over:** **Topotecan ($n = 61$)** **Age (years)** <40: 1 (1.6%) 41–64: 46 (75.4%) ≥ 65: 14 (23.0%) Mean: 56.9 Range: 29–77 **Race** Caucasian: 57 (93.4%) Black: 3 (4.9%) Other: 1 (1.6%) **Weight (kg)** Mean: 66.4 Range: 46–100 **Body surface area (m^2)** Mean: 1.71 Range: 1.45–2.10 **Paclitaxel ($n = 49$)** **Age (years)** <40: 1 (2.0%) 41–64: 28 (57.1%) ≥ 65: 20 (40.8%) Mean: 60.3 Range: 30 – 75 **Race** Caucasian: 49 (100%) Black: 0 Other: 0 **Weight (kg)** Mean: 66.2 Range (42–90)

continued

Outcome 1	Outcome 2	Outcome 3
		Body surface area (m^2) Mean: 1.70 Range: 1.33–2.04 **Baseline disease characteristics** **Topotecan (*n* = 61)** Primary tumour histology: 28 (25.6%) Malignant serous: 4 (3.6%) Malignant endometrioid: 9 (8.2%) Undifferentiated: 7 (6.4%) Other: 13 (11.8%) Histological grade: 1: 5 (8.2%) 2: 14 (23.0%) 3: 24 (39.3%) 4: 8 (13.1%) Missing: 10 (16.4%) Unknown: 0 Prior therapy: Radiotherapy: 2 (3.3%) Hormonal therapy: 3 (4.9%) Immunotherapy: 1 (1.6%) Performance status at end of randomised treatment: 0: 15 (24.6%) 1: 37 (60.7%) 2: 6 (9.8%) 3: 3 (4.9%) Platinum sensitivity at baseline: Refractory: 18 (29.5%) Early relapse: 7 (11.5%) Interim relapse: 9 (14.8%) Late relapse: 26 (42.6%) Missing: 1 (1.6%) Largest measurable lesions (end of randomised treatment): <2 cm: 0 2–< 5 cm: 26 (42.6%) 5 –10 cm: 25 (41.0%) >10 cm: 8 (13.1%)

continued

Outcome 1	Outcome 2	Outcome 3
		Data missing: 2 (3.3%) Number of courses of randomised treatment: Median courses (range): 5 (1–13) Best response to randomised treatment: Partial response: 2 (3.3%) Stable disease: 23 (37.7%) Progressive disease: 35 (57.4%) Not evaluated: 1 (1.6%) Time to progression while on randomised therapy (weeks): Median: 11.9 Minimum: 2.4 Maximum: 49 (censored event) **Paclitaxel (*n* = 49)** Primary tumour histology: 27 (24.5%) Malignant serous: 3 (2.7%) Malignant endometrioid: 4 (3.6%) Undifferentiated: 7 (6.4%0 Other: 8 (7.3%) Histological grade: 1: 2 (4.1%) 2: 9 (18.4%) 3: 23 (47.0%) 4: 9 (18.4%) Missing: 5 (10.2%) Unknown: 1 (2.0%) Prior therapy: Radiotherapy: 2 (4.1%) Hormonal therapy: 0 Immunotherapy: 0 Performance status at end of randomised treatment: 0: 17 (34.7%) 1: 23 (46.9%) 2: 7 (14.3%) 3: 2 (4.1%) Platinum sensitivity at baseline: Refractory: 15 (30.6%) Early relapse: 2 (4.1%)

continued

Outcome 1	Outcome 2	Outcome 3
		Interim relapse: 14 (28.6%) Late relapse: 18 (36.7%) Missing: 0 Largest measurable lesions (end of randomised treatment): <2 cm: 6 (12.2%) 2 –<5 cm: 21 (42.9%) 5–10 cm: 18 (36.7%) >10 cm: 3 (6.1%) Data missing: 1 (2.0%) Number of courses of randomised treatment: Median courses (range): 6 (2–13) Best response to randomised treatment: Partial response: 7 (14.3%) Stable disease: 17 (34.7%) Progressive disease: 22 (44.9%) Not evaluated: 3 (6.1%) Time to progression while on randomised therapy (weeks): Median: 18.0 Minimum: 3.1 Maximum : 53.0 (censored event) Demographic characteristics were similar between the two groups who crossed over to third-line therapy. A total of 110 patients received the alternate drug (61 topotecan, 49 paclitaxel). Response rates of 13.1% for topotecan (8 of 61) and 10.2% for paclitaxel (5 of 49) were demonstrated. Seven patients who failed to respond to second-line treatment with paclitaxel responded to topotecan third-line, as did four to paclitaxel third-line **Topotecan** All 8 (13.1%) responses were partial responses (95% CI: 4 to 21). Median duration of response was 29 weeks; median time to progression was 9 weeks, median survival was 40 weeks Completed study: 50 (82%) Reasons for withdrawal:

continued

Outcome 1	Outcome 2	Outcome 3
		Adverse experience: 3 (4.9%) Other: 7 (11.5%) Protocol violation: 1 (1.6%) **Paclitaxel** 2 complete responses (4%) and 3 partial responses (6%) occurred. Total: 5 (10.2%) (95% CI: 0.5 to 14). Median duration of response was 27 weeks; median time to progression was 9 weeks, median survival was 48 weeks **Completed study: 44 (89.8%)** Reasons for withdrawal: Adverse experience: 3 (6.1%) Other: 2 (4.1%) Protocol violation: 0 (0%)

Study details and design	Participant details	Intervention details	Adverse events	Conclusion and comments
Author: Gore, 2001[26] **Objective** In a large RCT comparing the efficacy and safety of topotecan versus paclitaxel, a number of patients crossed over to the alternative drug as third-line therapy, i.e. from paclitaxel to topotecan and vice versa. It was therefore aimed to assess the degree of non-cross-resistance between these two compounds in these patient groups	**Topotecan (*n* = 61)** Age: mean 57 (range 29–77) years Histology grade[a]: 0/1: 5/61 (8%) 2: 14/61 (23%) 3: 24/61 (39%) 4: 8/61 (13%) Unknown: 10/61 (16%) **ECOG performance status[b]** 0: 15/61 (25%) 1: 37/61 (61%) 2: 6/61 (10%) 3: 3/61 (5%) **Platinum sensitivity at baseline[c]** Refractory: 18/61 (30%) Early relapse: 7/61 (11%) Interim relapse: 9/61 (15%) Late relapse: 26/61 (43%) Missing: 1/61 (2%) **Tumour size[b]** <5 cm: 26/61 (43%) 5–10 cm: 25/61 (41%) >10 cm: 8/61 (13%) Missing: 2/61 (3%) **Paclitaxel (*n* = 49)** Age: mean 60 (range 30–75) years Histology grade[a]: 0/1: 2/49 (4%) 2: 9/49 (18%) 3: 23/49 (47%) 4: 9/49 (18%) Unknown: 6/49 (12%) **ECOG performance status[b]** 0: 17/49 (35%) 1: 23/49 (47%) 2: 7/49 (14%) 3: 2/49 (4%)	Patients were permitted to cross over and receive the alternative drug as third-line therapy, i.e. patients who were randomised to topotecan crossed over to receive paclitaxel and those who were treated with paclitaxel crossed over to receive topotecan. This crossover occurred at the investigator's discretion but was usually for one of three reasons: (1) failure to respond to second-line therapy, (2) relapse after an initial response to second-line therapy or (3) toxicity A total of 110 patients crossed over to the alternative drug as third-line therapy: 61 patients crossed over from paclitaxel to topotecan and 49 patients crossed over from topotecan to paclitaxel The 61 patients treated with topotecan received 270 courses of treatment and the 49 patients treated with paclitaxel received 223 courses. Patients in the topotecan group received a median of 3 courses of treatment (range 1–23) and those in the paclitaxel group received a median of 4 courses (range 1–12). The planned dose was maintained in 95% of courses of topotecan and 94% of courses of paclitaxel. Haematological toxicity caused dose delays of >7 days in only 1.4% of topotecan courses and in none of the paclitaxel courses Prophylactic G-CSF was administered to 23% of patients (22% of courses)	**Hematological toxicity during crossover (third-line) treatment** **Topotecan (*n* = 61)** Neutropenia: Grade 1: 0% Grade 2: 3% Grade 3: 14% Grade 4: 81% Thrombocytopenia: Grade 1: 47% Grade 2: 12% Grade 3: 8% Grade 4: 22% Anaemia: Grade 1: 8% Grade 2: 62% Grade 3: 27% Grade 4: 2% **Paclitaxel (*n* = 49)** Neutropenia: Grade 1: 15% Grade 2: 15% Grade 3: 31% Grade 4: 23% Thrombocytopenia: Grade 1: 17% Grade 2: 0% Grade 3: 2% Grade 4: 0% Anaemia: Grade 1: 52% Grade 2: 42% Grade 3: 2% Grade 4: 0%	**Authors' conclusions** Topotecan and paclitaxel have similar activity as second-line therapies with regard to response rates and PFS and overall survival. The results of the long-term follow-up of patients who crossed over between the two regimens demonstrated that the two drugs have a degree of non-cross-resistance. Hence there is a good rationale for incorporating these drugs into future first-line regimens

continued

Study details and design	Participant details	Intervention details	Adverse events	Conclusion and comments
	Platinum sensitivity at baseline[a] Refractory: 15/49 (31%) Early relapse: 2/49 (4%) Interim relapse: 14/49 (29%) Late relapse: 18/49 (37%) Missing: 0 (0%) **Tumour size**[b] <5 cm: 27/49 (55%) 5–10 cm: 18/49 (37%) >10 cm: 3/49 (6%) Missing: 1/49 (2%) **At third-line therapy there were differences in the two groups' potential chemo-responsiveness.** **Response to second-line treatment** **Topotecan (*n* = 61)** Partial response: 2/61 (3%) Stable disease: 23/61 (38%) Progressive disease: 35/61 (57%) Non-assessable: 1/61 (2%) **Paclitaxel (*n* = 49)** Partial response: 7/49 (14%) Stable disease: 17/49 (35%) Progressive disease: 22/49 (45%) Non-assessable: 3/49 (6%) **Platinum sensitivity to initial chemotherapy** **Topotecan (*n* = 61)** **Refractory *n* = 18** Early relapse (within 3 months) *n* = 7 Interim relapse (within 3–6 months) *n* = 9 Late relapse (>6 months) *n* = 6 Missing: *n* = 1 **Paclitaxel (*n* = 49)** Refractory *n* = 15	in the topotecan group and 12% of patients (6% of courses) in the paclitaxel group. Treatment with G-CSF was administered to 8 and 2% of patients (3 and 0% of courses) in the topotecan and paclitaxel groups, respectively. I.v. antibiotics were administered to 26% of patients in the topotecan group and 12% of patients in the paclitaxel group. Thirteen patients (21%) who received topotecan and one who received paclitaxel (2%) were hospitalised because of infection	**Non-hematological toxicity to crossover (third-line) treatment** **Topotecan (*n* = 61)** Nausea (grade 1/2): 59% Nausea (grade 3/4): 13% Vomiting (grade 1/2): 36% Vomiting (grade 3/4): 12% Diarrhoea (grade 1/2): 33% Diarrhoea (grade 3/4): 3% Abdominal pain (grade 1/2): 25% Abdominal pain (grade 3/4): 8% Constipation (grade 1/2): 26% Constipation (grade 3/4): 5% Fatigue (grade 1/2): 23% Fatigue (grade 3/4): 8% Alopecia (grade 1/2): 21% Alopecia (grade 3/4): 0% Myalgia (grade 1/2):16% Myalgia (grade 3/4): 0% Arthralgia (grade 1/2): 13% Arthralgia (grade 3/4): 2% Paresthesia (grade 1/2): 8% Paresthesia (grade 3/4): 0% **Paclitaxel (*n* = 49)** Nausea (grade 1/2): 39% Nausea (grade 3/4):10% Vomiting (grade 1/2): 27% Vomiting (grade 3/4): 8% Diarrhoea (grade 1/2):35% Diarrhoea (grade 3/4): 2% Abdominal pain (grade 1/2):20% Abdominal pain (grade 3/4): 8% Constipation (grade 1/2): 35% Constipation (grade 3/4): 0% Fatigue (grade 1/2):16% Fatigue (grade 3/4): 0% Alopecia (grade 1/2): 41% Alopecia (grade 3/4): 0%	

continued

Study details and design	Participant details	Intervention details	Adverse events	Conclusion and comments
	Early relapse (within 3 months) $n = 2$ Interim relapse (within 6 months) $n = 14$ Late relapse (>6 months) $n = 18$		Myalgia (grade 1/2): 31% Myalgia (grade 3/4): 2% Arthralgia (grade 1/2): 37% Arthralgia (grade 3/4): 0% Paresthesia (grade 1/2): 31% Paresthesia (grade 3/4): 0% At the time of analysis, 46 (75%) of the patients who were treated with topotecan as third-line therapy had died, 45 from progressive disease. One patient died as a result of paralytic ileus and septic shock, which was not thought to be drug related. Thirty-three (67%) patients in the paclitaxel group were reported to have died, all as a result of progressive disease	

[a] At entry to the randomised phase of the study.
[b] ECOG; assessed separately at the start of each phase.

Results

Outcome 1	Outcome 2
Outcome: response rate **Topotecan ($n = 61$)** Median response duration = 29 weeks (range 18–70) Median time to progression = 9 weeks Median survival = 40 weeks (range 1–123) p = NS Complete response: 0 (0%) Partial response: 8/61 (13%) Stable disease: 8/61 (13%) Progressive disease: 35/61 (57%) Non-evaluable: 10/61 (16%) Overall response: 13% (95% CI: 4 to 21%)	**Outcome: Response stratified by sensitivity to first-line platinum therapy** Only those patients who had a treatment-free interval of >6 months after completion of first-line platinum therapy responded to third-line topotecan, although four patients who relapsed within 6 months of their first-line platinum therapy responded to paclitaxel at the third-line phase. There were no responders to any third-line treatment in patients who had platinum-refractory disease (relapse within 4 months or no response or progressive disease to first-line therapy)

continued

Outcome 1	Outcome 2
Paclitaxel (n = 49) Median response duration: 27 weeks (range 13–66) Median time to progression: 9 weeks Median survival: 48 weeks (range 2–86) p = not significant Complete response: 2/49 (4%) Partial response: 3/49 (6%) Stable disease: 12/49 (25%) Progressive disease: 25/49 (51%) Non-evaluable: 7/49 (14%) Overall response: 10% (95% CI: 0.5%, 14%)	

Outcomes

Response to topotecan (third-line) treatment according to response to paclitaxel (second-line) treatment

Patient response to paclitaxel (third-line) treatment	Response to topotecan (second-line) treatment (no.)				
	CR	**PR**	**SD**	**PD**	**NE**
PR, n = 7	1	0	2	4	0
SD, n =27	0	2	4	10	1
PD, n =22	1	1	6	10	4
NE, n = 3	0	0	0	1	2

Response to paclitaxel (third-line) treatment according to response to topotecan (second-line) treatment

Response to paclitaxel (second-line) treatment	Patient response to topotecan (third-line) treatment (no.)				
	CR	**PR**	**SD**	**PD**	**NE**
PR, n = 2	0	0	1	1	0
SD, n = 17	0	4	4	10	5
PD, n = 35	0	3	3	24	5
NE, n = 1	0	1	0	0	0

Trial: ICON4/AGO-OVAR-2.2[29]

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
Author: The ICON and AGO Collaborators, 2003[29] **Objective:** To compare the efficacy and safety of paclitaxel in combination with platinum-based chemotherapy compared with platinum-based chemotherapy alone in patients with epithelial ovarian carcinoma who had relapsed after 6 months following first-line platinum-based chemotherapy. **Trial ID:** ICON4/AGO-OVAR-2.2 **Phase:** Phase III **Length of follow-up:** Median 42 months	**Number randomised** 802 (paclitaxel plus platinum chemotherapy $n = 392$; platinum-based monotherapy $n = 410$) **Disease type:** Epithelial **Disease stage:** Advanced **Occurrence of secondary spread:** Not reported. **Therapy stage:** Second-line with some third and fourth-line permitted in the MRC CTU protocol **Previous treatments** Paclitaxel plus carboplatin/cisplatin (intervention): Last chemotherapy received: Paclitaxel and carboplatin: 133/392 (34%) Carboplatin: 119/392 (30%) CAP: 62/392 (16%) Paclitaxel and cisplatin: 27/392 (7%) Docetaxel and carboplatin: 7/392 (2%) Other platinum-based: 34/392 (9%) Other non-platinum-based: 10/392 (3%) **No. of previous chemotherapy lines:** 1: 354/392 (90%) 2[a]: 22/392 (6%) >2[a]: 15/392 (4%) Not yet known: 1/392 (<1%) **Time since completion of last chemotherapy (months):** ≤ 12: 92/392 (23%) >12: 300/392 (77%)	**Intervention (I)** **Type:** Paclitaxel in combination with carboplatin or cisplatin **No. randomised:** 392 **Route of administration:** i.v. **Dose:** ICON4 (MRC CTU & IRFMN) paclitaxel 175 mg/m^2 given as a 3-h infusion, followed by either carboplatin at 5 (GFR + 25) mg (where GFR was the GFR determined by radioisotope method or 24-h urine collection) or 6 (GFR + 25) mg (where GFR was assessed by the Cockcroft method) or a minimum dose of 50 mg/m^2 cisplatin as a 3-h infusion **AGO**: Paclitaxel 185 mg/m^2 given as a 3-h infusion, followed by carboplatin at 5(GFR + 25) mg (where GFR was the GFR determined by radioisotope method or 24-h urine collection) or 6(GFR + 25) mg (where GFR was assessed by the Cockcroft method) as a 3-h infusion **No. of cycles**: MRC CTU protocol: at least 6 cycles IRFMN: At least 3 cycles and a further 3 cycles being administered according to the results of response assessment AGO protocol: A minimum of 6 cycles and a maximum of 8 cycles, with response assessment done after 2nd and 4th cycles **Length per cycle:** 21 days	**Withdrawals from intervention (I)** 8 in total: 1 treatment never began, 7 missing details (no further details reported) **Withdrawals from control (C)** 18 in total: 2 treatment never began, 16 missing details (no further details reported) **Adverse events** Paclitaxel/platinum ($n = 392$) Neurological (grade 2–4): 76/392 (19%) Not yet known: 15/392 Haematological[b]: 111/392 (28%) Not yet known: 8/392 Infection[b]: 64/392 (16%) Not yet known: 15/392 Renal[b]: 31/392 (8%) Not yet known: 8/392 Mucositis (grade 2/3): 26/392 (7%) Not yet known: 15/392 Nausea and vomiting (grade 2–4): 131/392 (33%) Not yet known: 15/392 Alopecia (grade 2-4): 322/392 (82%) Not yet known: 19/392	**Authors' conclusions** Paclitaxel plus platinum chemotherapy seems to improve survival and PFS among patients with relapsed platinum-sensitive ovarian cancer compared with conventional platinum-based chemotherapy

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Carboplatin/cisplatin (control) **Last chemotherapy received** Paclitaxel and carboplatin: 141/410 (34%) Carboplatin: 128 /410 (31%) CAP: 72/410 (18%) Paclitaxel and cisplatin: 20/410 (5%) Docetaxel and carboplatin: 14/410 (3%) Other platinum-based: 30/410 (7%) Other non-platinum-based: 5/410 (1%) **Number of previous chemotherapy lines** 1: 380/410 (93%) 2[a]: 24/410 (6%) >2[a]: 6/410 (1%) Not yet known: 0/410 (0%) **Time since completion of last chemotherapy (months):** ≤ 12: 111/410 (27%) >12: 299/410 (73%) **Disease present after first-line treatment?** **Residual:** In IRFMN protocol, but not in MRC CTU or AGO **Refractory:** No **Age/age range of participants** Paclitaxel/platinum: median 60.0 years. Platinum monotherapy: median: 59.2 years **Characteristics** Paclitaxel/platinum (*n* = 392) **Age (years):** <55: 127/392 (32%) 55–65: 151/392 (39%) >65: 114/392 (29%) Median: 60.0	**Control (C)** Type: Carboplatin or cisplatin monotherapy No. randomised: 410 Route of administration: i.v. Dose: ICON4 (MRC CTU & IRFMN) carboplatin at 5(GFR + 25) mg (where GFR was the GFR determined by radioisotope method or 24-h urine collection) or 6(GFR + 25) mg (where GFR was assessed by the Cockcroft method) or a minimum dose of 75 mg/m^2 cisplatin as a 3-h infusion **AGO:** carboplatin at 5(GFR + 25) mg (where GFR was the GFR determined by radioisotope method or 24-h urine collection) or 6(GFR + 25) mg (where GFR was assessed by the Cockcroft method) as a 3-h infusion **No. of cycles:** MRC CTU protocol: at least 6 cycles IRFMN: At least 3 cycles and a further 3 cycles being administered according to the results of response assessment AGO protocol: A minimum of 6 cycles and a maximum of 8 cycles, with response assessment done after 2nd and 4th cycles **Length per cycle:** 21 days **Comments about intervention/control:** **Protocol treatments received during the trial**	**Platinum monotherapy (*n* = 410)** Neurological (grade 2–4): 4/410 (1%) Not yet known: 31/410 Haematological[b]: 182/410 (44%) Not yet known: 16/410 Infection[b]: 53/410 (13%) Not yet known: 24/410 Renal[b]: 37/410 (9%) Not yet known: 16/410 Mucositis (grade 2/3): 21/410 (5%) Not yet known: 31/410 Nausea and vomiting (grade 2–4): 153/410 (37%) Not yet known: 29/410 Alopecia (grade 2–4): 95/410 (23%) Not yet known: 28/410	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Accrual by randomisation group: ICON MRC CTU: 266/392 (68%) ICON IRFMN: 100/392 (26%) AGO: 26/392 (7%) **WHO performance status:** 0: 246/392 (63%) 1: 121/392 (31%) 2-3: 25/392 (6%) **Intended platinum agent:** Carboplatin: 332/392 (85%) Cisplatin: 60/392 (15%) **Platinum monotherapy (*n* = 410)** **Age (years)** <55: 123/410 (30%) 55–65: 162/410 (40%) >65: 125/410 (30%) Median: 59.2 **Accrual by randomisation group:** ICON MRC CTU: 270/410 (66%) ICON IRFMN: 113/410 (28%) AGO: 27/410 (7%) **WHO performance status:** 0: 262/410 (64%) 1: 122/410 (30%) 2–3: 26/410 6%) **Intended platinum agent:** Carboplatin: 341/410 (83%) Cisplatin: 69/410 (17%) **Inclusion/exclusion criteria:** Eligible patients had: relapsed epithelial ovarian cancer requiring chemotherapy; previously received platinum-based chemotherapy; been treatment-free for >6 months (>12 months in the ICON IRFMN group) and no concomitant or	**Paclitaxel plus platinum chemotherapy (intervention) *n* = 392)** Carboplatin alone: 1/392 (<1%) CAP: 0 Carboplatin and cisplatin[c]: 0 Cisplatin and doxoruicin: 0 Cisplatin alone: 0 Carboplatin in combination (non-taxane): 0 Paclitaxel and carboplatin: 314/392 (80%) Paclitaxel and cisplatin: 38/392 (10%) Paclitaxel, carboplatin and cisplatin[c]: 19/392 (5%) Paclitaxel alone: 17/392 (4%) Other: 1/392 (<1%) Treatment not received or not yet known: 2/392 (<1%) **Carboplatin/cisplatin monotherapy (control) (*n* = 410)** Carboplatin alone: 292/410 (71%) CAP: 68/410 (17%) Carboplatin and cisplatin[c]: 18/410 (4%) Cisplatin and doxoruicin: 12/410 (3%) Cisplatin alone: 8/410 (2%) Carboplatin in combination (non-taxane): 3/410 (<1%) Paclitaxel and carboplatin: 1/410 (<1%) Paclitaxel and cisplatin: 0 Paclitaxel, carboplain and cisplatin[c]: 0 Paclitaxel alone: 4/410 (1%) Other: 3/410 (<1%) Treatment not received or not yet known: 1/410 (<1%) **Actual study treatment administration** 580 (72%) patients in the two treatment		

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	previous malignant disease likely to interfere with treatment or outcomes Eligibility criteria differed slightly across the three protocols. Patients in the MRC CTU protocol trial were permitted to have had more than one line of previous chemotherapy, whereas those randomised in the IRFMN and AGO protocols must have had only one previous line. Measurable disease was required for patients randomised in the IFRMN protocol, but not in the MRC CTU or AGO protocols. The diagnosis of relapsed disease at entry into the trial in 18 patients in the MRC CTU protocol was based on raised CA-125 concentrations. Patients randomised into the AGO protocol must have previously received cisplatin plus paclitaxel or carboplatin plus paclitaxel; all patients in ICON 4 (MRC CTU and IRFMN) were required to have had previous platinum-based chemotherapy, with or without paclitaxel **Comments about participants** Randomisation was undertaken independently in the 3 protocols. The randomisation ratio between treatment groups was 1:1. In the 2 ICON protocols (MRC CTU and IRFMN) stratification was undertaken by centre, age, last chemotherapy received, time since completion of last chemotherapy and intended platinum treatment. The platinum treatment to be used had to be specified prior to randomisation. In the AGO protocol, stratification was done by time since completion of last	groups received a minimum of 6 cycles of chemotherapy. Reasons for not completing the 6 cycles of treatment were: disease progression or death [109 (56%)], toxic effects during treatment [77 (39%)], and patient's preference [9 (5%)]. Only 3 patients received no assigned chemotherapy. 123 (41%) of 300 patients in the control group and 129 (40%) of 322 in the paclitaxel and carboplatin group received >90% of the planned total dose, and 54 (18%) of 300 and 76 (23%) of 330, respectively, received >90% of the dose intensity of carboplatin. The relevant values for paclitaxel in the paclitaxel and carboplatin group were 266 (71%) of 376 for total dose and 160 (43%) of 376 for total dose intensity **Protocol deviations** None reported		

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	chemotherapy and whether the patient had undergone secondary debulking surgery Pretreatment data was collected at the time of randomisation. Treatment data was collected at each cycle of treatment. Further follow-up data were collected every 3 months for the first 2 years and every 6 months thereafter. QoL data were collected for all patients in the MRC CTU and AGO protocols using the EORTC QLQ-C30 (version 2.0). Patients in the MRC CTU protocol complete the questionnaire at baseline, before each cycle of protocol treatment, and at follow-up visits at 6,9 and 12 months. Patients in the AGO protocol completed the questionnaire at baseline, before the second and third cycles of protocol treatment, at the end of protocol treatment and every 3 months for 1 year after the end of protocol treatment			

[a] MRC CTU patients only.
[b] Toxic effect leading to treatment modification or interruption reported.
[c] Switches between platinum during treatment.

Results

Outcome 1	Outcome 2	Outcome 3
Outcome: Survival (the time from randomisation to death from any cause) (patients known to still be alive at the time of the analysis were censored at the time of their last follow-up) 530/802 patients died. HR = 0.82 (95% CI: 0.69 to 0.97); $p = 0.02$ Absolute difference in 2-year survival: Paclitaxel/platinum: 57% Platinum monotherapy: 50% (95% CI for difference: 1 to 12) Median survival (months): Paclitaxel/platinum: 29 Platinum monotherapy: 24 (95% CI for difference: 1 to 9)	**PFS, (time from randomisation to first appearance of progressive disease or death from any cause) (patients known to be alive and without progressive disease at the time of analysis were censored at their last follow-up)** 717/802 developed progressive disease or died. HR = 0.76 (95% CI: 0.66 to 0.89); $p = 0.0004$ Absolute difference in 1-year PFS: Paclitaxel/platinum: 50% Platinum monotherapy: 40% (95% CI for difference: 4 to 15) Absolute difference in median PFS: Paclitaxel/platinum: 12 months Platinum monotherapy: 9 months (95% CI for difference: 1 to 4)	**Outcome: Tumour response (not defined)** Complete or partial response: Paclitaxel/platinum: 78/119 (66%) Platinum monotherapy: 69/128 (54%) Difference: 12% (95% CI for difference: –0.1 to 24%); $p = 0.06$
Outcome 4	**Outcome 5**	
Outcome: QoL assessment (EORTC QLQ-C30) 482/536 (90%) of patients completed a questionnaire at baseline, before treatment. Most patients had few or no functional difficulties and few moderate or severe symptoms at baseline. In the first 6 months after randomisation the worst scores and the CS did not differ between treatment groups for all five functional scales (physical, role, emotional, cognitive and social), for eight of the nine symptom scales (fatigue, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) or global health. The exception was nausea and vomiting, which were worse for the patients receiving conventional chemotherapy ($p = 0.0014$ for worst score, $p = 0.005$ for AUC)	**Outcome: Overall survival in subgroups** **Paclitaxel/platinum ($n = 392$)** **Randomised group:** MRC CTU: 243/266 IRFMN: 80/100 AGO: 23/26 ($p = 0.93$) **Age (years)** 55: 114/127 55–65: 135/151 >65: 97/114 ($p = 0.08$) **WHO performance status:** WHO 0: 212/246 WHO >0: 134/146 ($p = 0.66$)	

continued

Outcome 4	Outcome 5
	Intended platinum agent: Carboplatin: 294/332 Cisplatin: 52/60 (p = 0.17) **Previous lines of chemotherapy:** 1: 310/354 2: 22/22 >2: 14/15 (p = 0.19) **Time since completion of last chemotherapy cycle (months):** ≤ 12: 90/92 >12: 256/300 (p = 0.87) **Previous exposure to taxanes:** No: 195/223 Yes: 151/169 (p = 0.62) **Platinum monotherapy (n = 410)** **Randomised group:** MRC CTU: 253/270 IRFMN: 94/113 AGO: 24/27 (p = 0.93) **Age (years)** 55: 111/123 55–65: 146/162 >65: 114/125 (p = 0.08) **WHO performance status:** WHO 0: 232/262 WHO >0: 139/148 (p = 0.66) **Intended platinum agent:** Carboplatin: 303/341 Cisplatin: 68/69

continued

Outcome 4	Outcome 5
	(p = 0.17) **Previous lines of chemotherapy:** 1: 343/380 2: 22/24 >2: 6/6 (p = 0.19) **Time since completion of last chemotherapy cycle (months):** ≤ 12: 109/111 >12: 262/299 (p = 0.87) **Previous exposure to taxanes:** No: 214/235 Yes: 157/175 (p = 0.62)

Trial: Cantu and colleagues[28]

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
Author: Cantu, 2002[28] **Objective** To assess the activity, efficacy and tolerability of single-agent paclitaxel and a platinum-containing regimen in previously treated patients with recurrent ovarian cancer Trial ID: None Phase: Phase II	**Number randomised** 97 (paclitaxel $n = 50$; CAP $n = 47$) **Disease type:** Epithelial **Disease stage:** Advanced **Occurrence of secondary spread:** In some patients; most had regional spread Therapy stage: Second-line **Previous treatments** Chemotherapy: platinum-based first-line. All patients had previously been treated with 2 or 3 chemotherapy regimens **Disease present after first-line treatment?** Residual: Yes Refractory: Yes **Age/age range of participants** Paclitaxel Median: 54.8 years (range: 35–72) CAP Median: 53 years (range: 27–69) **Characteristics** **Paclitaxel ($n = 47$)** **Age (**years) Median: 54.8 Range: 35–72 <45: 7/47 (15%) 46–55: 23/47 (49%) ≥56: 17/47 (36%) Serous histology: 31/47 (66%) Other histology: 16/47(34%) Poor differentiation: 35/47 (74%)	**Intervention (I):** **Type:** Paclitaxel **No. randomised:** 50. Route of administration : i.v. **Dose:** 175 mg/m^2 over 3-h. Premedication: dexamethasone 40 mg in 20 mg doses 12 and 6 h before paclitaxel, cimetidine 300 mg i.v. and chlorpheniramine 10 mg i.v. both 30 min before treatment **No. of cycles**: 6 cycles planned **Length per cycle:** 21 days **Control (C)** **Type:** Cyclophosphamide, doxorubicin and cisplatin (CAP) **No. randomised:** 47 **Route of administration:** i.v. **Dose:** cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, cisplatin 50 mg/m^2 **No. of cycles:** 6 cycles **Length per cycle:** 21 days **Comments about intervention/control** Treatment administration regulated by evaluation of blood cell count before start of treatment cycle. Treatment given if granulocyte count was ≥2000 µl and platelet count was ≥100,000 µl. Otherwise treatment was delayed 1 week When chemotherapy failed patients were crossed over to the alternative intervention. 23 crossed from CAP to paclitaxel, 30 from paclitaxel to CAP. It is not stated at what point crossover took place or how treatment failure was defined	**Withdrawals from intervention (I)** **3 lost to follow-up** **Withdrawals from control (C)** None **Adverse events** **Paclitaxel ($n = 47$)** Leukopenia (grade 3–4): 2 (4%); $p = 0.001$ Neutropenia (grade 3-4): 6 (13%); $p = 0.009$ Thrombocytopenia (grade 3–4): 0 (0%); $p = 0.012$ Nausea and vomiting (grade 2–3): 8 (17%); $p = 0.004$ Alopecia: 41 (87%); $p = 0.010$ Allergic reactions: 7 (15%); $p = 0.085$ Sensory neuropathy ≥ grade 2: 5 (11%); $p = 0.002$ Myalgia (grade 2): 9 (19%); $p = 0.025$ Other (cardiac toxicity, renal toxicity, stomatitis); 4 (8%): $p > 0.05$ No. of cycles delivered: median (main reason for stopping treatment was disease progression): 6 **CAP ($n = 47$)** Leukopenia (grade 3–4): 16 (34%); $p = 0.001$ Neutropenia (grade 3–4): 17	**Authors' conclusions** Rechallenge with either single-agent paclitaxel or platinum-based chemotherapy is effective in this patient population. Preliminary results suggest that single-agent paclitaxel may not be as active as platinum-based chemotherapy in recurrent ovarian cancer. Larger randomised trials are needed **Comments** The inclusion of a crossover for non-responders compromises study design. It is not stated whether the assessors were blinded to allocation and it is not clear whether randomisation was appropriate or allocation concealment adequate

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Disease site: Pelvis: 17/47 (36%) Abdomen: 5/47 (11%) Retroperitoneal nodes: 5/47 (11%) Multiple: 16/47 (34%) Other: 3/47 (6%) Residual bulk >2 cm: 27 (57%) Median time since last chemotherapy (months): 30.2 Time since last chemotherapy >2 years: 23/47 (49%) **Prior therapy** Cisplatin alone: 6/47(13%) Carboplatin alone: 7/47 (15%) Carboplatin combination: 34/47 (72%) Cisplatin + doxorubicin: 31/47 (66%) Dose of previously administered carboplatin/cisplatin: median (range) mg/m^2: Cisplatin: 553 (240–1000) Carboplatin: 2130 (600–2400) **CAP (n = 47)** **Age (years)** Median: 53 Range: 27–69 ≤ 45: 10/47 (21%) 46–55: 15/47 (32%) ≥ 56: 22/47 (47%) Serous histology: 31/47 (66%) Other histology: 16/47 (34%) Poor differentiation: 28/47 (60%) **Disease site** Pelvis: 14/47 (30%) Abdomen: 5/47 (11%)	**Actual study treatment administration** Not reported	(36%); p = 0.009 Thrombocytopenia (grade 3–4): 6 (13%); p = 0.012 Nausea and vomiting (grade 2–3): 24 (51%); p = 0.004 Alopeica: 28 (60%); p = 0.010 Allergic reactions: 1 (2%); p = 0.085 Sensory neuropathy ≥ grade 2: 3 (6%); p = 0.002 Myalgia (grade 2): 2 (4%); p = 0.025 Other (cardiac toxicity, renal toxicity, stomatitis): 1 (2%); p > 0.05 No. of cycles delivered: median (main reason for stopping treatment was disease progression): 6	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Retroperitoneal nodes: 10/47 (21%) Multiple: 14/47 (30%) Other: 2/47 (4%) Residual bulk >2 cm: 16/47 (34%) Median time since last chemotherapy (months): 38.8 Time since last chemotherapy >2 years: 21/47 (45%) **Prior therapy** Cisplatin alone: 9/47 (19%) Carboplatin alone: 5/47 (11%) Carboplatin combination: 30/47 (64%) Cisplatin + doxorubicin: 26/47 (55%) Dose of previously administered carboplatin/cisplatin: median (range) mg/m^2 Cisplatin: 530 (300–1000) Carboplatin: 2400 (2400–2400) **Inclusion/exclusion criteria** 1. Histologically proven ovarian carcinoma. 2. Disease recurred or progressed after 12 months since end of first-line therapy including cisplatin or carboplatin. 3. Measurable disease (not defined) 4. WHO performance status ≤2 5. Adequate bone marrow function (absolute granulocyte count ≥2000/ul, platelet count ≥100,000/ul) 6. Adequate renal, hepatic and cardiac function (not defined)			

Results

Outcome 1	Outcome 2
Outcome: Overall survival. Defined as time from randomisation to death by any cause. Progression-free survival defined as interval from randomisation to first appearance of progressive disease (not defined) Times of follow-up: median 49 months (range: 40–54) Paclitaxel (n = 47) Survival Median: 25.8 months At 4-year follow up: Deaths: 34/47 (with progression 31; without progression 3) Still alive: 13 HR = 0.70 (95% CI: 0.42 to 1.15; p = 0.160). Adjusted for residual tumour, time since end of last therapy and age: HR = 0.58 (95% CI: 0.34 to 0.98; p = 0.043) Multivariate analysis: mortality risk (calculated using Cox proportional hazards regression model): Age (years): ≤ 50: HR = 1 >50: HR = 1.70 (95% CI: 0.90 to 3.19; p = 0.10) Residual disease: ≤ 2 cm: HR = 1 >2 cm: HR = 0.49 (95% CI: 0.28 to 0.86; p = 0.013) Time since end of last chemotherapy (years): ≤ 2: HR = 1 >2: HR = 0.62 (95% CI: 0.36 to 1.08; p = 0.091) Arm: Paclitaxel: HR = 1 CAP: HR = 0.58 (95% CI: 0.35 to 0.98; p = 0.043) Progression-free survival: Median: 9 months Alive at time of follow up with progression: 10 Alive no progression (extrapolated): 3 Died: 34 Died without progression: 4 HR = 0.65 (95% CI: 0.41 to 1.02; p = 0.08). Adjusted for residual tumour, time since end of last therapy and age: HR = 0.60 (95% CI: 0.37 to 0.97; p = 0.038)	**Outcome: Tumour responses (ECOG criteria)** **Paclitaxel (n = 47)** CR: 8/47 (17%) PR: 13/47 (28%) Total: 21/47 (45%) SD: 10/47 (21%) PD: 16/47 (34%) **Responses after crossover following no response to paclitaxel treatment, i.e. response to CAP:** **Total number crossed over: 30** CR: 7/30 (23%) PR: 7/30 (23%) Total: 14/30 (46%) SD: 7/30 (23%) PD: 9/30 (30%) CAP (n = 47) CR: 14/47 (30%) PR: 12/47 (25%) Total: 26/47 (55%) SD: 14/47 (30%) PD: 7/47 (15%) **Responses after crossover following no response to CAP treatment, i.e. response to paclitaxel** **Total number crossed over: 23** CR: 3/23 (13%) PR: 2/23 (9%) Total: 5/23 (22%) SD: 7/23 (30%) PR: 11/23 (48%)

continued

Outcome 1	Outcome 2
Multivariate analysis: progression risk Age (years): ≤ 50: HR = 1 >50: HR = 1.26 (95% CI: 0.72 to 2.20; $p = 0.412$) Residual disease: ≤ 2 cm: HR = 1 >2 cm: HR = 0.81 (95% CI: 0.50 to 1.33; $p = 0.420$) Time since end of last chemotherapy (years): ≤ 2: HR = 1 >2: HR = 0.76 (95% CI: 0.47 to 1.23, $p = 0.270$) Arm: Paclitaxel: HR = 1 CAP: HR = 0.60 (95% CI: 0.37 to 0.97, $p = 0.038$) CAP ($n = 47$): Survival: Median: 34.7 months At 4-year follow-up: Deaths: 27/47 (with progression 23; without progression 4) Still alive: 20 HR = 0.70 (95% CI: 0.42 to 1.15; $p = 0.160$). Adjusted for residual tumour, time since end of last therapy and age: HR = 0.58, (95% CI: 0.34 to 0.98, $p = 0.043$) Multivariate analysis: mortality risk (calculated using Cox proportional hazards regression model): Age (years): ≤ 50: HR = 1 >50: HR = 1.70 (95% CI: 0.90 to 3.19; $p = 0.10$) Residual disease: ≤ 2 cm: HR = 1 >2 cm: HR = 0.49 (95% CI: 0.28 to 0.86; $p = 0.013$) Time since end of last chemotherapy (years): ≤ 2: HR = 1 >2: HR = 0.62 (95% CI: 0.36 to 1.08; $p = 0.091$) Arm: Paclitaxel: HR = 1 CAP: HR = 0.58 (95% CI: 0.34 to 0.98; $p = 0.043$)	

Outcome 1	Outcome 2
Progression-free survival: Median: 15.7 months Alive at time of follow-up with progression: 14 Alive no progression (extrapolated): 6 Died: 27 Died without progression: 3 HR = 0.65 (95% CI: 0.41 to 1.02; $p = 0.08$). Adjusted for residual tumour, time since end of last therapy and age: HR = 0.60 (95% CI: 0.37 to 0.97; $p = 0.038$) Multivariate analysis: progression risk: Age years: ≤ 50: HR = 1 >50: HR = 1.26 (95% CI: 0.72 to 2.20; $p = 0.412$) Residual disease: ≤ 2 cm: HR = 1 >2 cm: HR = 0.81 (95% CI: 0.50 to 1.33; $p = 0.420$) Time since end of last chemotherapy (years): ≤ 2: HR = 1 >2: HR = 0.76 (95% CI: 0.47 to 1.23; $p = 0.270$) Arm: Paclitaxel: HR = 1 CAP: HR = 0.60 (95% CI: 0.37 to 0.97; $p = 0.038$)	

Trial: Piccart and colleagues[30]

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
Author: Piccart, 2000[30] **Objective** To evaluate the efficacy of oxaliplatin in relapsing progressive ovarian cancer patients and to analyse the safety profile and impact of single-agent paclitaxel and oxaliplatin on QoL, TTP and survival **Trial ID:** None **Phase:** Phase II **Length of follow-up:** Unclear	**Number randomised** 86 randomised (paclitaxel $n = 41$; oxaliplatin $n = 45$) **Disease type:** Epithelial **Disease stage:** Advanced **Occurrence of secondary spread:** Yes in all patients. **Therapy stage:** Second-line **Previous treatments** At least 1 and not more than 2 platinum-based chemotherapy regimens with last regimen featuring carboplatin or cisplatin at therapeutically adequate and potentially active doses **Disease present after first-line treatment?** Residual: Yes Refractory: Yes **Age/age range of participants** Paclitaxel: median 62.0 years (range 37–81 years) Oxaliplatin: median 59.0 years (range 28–71 years) **Characteristics** **Paclitaxel (n =41):** Age (years): Median: 62 Range: 37–81 **WHO performance status** 0–1: 35/41 (85%) 2: 6/41 (15%)	**Intervention (I)** **Type:** Paclitaxel **No. randomised:** 41 **Route of administration:** i.v. **Dose:** 175 mg/m^2 3 weeks over 3 h **No. of cycles:** median per every 6 (range: 1–8) **Length per cycle:** 21 days **Control (C)** **Type:** Oxaliplatin **No. randomised:** 45 **Route of administration:** i.v. **Dose:** 130mg/m^2 every 3 weeks over 2 h **No. of cycles:** median 4 (range 1–8) **Length per cycle:** 21 days **Comments about intervention/control:** Paclitaxel: Recommended premedication: oral dexamethasone (20 mg), 12 and 6 h before infusion, diphenhydramine 50 mg i.v, cimetidine 300 mg or ranitidine 50 mg i.v. 30 minutes before paclitaxel **Oxaliplatin:** Recommended premedication 5HT3 with a single dose of corticosteroid (e.g. dexamethasone 20 mg) Regime to be continued until disease progression, unacceptable toxicity or patient refusal. Initial doses could be reduced in subsequent cycles or cycles could be delayed by 1 or 2 weeks depending on toxicity. When dose reduction was required, no subsequent dose escalation was allowed. Dose	**Withdrawals from intervention:** 2: both were ineligible. Of the total of 4 patients who were ineligible, 1 had relapsed disease >1 year after last platinum-based chemotherapy regimen and 3 had no measurable lesions at study entry, according to independent radiological experts **Withdrawals from control** 3: 2 were ineligible and 1 died of massive pulmonary thromboembolism 6 days after first cycle (not related to treatment). Of the total of 4 patients who were ineligible, 1 had relapsed disease >1 year after last platinum-based chemotherapy regimen and 3 had no measurable lesions at study entry, according to independent radiological experts **Adverse events** Severe [National Cancer Institute of Canada (NCIC) grade 3/4] haematological and non-haematological toxicity by patient	**Authors' conclusions** Single-agent oxaliplatin at 130 mg/m^2 every 3 weeks is active with moderate toxicity in patients with cisplatin/carboplatin-pretreated advanced ovarian cancer **Comments** It is not clear what the length of follow-up was and this may have implications for the usefulness of survival data (see outcomes) **Comments on the results:** The overall survival results are based on estimates, without further explanation of how these estimates were derived. Given that it is unclear what the length of follow-up was, it is difficult to ascertain how many patients were censored at follow-up and what the impact of this on survival figures may have been

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	FIGO initial stage I: 5/41 (12%) II: 2/41 (5%) III: 26/41 (63%) IV: 8/41 (20%) **Histological subtype after central review** Serous: 17/41 (41%) Other: 24/41 (59%) **Prior chemotherapy** 1 regimen: 30/41 (73%) 2 regimens: 11/41 (27%) **Time since last chemotherapy** 0–6 months (platinum-refractory): 31/41 (76%) 6–12 months (platinum-sensitive): 10/41 (24%) **No. of involved sites** 0: 0/41 1: 22/41 (54%) 2: 17/41 (41%) 3: 2/41 (5%) >3: 0/41 **Involved site** Pelvi-peritoneum: 30/41 (73%) Lymph nodes: 15/41 (37%) Lung: 2/41 (5%) Liver: 7/41 (17%) Other: 7/41 (17%) **CA-125 level (IU/ml)** Median: 222 range: 8–8,165 <20 IU/ml: 2/41 (5%) ≥ 20 IU/mL: 29/41 (71%)	reduction could be cumulative from cycle to cycle if required by haematological or non-haematological toxicities but doses could not fall below established minimum dose per cycle (90 mg/m^2 paclitaxel and 75 mg/m^2 oxaliplatin); patients who required lower doses than the minimum went off-study CR defined as disappearance of all known disease, without appearance of new lesions, lasting more than 4 weeks. An elevated CA-125 serum level had to regain normal levels for a response to qualify as complete. PR was defined as a decrease of at least 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions being confirmed by a further observation no less than 4 weeks later without any new lesions No change was defined in the case of bidimensional lesions as a decrease of <50% and an increase of <25% in the sum of the products of the largest perpendicular dimensions of all measurable lesions PD was defined as an increase of at least 25% in the sum of the products of the largest perpendicular diameters of measurable lesions or the appearance of a new lesion. The occurrence of positive cytology, pleural effusion or ascites was also considered as PD QoL was assessed using the EORTC QLQ-C30	**Paclitaxel (*n* = 41)** **Hematological:** Neutropenia: Grade 3: 6/41 (15%) Grade 4: 3/41 (7%) Anaemia: Grade 3: 0/41 Grade 4: 1/41 (2%) Thrombocytopenia: Grade 3: 0/41 Grade 4: 0/41 Liver function: AST: Grade 3: 0/41 Grade 4: 0/41 ALT: Grade 3: 2/41 (5%) Grade 4: 0/41 Gastrointestinal: Nausea Grade 3: 1/41 (2%) Grade 4: n/a Vomiting Grade 3: 1/41 (2%) Grade 4: 0/41 Diarrhoea Grade 3: 0/41 Grade 4: 0/41 Neurosensory: Grade 3: 3/41 (7%) Grade 4: A	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Regimens containing Cisplatin: 16/41 (39%) Median dose, mg: 442 Range, mg: 223–456 Carboplatin: 21/41 (51%) Median dose, mg: 1970 Range, mg: 652–3600 Both cisplatin and carboplatin: 4/41 (10%) **Oxaliplatin (*n* = 45)** Age (years): Median: 59 Range: 28–71 **WHO performance status** 0–1: 38/45 (84%) 2: 7/45 (16%) **FIGO initial stage** I: 7/45 (16%) II: 1/45 (2%) III: 29/45 (64%) IV: 8/45 (18%) **Histological subtype after central review** Serous: 33/45 (73%) Other: 12/45 (27%) **Prior chemotherapy** 1 regimen: 29/45 (64%) 2 regimens: 16/45 (36%) **Time since last chemotherapy** 0–6 months (platinum-refractory): 32/45 (71%) 6–12 months (platinum-sensitive): 13/45 (29%) **No. of involved sites** 0: 1/45 (patient with no target lesion at study entry) 1: 30/45 (67%)	**Dose modifications** Exposure to treatment Paclitaxel (*n* = 41) **No. of cycles administered** Median: 197 No. per patient: 6 Range: 1–8 **Cumulative dose per patient, mg/m^2** Median: 1028 Range: 173–1453 **Dose intensity, mg/m^2/week** Median: 57 Median at cycle 3: 58 **No. of patients given relative dose intensity** <80%: 0 80–95%: 11 95–100%: 30 **Exposure to treatment** Oxaliplatin (*n* = 45) **No. of cycles administered:** Median: 181 No. per patient: 4 Range: 1–8 **Cumulative dose per patient, mg/m^2** Median: 504 Range: 132–993 **Dose intensity, mg/m^2/week** Median: 42 Median at cycle 3: 42 **No. of patients given relative dose intensity** <80%: 4 80–95%: 15 95–100%: 26	Other: Lethargy: Grade 3: 3/41 (7%) Grade 4: NA Pain: Grade 3: 5/41 (12%) Grade 4: 0/41 **Oxaliplatin (*n* = 45)** **Haematological:** Neutropenia: Grade 3: 0/45 Grade 4: 0/45 Anaemia: Grade 3: 1/45 (2%) Grade 4: 2/45 (4%) Thrombocytopenia: Grade 3: 2/45 (4%) Grade 4: 0/45 Liver function: AST: Grade 3: 0/45 Grade 4: 0/45 ALT: Grade 3: 0/45 Grade 4: 0/45 Gastrointestinal: Nausea: Grade 3: 2/45 (4%) Grade 4: n/a Vomiting: Grade 3: 3/45 (7%) Grade 4: 0/45 Diarrhoea:	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	2: 11/45 (25%) 3: 2/45 (4%) >3: 1/45 (2%) **Involved site** Pelvi-peritoneum: 25/45 (56%) Lymph nodes: 13/45 (29%) Lung: 2/45 (4%) Liver: 15/45 (33%) Other: 7/45 (16%) **CA-125 level (IU/ml)** Median: 316 range: 7–14,350 < 20: 5/45 (11%) ≥ 20: 32/45 (71%) **Regimens containing** Cisplatin: 19/45 (42%) Median dose, mg: 440 Range, mg: 223–478 Carboplatin: 21/45 (47%) Median dose, mg: 1,888 Range, mg: 1402–3568 Both cisplatin and carboplatin: 5/45 (11%) **Inclusion/exclusion criteria** 1. Histologically or cytologically proven metastatic ovarian carcinoma excluding Brenner or borderline tumour, low potential (grade 0 tumours), squamous cell carcinoma and granulosa theca cell tumours. 2. Progressed or stabilised after prior treatment with relapse observed within 1 year of last platinum-based chemotherapy 3. Received at least 1 and no more than 2 chemotherapeutic regimens, with the last regimen featuring carboplatin or cisplatin at therapeutically		Grade 3: 2/45 (4%) Grade 4: 0/45 Neurosensory: Grade 3: 4/45 (9%) Grade 4: NA Other: Lethargy: Grade 3: 3/45 (7%) Grade 4: NA Pain: Grade 3: 2/45 (4%) Grade 4: 0/45	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	adequate and potentially active doses 4. Those with progressive or stable disease must have received at least 2 or 4 consecutive cycles, respectively, and must have 1 bidimensionally measurable lesion by CT scan or MRI with at least one diameter of ≥ 2 cm 5. 18 years old or over 6. WHO performance status of 0 to 2 7. Estimated life expectancy of ≥12 weeks 8. Baseline blood laboratory criteria: neutrophil count $\geq 1.5 \times 10^9$ cells/l; platelet count ≥100 × 10 to the 9 platelets/l; creatinine level ≤ 140 µml/l; total bilirubin level ≤ 1.25 × upper limit of normal: AST level ≤ 2 × upper limit of normal (≤3 in the case of liver metastasis) 9. Agreement to complete a QoL questionnaire at baseline and every 2 cycles thereafter 10. No prior treatment with platinum derivatives other than cisplatin and carboplatin or with paclitaxel, docetaxel or high-dose chemotherapy with haematopoietic stem cell support 11. No brain or leptomeningeal metastases. No previous or concurrent malignancies at other sites including abdominal adenocarcinoma of unknown origin (except cone-biopsied *in situ* cervix carcinoma and basal or squamous cell skin carcinoma) 12. No symptomatic peripheral neuropathy ≥ grade 2 (NCIC criteria) or any other serious illness			

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Comments about participants Patients were stratified by centre, performance status (0, 1 or 2), platinum-free interval (0–6 vs 6–12 months) and number of previous platinum-based treatments			

Results

Outcome 1	Outcome 2	Outcome 3
Outcome: Survival (not defined) **Paclitaxel group (*n* = 41):** Median duration of response: 33 weeks Median TTP: 14 weeks Estimated median PFS: 14 weeks Median time to treatment failure: 13 weeks Number of deaths: 25 Median overall survival estimated: 37 weeks **Oxaliplatin group (*n* = 45):** Median duration of response; 31 weeks Median TTP: 12 weeks Estimated median PFS: 12 weeks Median time to treatment failure: 12 weeks Number of deaths: 20 Median overall survival estimated: 42 weeks	**Outcome: Tumour response** **Paclitaxel group (*n* = 41)** CR: 0 (1 patient had a CR in a pelvic mass) PR : 7 (17%) (95% CI: 7 to 32%); 5/7 had a sustained CA-125 serum level decrease, 1 did not show a significant decrease of CA-125 and 1 was not assessable by this method Platinum-sensitive: 2/10 (20%) Platinum-refractory: 5/31 (16%) 2 prior chemotherapy regimens: 3/7 NC: 18 (44%) PD: 14 (34%) Not assessable: 2 (5%) Total: 41 (100%) **Oxaliplatin group (*n* = 45)** CR: 0 PR : 7 (16%) (95% CI: 7 to 29%); 4/7 had a sustained CA-125 serum level decrease, 2 did not show a significant decrease in CA-125 and 1 was not assessable by this method Platinum-sensitive: 5/13 (38%) Platinum-refractory: 2/32 (6%) 2 prior chemotherapy regimens: 4/16 NC: 20 (44%) PD: 15 (33%) Not assessable: 3 (7%) Total: 45 (100%)	**Outcome: Quality of life (EORTC QLQ-C30)** Completion and follow-up of QoL data: 66 patients completed at baseline 47 at end of 2nd cycle 31 at end of 4th cycle **Results:** **Paclitaxel:** Mean QoL scores increased by 10 points between baseline and cycle 4, regardless of time of study withdrawal **Oxaliplatin:** Mean QoL scores decreased by <10 points through cycle 2 then tended to return to baseline values for the majority of patients after 2 cycles

Trial: Omura and colleagues[32]

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
Author: Omura, 2003[32] **Objective** To determine whether increasing the dose of paclitaxel increases the probability of response, PFS or overall survival in women who have persistent or recurrent ovarian cancer, and whether doubling the dose of prophylactic filgrastim accompanying the higher paclitaxel dose decreases the frequency of neutropenic fever **Trial ID:** None **Phase:** Phase III **Length of follow-up:** 36 months	**Number randomised** 477 (250 mg/m^2 paclitaxel n = 188; 175 mg/m^2 paclitaxel n = 184) **Disease type:** Epithelial **Disease stage:** Advanced **Occurrence of secondary spread:** Not reported. **Therapy stage:** Second-line **Previous treatments** Chemotherapy; no more than 1 platinum-containing first-line regimen **Disease present after first-line treatment?** **Residual:** Yes **Refractory:** Yes **Age/age range of participants** 250 mg/m^2 paclitaxel: Median: 62 years (range: 24–80) 175 mg/m^2 paclitaxel: Median: 60 years (range: 23–88) **Characteristics** **250 mg/m^2 paclitaxel (n = 166)** **Age (years)** Median: 62 Range: 24–80 <40: n (%): 9 (5) 40–49: n (%): 30 (18) 50–59: n (%): 31 (19) 60–69: n (%): 64 (39) ≥ 70: n (%): 32 (19) **Histology (cell type)** Serous: n (%): 100 (60)	**Intervention (I)** **Type:** Paclitaxel **No. randomised:** 188 **Route of administration:** i.v. **Dose:** 250 mg/m^2 given as a 24-h i.v. infusion. Patients were also assigned to 5 or 10 μg/kg of filgrastim per day subcut. G-CSF was started on 3rd day after paclitaxel administration and continued through the neutrophil nadir until the absolute neutrophil count was at least 10,000/μl **No. of cycles:** Protocol specified 6 but treatment could continue indefinitely if clinical progression or excess toxicity were not experienced **Length per cycle:** 21 days **Control (C)** **Type:** Paclitaxel **No. randomised:** 184 **Route of administration:** i.v. **Dose:** 175 mg/m^2 given as a 24-h i.v. infusion **No. of cycles:** Protocol specified 6 but treatment could continue indefinitely if clinical progression or excess toxicity were not experienced. **Length per cycle:** 21 days **Comments about intervention/control** Patients were initially (1st year of recruitment) randomised to 3 groups. Assignment to 135 mg/m^2 group ceased after the accession of 77 patients (88% deemed eligible) who are only partially	**Withdrawals from intervention (I)** 22 patients from this group were randomised but did not receive treatment as they were not deemed eligible. Total exclusions before trial, 42: inappropriate primary disease site (n = 34), improper prior treatment (n = 7), inadequately documented histology (n = 3), 2nd primary cancer (n = 3), inadequate documentation of recurrence (n = 2), borderline tumour histology (n = 1) and wrong stage (n = 1). Not stated which group patients had been randomised to **Withdrawals from control (C)** 20 patients from this group randomised but did not receive treatment as they were not deemed eligible. Total exclusions before trial, 42: inappropriate primary disease site (n = 34), improper prior treatment (n = 7), inadequately documented histology (n = 3), 2nd primary cancer (n = 3), inadequate documentation of recurrence (n = 2), borderline tumour histology (n = 1) and	**Authors' conclusions** Paclitaxel exhibits a dose effect with regard to response rate, but there is more toxicity and no survival benefit to justify paclitaxel 250 mg/m^2 plus filgrastim. Doubling the dose of filgrastim from 5 to 10 μg/kg did not reduce the probability of neutropenic fever after high-dose paclitaxel **Comments** The inclusion criteria were altered in two critical respects during recruitment: including patients without measurable disease who were subsequently excluded from tumour response analysis and including patients who were platinum sensitive. This raises questions about the screening of patients for the trial and application and appropriateness of the inclusion criteria

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Endometrioid: *n* (%): 22 (13) Mucinous: *n* (%): 7 (4) Clear cell: *n* (%): 11 (7) Other: *n* (%): 26 (16) **Measurable disease: *n* (%): 134 (81)** **Platinum sensitivity** Resistant: *n* (%): 132 (79) Sensitive: *n* (%): 34 (21) **GOG performance status** 0: *n* (%): 88 (53) 1: *n* (%): 63 (38) 2: *n* (%): 15 (9) **Race** Black: *n* (%): 7 (4) Hispanic: *n* (%): 6 (4) White: *n* (%): 146 (88) Other/not specified: *n* (%): 7 (4) **Paclitaxel 175 mg/m^2 (*n* = 164)** **Age (years)** Median: 60 Range: 23–88 <40: *n* (%): 12 (7) 40–49: *n* (%): 25 (15) 50–59: *n* (%): 46 (28) 60–69: *n* (%): 53 (32) ≥ 70: *n* (%): 28 (17) **Histology** Serous: *n* (%): 105 (63) Endometrioid: *n* (%): 17 (10) Mucinous: *n* (%): 0 (0) Clear cell: *n* (%): 8 (5) Other: *n* (%): 34 (21)	reported **Actual study treatment administration** **Paclitaxel 250 mg/m^2** 55% of patients received 6 or more cycles of therapy. Over the first 6 courses of treatments ~70% of the planned ideal dose was delivered to patients. Although dose reductions occurred in both arms, a difference in the total dose and dose intensity was maintained during the first 6 courses of therapy **Paclitaxel 175 mg/m^2** 58% of patients received 6 or more cycles of therapy. Over the first 6 courses of treatments ~76% of the planned ideal dose was delivered to patients. Although dose reductions occurred in both arms, a difference in the total dose and dose intensity was maintained during the first 6 courses of therapy % planned ideal dose delivered over first 6 cycles: 250 mg/m^2: 70% 175 mg/m^2: 76% **Outcome definitions** **Tumour responses** **Complete response** (defined as disappearance of all gross evidence of disease for at least 4 weeks) **Partial response** (defined as a reduction of ≥ 50% in the product of perpendicular measurements of each lesion for at least 4 weeks)	wrong stage (*n* = 1). Not stated which group patients had been randomised to **Adverse events** 250 mg/m^2 (also given G-CSF): Neutropenic fever [defined as grade 4 neutropenia (absolute neutrophil count <500/μl) and grade 2 (≥ 38.1 °C fever)]: 19% (*n* = not reported) (19% on 5 μg/kg filgrastim, 18% on 10 mg/kg filgrastim). (95% CI for differences between 2 doses: –11 to 13%) All other adverse events were grade 3/4 (*n* = not reported): Anaemia: 15%, *p* = 0.102 Thrombocytopenia: 15%, *p* = 0.009 Nausea and vomiting: 10%, *p* = 0.211 Neuropathy: 16%, *p* = 0.024 Myalgia/arthralgia: 10%, *p* = 0.022 175 mg/kg: Neureopenic fever [defined as grade 4 neutropenia (absolute neutrophil count <500/μl) and grade 2 (≥ 38.1 °C fever)]: 22% (*n* = not reported) All other adverse events were grade 3/4 (*n* = not reported): Anaemia: 7%, *p* = 0.102 Thrombocytopenia: 5%,	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Measurable disease: *n* (%): 131 (80) **Platinum sensitivity** Resistant: *n* (%): 125 (76) Sensitive: *n* (%): 39 (24) **GOG performance status** 0: *n* (%): 89 (54) 1: *n* (%): 65 (40) 2: *n* (%): 10 (6) **Race** Black: *n* (%): 4 (2) Hispanic: *n* (%): 5 (3) White: *n* (%): 149 (91) Other/not specified: *n* (%): 6 (4) **Inclusion/exclusion criteria** 1. Histologically confirmed epithelial ovarian cancer 2. No more than 1 prior platinum-based regimen 3. No prior taxane therapy 4. Platinum-resistant disease defined as progression during first-line platinum treatment or within 6 months of completing therapy, a best response of stable disease after 6 courses of platinum or stable disease with a rising CA-125 while on platinum or recurrence, were included (see comments on participants). 5. Clinically measurable disease (see comments about participants). 6. Performance status of 0, 1 or 2. 7. Adequate marrow, renal and hepatic function Ineligible patients included those with: A diagnosis of borderline carcinoma (grade 0) or neoplasm termed probably		$p = 0.009$ Nausea and vomiting: 5%, $p = 0.211$ Neuropathy: 7%, $p = 0.024$ Myalgia/arthralgia: 3%, $p = 0.022$	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	malignant. Patients who had received prior paclitaxel, irradiation or more than one prior chemotherapy regimen. Patients with septicaemia, other active infection, acute hepatitis, severe gastrointestinal bleeding or other serious medical conditions likely to limit a patient's ability to tolerate treatment. Patients with a history of congestive heart failure, unstable angina or a myocardial infarction within the last 6 months, or a history of cardiac arrhythmia requiring antiarrythmic medication. Patients with unclassified ovarian cancer (cancers thought to be of ovarian origin but not explored, or where it was not possible to verify tumour arising from ovarian tissue). Patients with a past or concomitant malignancy other than skin (excluding melanoma), or known hypersensitivity to an *Escherichia coli*-derived drug preparation were also ineligible **Comments about participants** Inclusion criteria were altered during selection to allow patients without measurable disease or who were defined as platinum-sensitive (patients with an initial response to platinum therapy lasting at least 6 months) to participate			

Results

Outcome 1	Outcome 2	Outcome 3
Outcome: Survival (months) (measured from date registered on to study to date of 1st progression/death from any cause (PFS) and death or last contact if date of death unknown (overall survival) **Paclitaxel 250 mg/m^2 (n = 166)** **PFS:** Median: 5.5 months Without progression at 36 months: 5/166 (3%) **Survival:** Median: 12.3 months Alive at 36 months: 9/1665% **Paclitaxel 175 mg/m^2 (n = 164)** PFS: Median: 4.8 months Without progression at 36 months: 2/164 (1%) Survival: Median: 13.1 months Alive at 36 months: 8/164 (5%) From both groups: survival (median): Platinum-resistant: 11.0 months Platinum-sensitive: 19.6 months (p < 0.001) Multivariate analysis: survival (relative HR): Paclitaxel regimen: 175 mg/^{2}: 1.0 250 mg/^{2}: 0.972 (95% CI: 0.772 to 1.22) Platinum-sensitive (relative HR): Resistant: 1.0 Sensitive: 0.576 (95% CI: 0.434 to 0.764) Clinically measurable disease (relative HR): No: 1.0	**Outcome: Tumour response in patients with measurable disease.** Covariates adjusted for 1, initial performance status; 2, cell type; 3, response to prior platinum; 4 cooperative group; 5, measurable disease status Paclitaxel 250 mg/m^2 (n = 134) CR: 17/134 Platinum-resistant: 13/109 (12%) Platinum-sensitive: 4/25 (16%) PR: 32/134 Platinum resistant: 27/109 (25%) Platinum-sensitive: 5/25 (20%) Total: 49 (36%) Platinum-resistant: 40/109 Platinum-sensitive: 9/25 Filgrastim dosage: 5 μg/kg: (n = 68) 24/68 (35%) (95% CI: 24 to 48%) 10 μg/kg: (n = 66) 25/66 (37.9%) (95% CI: 26% to 51%) Paclitaxel 125 mg/m^2 (n = 131) CR: 9/131 Platinum-resistant: 5/104 (5%) Platinum-sensitive: 4/27 (15%) PR: 27/131 Platinum-resistant: 18/104 (17%) Platinum-sensitive: 9/27 (33%) Total: 36/131 (27%) Platinum-resistant: 23/104 Platinum-sensitive: 13/27 For both groups: OR responding to 250 compared with 175 mg/m^2 = 1.89 (95% CI: 1.07 to 3.31; p = 0.027) after adjusting for other factors (see above)	**Outcome: Quality of life** Baseline data: For both the PLDH and topotecan groups: not reported; questionnaire only completed by 82% of participants. However, function and symptom scale scores were similar between the two treatment groups Follow-up data: For both the PLDH and topotecan groups: No significant differences between the intervention and control groups at 12-week follow-up **Comments:** QoL (assessed by EORTC QLQ-C30): 82% of participants completed QoL measure at baseline, at 12 weeks <50% of participants in either treatment arm were still in the health-related QoL study

continued

Outcome 1	Outcome 2	Outcome 3
Yes: 1.97 (95% CI: 1.44 to 2.69) Histological cell type (relative HR): Papillary serous adeno: 1.0 Clear cell or mucinous: 2.13 (95% CI: 1.38 to 3.27) Other: 1.04 (95% CI: 0.810 to 1.34) Initial performance status (relative HR): 0: 1.0 1: 1.17 (95% CI: 0.915 to 1.49) 2: 5.23 (95% CI: 3.36 to 8.15)	Platinum-resistant: (n = 213) OR = 2.59 (95% CI: 1.36 to 4.95) Platinum-sensitive: (n = 52) OR = 0.630 (95% CI: 0.191 to 2.07) Serous histology: 66/165 (40%) (95% CI: 32 to 48%) Mucinous/clear cell histology: 1/21 (5%) (95% CI: 0.1 to 24%) Other histology: 18/79 (23%) (95% CI: 14 to 34%) No response: 85 Platinum-resistant: 69/109 (63%) Platinum-sensitive: 16/25 (64%) Not assessed due to death, toxicity or withdrawal: 7/134	

Trial: Rosenberg and colleagues[31]

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
Author: Rosenberg, 2002[31] **Objective** To evaluate the efficacy and toxicity of paclitaxel given at the same dose intensity and administered weekly or every 3 weeks and to assess the safety of intravenous steroids versus standard peroral premedication **Trial ID:** None **Phase:** Not reported **Length of follow-up:** median 27 months (range: 7–47+)	**Number randomised** 208 randomised (paclitaxel weekly n = 105; paclitaxel 3-weekly n = 103) **Disease type:** Epithelial **Disease stage:** Advanced **Occurrence of secondary spread:** Not stated **Therapy stage:** Second-line **Previous treatments** One prior platinum-containing regimen of chemotherapy not containing a taxane **Disease present after first-line treatment?** **Residual:** Yes	**Intervention (I)** **Type:** Paclitaxel weekly **No. randomised:** 105 **Route of administration:** i.v. **Dose:** 67 mg/m^2/week. Group randomised to oral steroids 12 and 6 h before paclitaxel OR parenteral steroids 30 minutes before paclitaxel. All patients received clemastine 2 mg and cimetidine 300 mg or ranitidine 50 mg i.v. 30 minutes before paclitaxel **No. of cycles:** Protocol allowed indefinite treatment (see below) **Length per cycle:** 21 days **Control (C)** **Type:** Paclitaxel 3-weekly	**Withdrawals from intervention (I)** 1: ineligible – had non-measurable disease at inclusion **Withdrawals from control (C)** In total 2: 1 ineligible (was aged 75), 1 not stated **Adverse events** **Paclitaxel 67 mg/m^2/week (n = 104)** **Haematological toxicity (lowest value per patient)** Haemoglobin: 81/104 (78%); p = 0.04	**Authors' conclusions** Weekly paclitaxel has a better safety profile and was as effective as the equivalently dosed schedule every 3 weeks. I.v. steroids are a safe alternative to oral steroids

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Refractory: Yes **Age/age range of participants** Weekly: median: 59 years (range: 37–74) 3 weekly: median: 60 years (range: 40–76) **Characteristics** **Paclitaxel 67 mg/m^2 weekly (n = 105)** **Age (years):** Median: 59 Range: 37–74 WHO performance status: 0: 57/105 1: 40/105 2: 8/105 Platinum-resistant: 57/105 Platinum-sensitive: 48/105 Tumour size at inclusion: ≤2 cm: 7/105 2–5 cm: 34/105 5–10 cm: 30/105 ≥10 cm: 33/105 Unknown: 1/105 Paresthesia at inclusion (WHO): Grade 0: 92/105 Grade 1: 13/105 **Paclitaxel 200 mg/m^2 3-weekly (n = 103)** **Age (years):** Median: 60 Range: 40–76 WHO performance status: 0: 56/103 1: 33/103 2: 14/103	**No. randomised:** 103 **Route of administration:** i.v. **Dose:** 200 mg/m^2 every 3 weeks. Group randomised to oral steroids 12 and 6 h before paclitaxel or parenteral steroids 30 minutes before paclitaxel. All patients received clemastine 2 mg and cimetidine 300 mg or ranitidine 50 mg i.v. 30 minutes before paclitaxel **No. of cycles:** Protocol allowed indefinite treatment (see below) **Length per cycle:** 21 days **Comments about intervention/control** If no haematological toxicity occurred, the dose was escalated maximally by 2 steps. Dose reduction was performed in the case of severe cytopenia. Patients who could not tolerate the lowest dose level were taken off the study treatment. No dose escalation was allowed once a dose reduction had been made. If infusion was interrupted owing to a hypersensitivity reaction, patients could be retreated at the investigator's discretion. Decision on whether or not to continue treatment was made on the basis of tumour assessments every 6 weeks. Patients with PD were taken off the study. Patients with SD received treatment until either progression or unacceptable toxicity occurred. Patients who achieved a CR or a PR continued study treatment for a	Grade 3–4: 4/104 (4%); p = 1.0 White blood cell: 74/104 (71%); p = 0.27 Grade 3–4: 17/104 (16%); p = 1.0 Neutrophils: 63/104 (61%); p < 0.01 Grade 3–4: 19/104 (18%); p < 0.001 Platelets: 1/104 (1%); p = 0.12 Grade 3–4: 0/104 (0%); p = 0.49 **Non-haematological toxicity (worst value/patient)** Neuropathy: 84/104 (81%); p = 0.72 Grade 3: 11/104 (11%); p < 0.001 Alopecia: 85/104 (82%); p = 0.11 Grade 3: 48/104 (46%); p < 0.001 Arthralgia/myalgia: 61/104 (59%); p < 0.001 Grade 3: 5/104 (5%); p = 0.40 Nausea/vomiting: 48/104 (46%); p = 0.57 Grade 3: 4/104 (4%); p = 1.0 Nails: 37/104 (36%); p < 0.001 Grade 3: 9/104 (9%); p < 0.01 **Withdrawals at 9 weeks:** Total: 32 Disease progression: 14 Prolongation of treatment-free interval: 8 Patient request: 4 Investigator decision: 2 Study drug toxicity: 1 Other reasons: 3	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Platinum-resistant: 51/103 Platinum-sensitive: 52/103 Tumour size at inclusion: ≤ 2 cm: 11/103 2–5 cm: 26/103 5–10 cm: 26/103 ≥ 10 cm: 40/103 Unknown: 0/103 Paresthesia at inclusion (WHO): Grade 0: 91/103 Grade 1: 12/103 **Inclusion/exclusion criteria** 1. Histologically proven diagnosis of epithelial ovarian carcinoma 2. 18–75 years old 3. Received no more than 1 prior platinum-based regimen 4. Evidence of progression during/relapse after administration of last platinum course documented before entering study 5. Measurable disease documented clinically and/or radiologically 6. Adequate physiologic function and status (absolute neutrophil count $\geq 2.0 \times 10^9$, platelet count $\geq 100 \times 10^9$, serum creatine ≤ 1.25 × upper limit of normal, total bilirubin ≤ 1.25 × upper limit of normal, Karnofsky performance status ≥60) 7. Anticipated survival ≥ 12 weeks 8. No atrial or ventricular arrythmias or congestive heart failure, even if medically controlled, or documented myocardial infarction within 6 months, or a history of 2nd- or 3rd-degree heart block.	minimum of 6 weeks and thereafter at the investigator's discretion to tumour progression/relapse or unacceptable toxicity, whichever came first. Cycles were to be given as planned; not permissible to prolong treatment-free interval	Death: 0 Dosage: Median dose intensity (mg/m^2/week): 77.6 mg/m^2/week; $p = 0.0001$ % doses increased by 2: 61% [Dose alterations] –2: 48 –1: 57 0: 67 +1: 75 +2: 81 **Paclitaxel 200 mg/m^2 every 3 weeks ($n = 101$)** **Haematological toxicity (lowest value per patient)** Haemoglobin: 65/101 (64%); $p = 0.04$ Grade 3–4: 4/101 (4%); $p = 1.0$ White blood cell: 79/101 (78%); $p = 0.27$ Grade 3–4: 17/101 (17%); $p = 1.0$ Neutrophils: 80/101 (79%); $p < 0.01$ Grade 3–4: 45/101 (45%); $p < 0.001$ Platelets: 5/101 (5%); $p < 0.12$ Grade 3–4: 1/101 (1%); $p < 0.49$ **Non-haematological toxicity (worst value/patient)** Neuropathy: 86/101 (85%); $p = 0.72$ Grade 3: 29/101 (29%); $p < 0.001$ Alopecia: 91/101 (90%); $p < 0.11$	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	9. No pre-existing motor or sensory neurotoxicity >grade 2 of WHO criteria **Comments about participants** Platinum-resistant defined as relapse <6 months after first-line therapy Patients were stratified prior to entry according to platinum resistance **Survival data** Response duration: Complete response was calculated from day of first observation of CR to day of documented PD or censored observation; PR calculated from first day of study treatment to day of documented PD or censored observation Tumour responses: If 2 observations were missing not less than 4 weeks apart, tumour response was judged as not confirmed Time to progression was calculated from first day of study treatment to day of documented PD or censored observation Overall survival was calculated from date of randomisation to death or censored observation		Grade 3: 80/101 (79%); $p < 0.001$ Arthralgia/myalgia: 85/101 (84%); $p < 0.001$ Grade 3: 8/101 (8%); $p = 0.40$ Nausea/vomiting: 42/101 (42%); $p = 0.57$ Grade 3: 3/101 (3%); $p = 1.0$ Nails: 2/101 (2%); $p < 0.001$ Grade 3: 0/101 (0%); $p < 0.01$ Withdrawals at 9 weeks: Total: 20 Disease progression: 9 Prolongation of treatment-free period: 3 Patient request: 2 Investigator decision: 0 Study drug toxicity: 4 Other reasons: 1 Death: 1 Dosage: Median dose intensity (mg/m^2/week): 72.7; $p = 0.0001$ % doses increased by +2: 28% Dose alterations: –2: 145 –1: 170 0: 200 +1: 225 +2: 242 Oral steroids 12 and 6 h prior to paclitaxel ($n = 106$) Hypersensitivity reactions (no. of events): Skin: 17/106 (16.0%); NS Grade 3–4: 3/106 (2.8%); NS	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
			Generalised urticaria: 1/106 (0.9%); NS Grade 3–4: 1/106 (0.9%); NS Dyspnoea: 4/106 (3.8%); NS Grade 3–4: 0/106 (0%); NS Respiratory distress requiring treatment: 1/106 (0.9%); NS Grade 3–4: 1/106 (0.9%); NS Hypotension: 1/106 (0.9%); NS Parenteral steroids 30 minutes prior to paclitaxel (n = 99) Hypersensitivity reactions (no. of events): Skin: 18/99 (18.2%); NS Grade 3–4: 4/99 (4.0%); NS Generalised urticaria: 0/99 (0%); NS Grade 3–4: 0/99 (0%); NS Dyspnoea: 4/99 (4.0%); NS Grade 3–4: 1/99 (1.0%); NS Respiratory distress requiring treatment: 1/99 (1.0%); NS Grade 3–4: 0/99 (0%); NS Hypotension: 1/99 (1.0%); NS	

Results

Outcome 1	Outcome 2	Outcome 3
Outcome: Survival	**Outcome: Time to progression**	**Outcome: Tumour responses (WHO criteria)**
Paclitaxel 67 mg/m^2/week (n = 105) Median 13.6 months (95% CI: 10.5 to 18.7); p = 0.98	Paclitaxel 67 mg/m^2/week (n = 105) Median 6.1 months (95% CI: 5.0 to 8.0); p = 0.85	Paclitaxel 67 mg/m^2/week (n = 105) **ITT analysis** CR: 13/105 (12.4%); 3 patients had unconfirmed CRs PR: 24/105 (22.8%); 7 patients had unconfirmed PRs Total response: 37/105 (35.2%) SD: 43/105 (41.0%) PD: 15/105 (14.3) Not evaluable: 9/105 (8.6%) Not treated 1/105 (0.9%) Response duration: 9.4 months (95% CI: 6.2 to 13.9) CR duration: 4.5 months (95% CI: 3.6 to 10.7; p = 0.84) **Per protocol analysis for patients treated for ≥ 9 weeks (n = 87)** CR: 12/87 (13.8%); 3 unconfirmed CRs PR: 24/87 (27.6%); 7 unconfirmed PRs Total response: 36/87 (41.4%) SD: 36/87 (41.4%) PD: 15/87 (17.2%) **Paclitaxel 200 mg^2 per 3 weeks (n = 103)** **ITT analysis** CR: 17/103 (16.5%); 3 patients had unconfirmed CRs PR: 21/103 (20.4%); 6 patients had unconfirmed PRs Total response: 38/103 (36.9%) SD: 33/103 (32.0%) PD: 19/103 (18.5) Not evaluable: 11/103 (10.7%) Not treated 2/103 (1.9%) Response duration: 12.4 months (95% CI: 9.1 to 14.3) CR duration: 7.8 months (95% CI: 4.2 to 10.2; p = 0.84) **Per protocol analysis for patients treated for ≥ 9 weeks (n = 90)** CR: 16/90 (17.8%); 2 unconfirmed CRs PR: 21/90 (23.3%); 6 unconfirmed PRs Total response: 37/90 (41.1%) SD: 34/90 (37.8%) PD: 19/90 (21.1%)
Paclitaxel 200 mg^2 every 3 weeks (n = 103) Median 14.7 months (95% CI: 12.3 to 19.1); p = 0.98	Paclitaxel 200 mg^2 every 3 weeks (n = 103) Median: 8.1 months (95% CI: 6.4 to 9.7); p = 0.85	

Trial: Gore and colleagues[33]

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
Author: Gore, 2002[33] **Objective** To compare the efficacy, safety and tolerability of oral topotecan compared with standard i.v. regimens in a similar group of patients with relapsed ovarian cancer **Trial ID:** None **Phase:** Not stated	**Number randomised** 266 randomised; 266 in ITT **Disease type:** Epithelial **Disease stage:** Stage III and IV **Occurrence of secondary spread:** Not stated **Therapy stage:** Second-line **Previous treatments:** One platinum-based chemotherapy regimen which could have included a taxane **Disease present after first-line treatment?** Residual: Yes Refractory: Yes **Age/age range of participants** I.v. topotecan: median 60 years (range: 27–80) Oral topotecan: median 60 years (range: 23–80) **Characteristics** I.v. topotecan (n = 131) **Age (years):** Median: 60 Range: 27–80 FIGO stage III: 82/131 (63%) FIGO stage IV: 42/131 (32%) Missing data: 7/131 (5%) **Performance status** 0: 47/131 (35%) 1: 77/131 (59%) 2: 11/131 (8%)	**Intervention (I):** **Type:** i.v. topotecan **No. randomised:** 131 **Route of administration:** i.v. **Dose:** 1.5 mg/m^2/day for 5 days **No. of cycles:** Discretion of investigator (see below). Median no. of cycles: 6 (range 1–26) **Length per cycle:** 21 days **Control (C)** **Type:** Oral topotecan **No. randomised:** 135 **Route of administration:** Oral. **Dose:** 2.3 mg/m^2/day **No. of cycles:** Protocol: Discretion of investigator (see below). Median no of cycles: 4 (range 1–23) **Length per cycle:** 21 days **Comments about intervention/control:** Response to study drug was based on objective tumour assessments and evaluated by abdominal/pelvic CT or MRI, chest X-ray or photography. All claimed responses were subjected to independent blinded radiological review. Complete response was defined as complete disappearance of all known measurable and evaluable disease determined by 2 measurements not less than 4 weeks apart. Partial response was defined as >50% decrease in measurable lesion size for ≥ 4 weeks with no simultaneous increase in a known lesion or appearance of new	**Withdrawals from intervention (I)** None **Withdrawals from control (C)** None **Adverse events** **I.v. topotecan (n = 131)** Grade 3–4 haematological toxicity per patient: Death from haematological toxicity: 5/131 Neutropenia Grade 3: 15/131 (11%) Grade 4: 110/131 (84%) Mean neutrophil nadir 0.7×10^9/l Leucopenia: Grade 3: 8/131 (6%) Grade 4: 40/131 (31%) Thrombocytopenia: Grade 3: 27/131 (21%) Grade 4: 23/131 (18%) Anaemia: Grade 3: 43/131 (33%) Grade 4: 10/131 (8%) Per cycle: >778 cycles Neutropenia: Grade 3: 249/778 (32%) Grade 4: 393/778 (51%) Leucopenia: Grade 3: 371/778 (48%) Grade 4: 68/778 (9%)	**Authors' conclusions** Oral topotecan is active as second-line therapy and is well tolerated. Although the response rate was lower (non-significant) and there was a small but significant survival benefit for i.v. topotecan, oral topotecan is well tolerated and convenient, important considerations where treatment is palliative

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Tumour size <5 cm: 65/131 (50%) 5–10 cm: 50/131 (38%) >10 cm: 11/131 (8%) Missing data: 5/131 (4%) **Classification of relapse** Platinum-refractory: 39/131 (30%) Platinum-resistant: 36/131 (27%) Platinum sensitive: 56/131 (43%) **Oral topotecan: (*n* = 135)** **Age (years):** Median: 60 Range: 23–80 **FIGO stage** Stage III: 84/135 (62%) Stage IV: 43/135 (32%) Missing data: 8/135 (6%) **Performance status** 0: 59/135 (45%) 1: 60/135 (46%) 2: 12/135 (9%) **Tumour size** <5 cm: 66/135 (49%) 5–10 cm: 58/135 (43%) >10 cm: 10/135 (7%) Missing data: 1/135 (1%) **Classification of relapse** Platinum-refractory: 40/135 (30%) Platinum-resistant: 37/135 (28%) Platinum-sensitive: 58/135 (43%) **Inclusion criteria** 1. Histological diagnosis of epithelial ovarian cancer 2. Originally FIGO stage III or IV disease 3. Either progressed on first line	lesions or increase in evaluable disease. Response rate was also evaluated by serial CA-125 value measurement. Response was defined as a 50% decrease in 2 samples, confirmed by a further sample, or serial decrease over 3 samples of >75%. The final sample had to be at least 28 days after the previous sample. Dose reductions in increments of 0.4 mg/m^2/day p.o. or 0.25 mg/m^2/day i.v. were made for grade 4 neutropenia lasting beyond day 21, grade 3–4 thrombocytopenia and any non-haematological toxicity of grade 3–4 (excluding grade 3–4 nausea and vomiting). The daily dose could be increased in similar increments if, during the previous course, there had been no toxicity greater than grade 2	Thrombocytopenia: Grade 3: 90/778 (12%) Grade 4: 29/778 (4%) Anaemia: Grade 3: 78/778 (10%) Grade 4: 10/778 (1%) Infectious complications needing i.v. antibiotics: 8% Sepsis or infection/fever grade 2: 3% Platelet transfusions: 3% Red blood cell transfusions: 20% Non-haematological toxicity: Nausea: 8/131 (16%) Grades 3–4: 6/131 (5%) Diarrhoea: 40/131 (31%) Grades 3–4: 6/131 (5%) Vomiting: 52/131 (40%) Grades 3–4: 4/131 (3%) Alopecia: 68/131 (52%) Grades 3–4: 8/131 (6%) Fatigue: 50/131 (38%) Grades 3–4: 5/131 (4%) Abdominal pain: 39/131 (30%) Grades 3–4: 9/131 (7%) Constipation: 42/131 (32%) Grades 3–4: 2/131 (2%) Fever: 31/131 (24%) Grades 3–4: 7/131 (5%) Dosing adjustments (*n* = 778): Courses at starting dose: 58% Courses above starting dose: 4% Dose reductions: 11% **Oral topotecan (*n* = 135)** Grade 3–4 haematological toxicity per patient	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	chemotherapy or relapsed within 12 months of completing initial treatment 4. First-line chemotherapy included a platinum compound which may have been combined with a taxane 5. Only 1 previous line of chemotherapy 6. Aged ≥18 years 7. Measurable disease with 1 lesion ≥2 cm in diameter or ≥1 cm for skin lesions 8. ECOG performance status ≤2 9. Life expectancy ≥ 3 months 10. No surgery, radiotherapy, chemotherapy or hormone therapy for 4 weeks prior to study entry or 60 days in case of prior immunotherapy 11. Adequate bone marrow, renal and hepatic function (haemoglobin ≥90 g/l, WBC ≥3.5 × 10^9/l, neutrophils ≥1.5 × 10^9/l, platelets ≥100 × 10^9/l, creatinine ≤132.6 μmol/l (or creatinine clearance >1 ml/s), serum bilirubin ≤34.2 μmol/l and liver enzymes ≤2 × upper limit of normal (or 5 × upper limit of normal if liver metastases present) 12. No malignancies at other sites except for basal and squamous cell carcinoma of the skin and carcinoma *in situ* of the cervix 13. No brain or leptomeningeal metastases 14. No uncontrolled infection or other severe medical problems 15. No peptic ulcers or other		Death from haematological toxicity: 2/135 Neutropenia: Grade 3: 40/135 (30%) Grade 4: 67/135 (50%) Mean neutrophil nadir 1.5 × 10^9/l Leucopenia: Grade 3: 59/135 (44%) Grade 4: 28/135 (21%) Thrombocytopenia: Grade 3: 30/135 (22%) Grade 4: 27/135 (20%) Anaemia: Grade 3: 51/135 (38%) Grade 4: 5/135 (4%) Per cycle: 729 cycles: Neutropenia: Grade 3: 190/729 (26%) Grade 4: 106/729 (15%) Leucopenia Grade 3: 163/729 (22%) Grade 4: 31/729 (4%) Thrombocytopenia: Grade 3: 70/729 (10%) Grade 4: 42/729 (6%) Anaemia: Grade 3: 85/729 (12%) Grade 4: 7/729 (1%) Infectious complications needing i.v. antibiotics: 6% Sepsis or infection/fever grade 2: 5% Platelet transfusions: 3% Red blood cell transfusions: 21%	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	gastrointestinal conditions affecting absorption or motility or patients receiving concomitant treatment for gastric or duodenal ulcers **Comments about participants** Patients were classified for platinum-sensitivity as follows: Refractory: progressive or stable disease during first-line chemotherapy Resistant: responded to first-line chemotherapy but relapsed within 6 months of treatment ending Sensitive: responded to initial therapy but relapsed after ≥6 months		**Non-haematological toxicity (n = 135)** Nausea: 92/135 (68%) Grades 3–4: 12/135 (9%) Diarrhoea: 76/135 (56%) Grades 3–4: 13/135 (10%) Vomiting: 74/135 (55%) Grades 3–4: 10/135 (7%) Alopecia: 72/135 (53%) Grades 3–4: 10/135 (7%) Fatigue: 50/135 (37%) Grades 3–4: 5/135 (4%) Abdominal pain: 49/135 (36%) Grades 3–4: 9/135 (7%) Constipation: 47/135 (35%) Grades 3–4: 4/135 (3%) Fever: 38/135 (28%) Grades 3–4: 14/135 (10%) Dosing adjustments (n = 729): Courses at starting dose: 60% Courses above starting dose: 19% Dose reductions: 9%	

Results

Outcome 1	Outcome 2
Outcome: Survival (not defined). Patients for whom an event had not occurred at the cut-off date for inclusion in the analysis were censored at time of last contract **I.v. Topotecan** *n* = 131: Survival: median = 58 weeks (range: 0.3–120.0); *p* = 0.033 Time to progression (median = 17 weeks (range 0.1–91.6) *n* = 26: Time to response: median = 8 weeks (range 5.1–25.4) Duration of response: median = 26 weeks (range 6.6–52.7) **Oral topotecan** *n* = 135: Survival: median = 51 weeks (range 1.6–109.0) Time to progression: median = 13 weeks (range: 1.6–76.6) *n* = 17 Time to response: median = 12 weeks (range: 5.6–18.1) Duration response: median = 34 weeks (range: 13.1–62.3)	**Outcome: Tumour response** **I.v. topotecan** CR: 4/131 (3%) PR: 22/131 (17%) Overall response: 26/131 (20%) (95% CI: 13.0 to 26.7%) Platinum-sensitive patients (*n* = 56): 20/56 (36%) Platinum-resistant patients (*n* = 36): 4/36 (11%) Platinum-refractory patients (*n* = 39): 2/39 (5%) Tumour size <5 cm (*n* = 65): 15/65 (23%) ≥ 5 cm: (*n* = 61): 10/61 (16%) First-line treatment: platinum/paclitaxel (*n* = 54): 12/54 (22%) SD: 35/131 (27%) PD: 59/131 (45%) Not evaluated 11/131 (8%) Response by CA-125 (*n* = 99): 28/99 (28%) ITT analysis: 28/131 (21%) **Oral topotecan** CR: 2/135 (1%) PR: 15/135 (11%) Overall response: 17/135 (13%) (95% CI: 7.6 to 19.1%) Platinum-sensitive patients (*n* = 58): 11/58 (19%) Platinum-resistant patients (*n* = 37): 3/37 (8%) Platinum refractory patients (*n* = 40): 3/40 (8%) Tumour size <5 cm (*n* = 66): 10/66 (15%) ≥5 cm (*n* = 68): 7/68 (10%) First-line treatment: platinum/paclitaxel (*n* = 53): 8/53 (15%) SD: 39/135 (29%) PD: 65/135 (48%) Not evaluated: 14/135 (10%) Response by CA-125 (*n* = 105): 21/105 (20%) ITT analysis: 21/135 (16%)

Trial: 30-57[27]

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
Author: Johnson & Johnson Pharmaceutical Research & Development **Objective** To compare the efficacy and safety of PLDH and paclitaxel in patients with epithelial ovarian carcinoma following failure of first-line platinum-based chemotherapy. **Trial ID:** 30-57 **Phase:** Phase III non-inferiority trial **Length of follow-up:** Treatment should have continued for up to 1 year in the absence of disease progression	**Number randomised** 438 planned enrolment; 216 randomised (PLDH n = 108, paclitaxel n = 108) **Disease type:** Epithelial **Disease stage:** Advanced **Therapy stage:** Second-line **Previous treatments** Chemotherapy (platinum-based first-line monotherapy regimen) **PLDH (n = 108)** Carboplatin alone: 63/108 (58.3%) Cisplatin alone: 35/108 (32.4%) Both: 10/108 (9.3%) Neither: 0 (0%) Prior anthracycline therapy: Yes: 10/108 (9.3%) No: 98/108 (90.7%) **Paclitaxel (n = 108)** Carboplatin alone: 58/108 (53.7%) Cisplatin alone: 39/108 (36.1%) Both: 10/108 (9.3%) Neither: 1/108 (0.9%) Prior anthracycline therapy: Yes: 15/108 (13.9%) No: 93/108 (86.1%) **Disease present after first-line treatment?** **Residual:** Yes **Refractory:** Yes	**Intervention (I)** **Type:** PLDH **No. randomised:** 108 **Route of administration:** i.v. **Dose:** 50 mg/m^2 as a 1-h infusion **No. of cycles:** at least 6 for participants who responded **Length per cycle:** 28 days **Control (C)** **Type:** Paclitaxel **No. randomised:** 108 **Route of administration:** i.v. **Dose:** 175 mg/m^2 as a 3-h infusion **No. of cycles:** at least 6 for participants who responded **Length per cycle:** 21 days All paclitaxel-treated participants were to be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to paclitaxel administration **Comments about intervention/control** Participants with ongoing clinical benefit were to have continued on the study drug as long as it was in their interest and in the absence of severe toxicity. Participants exhibiting a CR were to have received 2 subsequent cycles of treatment. Participants exhibiting PR were to have continued to receive study drug as long as therapeutic benefit was derived, with it recommended they received at	**Withdrawals from intervention (I)** **PLDH:** Disease progression: 42/108 (38.9%) Death: 12/108 (11.1%) Adverse event: 18/108 (16.7%) Lost to-follow up: 0 (0%) Other/unknown: 10/108 (9.3%) Completed protocol treatment: 26/108 (24.1%) **Withdrawals from control (C)** **Paclitaxel** Disease progression: 30/108 (27.8%) Death: 5/108 (4.6%) Adverse event: 7/108 (6.5%) Lost to-follow up: 1/108 (1.0%) Other/unknown: 12/108 (11.1%) Completed protocol treatment: 53/108 (49.1%) The majority of participants who discontinued from treatment for 'other' reasons did so because of the investigator's choice, patient choice or both **Adverse events** **PLDH (n = 108)** **Body as a whole** Asthenia: All grades: 42/108 (38.9%) Grade 3: 4/108 (3.7%) Grade 4: 0 (0%) Abdominal pain:	**Authors' conclusions** In this population of women with epithelial ovarian cancer whose disease did not respond to or relapsed after first-line platinum-based therapies, overall survival appears to be similar for participants treated with PLDH or paclitaxel. PLDH treatment was less often associated with alopecia and grade 3–4 haematological adverse events than paclitaxel treatment. Grade 3–4 hand–foot syndrome (PPE) and stomatitis were more frequently associated with PLDH treatment **Comments** The study was terminated early owing to poor patient accrual after paclitaxel was approved for use in combination with platinum-based therapy for first-line treatment by the European Agency for the Evaluation of Medicinal Products

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Characteristics **PLD (*n* = 108)** **Age (years):** Mean (SD): 58.4 Median: 60.5 (range 27–80) <65: 74/108 (68.5%) >65: 34/108 (31.5%) **Race** White: 105/108 (97.2%) Black: 0 (0%) Hispanic: 2/108 (1.9%) Asian: 1/108 (0.9%) **CA-125 at baseline (U/ml) (*n* = 105)** Mean (SD): 1165.69 (2117.529) Median: 470.00 (range 7.0–14513.0) **Histological tumour type** Serious papillary: 29/105 (26.9%) Mucinous: 0 (0%) Unspecified adenocarcinoma: 12/105 (11.1%) Not specified: 67/105 (62%) **Histological tumour grade** Moderate differentiated: 1/108 (0.9%) Poorly differentiated: 12/108 (11.1%) Unspecified differentiated: 28/108 (25.9%) Not specified: 67/108 (62%) **Ascites at baseline** Absent: 70/108 (64.8%) Present: 38/108 (35.2%) Not available: 0 (0%) **Platinum sensitivity** Platinum-sensitive: 44 (40.7%) Platinum-refractory: 64 (59.3%)	least 3 subsequent cycles of study drug No concurrent investigational agents or antineoplastic agents were permitted. The prophylactic use of haematopoietic cytokines was discouraged in conjunction with the first dose of study drug. Their use was recommended in subsequent cycles under specific circumstances: in participants with prolonged neutropenia (grade 4 neutropenia lasting >7 days, or failure of ANC to recover within 22 days), or the occurrence of febrile neutropenia in a prior cycle of treatment. Pyridoxine (B_6) was recommended for the treatment of hand–foot syndrome symptoms **Actual study treatment administration** **PLDH (*n* = 108)** **Cumulative dose (mg/m^2)** Mean (SD): 205.56 (121.998) Median: 199.99 (range 49–800) **Mean dose intensity (mg/m^2 per week) (*n* = 92)** Mean (SD): 11.09 (1.261) Median: 85.0 (range 1–448) **Days on drug (*n* = 92)** Mean (SD): 98.7 (77.05) Median: 85.0 (1–448) **Paclitaxel (*n* = 108)** Cumulative dose (mg/m^2) (*n* = 108) Mean (SD): 999.89 (392.622)	All grades: 34/108 (31.5%) Grade 3: 12/108 (11.1%) Grade 4: 0/ (0%) Fever: All grades: 28/108 (25.9%) Grade 3: 7/108 (6.5%) Grade 4: 0 (0%) Pain: All grades: 24/108 (22.2%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) Infection: All grades: 23/108 (21.3%) Grade 3: 2/108 (1.9%) Grade 4: 1/108 (0.9%) Headache: All grades: 12/108 (11.1%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) Ascites: All grades: 11/108 (10.2%) Grade 3: 6/108 (5.6%) Grade 4: 0 (0%) Backpain: All grades: 11/108 (10.2%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) **Cardiovascular system** Vasodilatation: All grades: 5/108 (4.6%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) **Digestive system** Nausea: All grades: 56/108 (51.9%) Grade 3: 6/108 (5.6%) Grade 4: 1/108 (0.9%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	Bulky disease Present: 61/108 (56.5%) Absent: 47/108 (43.5%) **Platinum sensitivity/bulky disease** Refractory/present: 37/108 (34.3%) Refractory/absent: 27/108 (25.0%) Sensitive/present: 24/108 (22.2%) Sensitive/absent: 20/108 (18.5%) **KPS at baseline** <80: 11/108 (10.2%) >80: 95/108 (88%) Not available: 2/108 (1.9%) **FIGO staging at initial diagnosis** 1: 10/108 (9.3%) 2: 11/108 (10.2%) 3: 64/108 (59.3%) 4: 22/108 (20.4%) Not available: 1/108 (0.9%) **Treatment-free interval (months)** Mean (SD): 9.0 (9.98) Median: 6.6 (1.0 – 69.4) **Sum of lesions at baseline (cm^2) (*n* = 107):** Mean (SD): 68.5 (111.72) Median: 30.0 (range 0.7–900) **Paclitaxel (*n* = 108)** **Age (years):** Mean (SD): 59.5 (10.79) Median: 61.0 (range 20–78) <65: 68/108 (63.0%) >65: 40/108 (37.0%) **Race (*n* = 108):** White: 105/108 (97.2%) Black: 1/108 (0.9%) Hispanic: 0 (0%) Asian: 2/108 (1.9%)	Median: 1049.8 (range 175–2221.1) **Mean dose intensity (mg/m^2 per week) (*n* = 104)** Mean (SD): 52.74 (4.787) Median: 54.69 **Days on drugs (*n* = 104)** Mean (SD): 106.2 (50.13) Median: 106.0 (range 1–260) **Protocol deviations:** One participant randomised to paclitaxel was classified as having platinum-sensitive disease. It was later discovered that the participant had never received prior platinum therapy. **Definition of response** Complete response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions and no disease-related symptoms. Partial response (PR): A >50% decrease in the sum of the products of bidimensional perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions Stable disease: Does not qualify for CR, PR or progression. Progressive disease (PD): A >50% increase in the sum of the products of bidimensionally measured lesions over the smallest sum observed (over baseline, if no increase), or reappearance of any lesion that had disappeared, or clear worsening of any evaluable disease, or failure to	Stomatitis: All grades: 52/108 (48.1%) Grade 3: 11/108 (10.2%) Grade 4: 0 (0%) Vomiting: All grades: 37/108 (34.3%) Grade 3: 10/108 (9.3%) Grade 4: 2/108 (1.9%) Constipation: All grades: 30/108 (27.8%) Grade 3: 4/108 (3.7%) Grade 4: 0 (0%) Diarrhoea: All grades: 23/108 (21.3%) Grade 3: 3/108 (2.8%) Grade 4: 0 (0%) Anorexia: All grades: 18/108 (16.7%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) Dyspepsia: All grades: 14/108 (13.0%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) **Haemic and lymphatic system** Neutropenia: All grades: 18/108 (16.7%) Grade 3: 6/108 (5.6%) Grade 4: 1/108 (0.9%) Anaemia: All grades: 17/108 (15.7%) Grade 3: 3/108 (2.8%) Grade 4: 0 (0%) Leukopenia: All grades: 15/108 (13.9%) Grade 3: 5/108 (4.6%) Grade 4: 1/108 (0.9%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	CA-125 at baseline (U/ml) (*n* = 102) Mean (SD): 1543.77 (3111.981) Median: 338.50 (range: 2.0–17374.0) **Histological tumour type (*n* = 102)** Serious papillary: 24/102 (23.5%) Mucinous: 1/102 (1%) Unspecified adenocarcinoma: 18/102 (17.6%) Not specified: 65/102 (64%) **Histologic tumour grade (*n* = 108)** Moderate differentiated: 6/108 (5.6%) Poorly differentiated: 13/108 (12.0%) Unspecified differentiated: 24/108 (22.2%) Not specified: 65/108 (60.2%) **Ascites at baseline** Absent: 69/108 (63.9%) Present: 38/108 (35.2%) . Not available: 1/108 (0.9%) **Platinum sensitivity** Platinum-sensitive: 41/108 (38%) Platinum-refractory: 67/108 (62%) **Bulky disease** Present: 56/108 (51.9%) Absent: 52/108 (48.1%) **Platinum sensitivity/bulky disease** Refractory/present: 36/108 (33.3%) Refractory/absent: 31/108 (28.7%) Sensitive/present: 20/108 (18.5%) Sensitive/absent: 21/108 (19.4%) **KPS at baseline** <80: 12/108 (11.1%) >80: 90/108 (83.3%) Not available: 6/108 (5.6%)	return for evaluation owing to death or deteriorating condition (unless clearly unrelated to this cancer), or appearance of any new lesion/site. For bone metastases, increased uptake on the scan does not constitute clear worsening of disease. Worsening of existing non-evaluable disease does not constitute progression	**Metabolic/nutritional disorder** Peripheral oedema: All grades: 14/108 (13.0%) Grade 3: 0 (0%) Grade 4: 0 (0%) **Musculoskeletal system** Myalgia: All grades: 4/108 (3.7%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) Arthralgia: All grades: 2/108 ((1.9%) Grade 3: 0 (0%) Grade 4: 0 (0%) **Nervous system** Paresthesia: All grades: 15/108 (13.9%) Grade 3: 0 (0%) Grade 4: 0 (0%) Somnolence: All grades: 11/108 (10.2%) Grade 3: 3/108 (2.8%) Grade 4: 0 (0%) **Respiratory system** Dyspnoea: All grades: 18/108 (16.7%) Grade 3: 6/108 (5.6%) Grade 4: 1/108 (0.9%) Pharyngitis: All grades: 8/108 (7.4%) Grade 3: 0 (0%) Grade 4: 0 (0%) **Skin and appendages** Hand–foot syndrome: All grades: 55/108 (50.9%) Grade 3: 16/108 (14.8%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	FIGO staging at initial diagnosis 1: 10/108 (9.3%) 2: 8/108 (7.4%) 3: 77/108 (71.3%) 4: 13/108 (12.0%) Not available: 0 (0%) **Treatment-free interval (months)** Mean (SD): 11.1 (17.34) Median: 6.7 (range: 0.9–109.1) **Sum of lesions at baseline (cm^2) (n = 107)** Mean (SD): 50.7 (60.95) Median: 32.5 (range: 1.1–420.0) **Inclusion/exclusion criteria** Participants with histologically proven epithelial ovarian carcinoma with measurable disease; a recurrence of disease or disease progression indicative of failure of first-line platinum-based chemotherapy; Karnofsky performance status (KPS) >60%; age >18 years; adequate bone marrow function: platelets >100,000/mm^3, haemoglobin > 9 g/dl and absolute neutrophil count (ANC) >1500 cells/mm^3; adequate renal function: creatinine <2.5 mg/dl (<220 µmol/l); adequate liver function: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <2 times upper limit or normal, alkaline phosphatase <2.0 times upper limit of normal, except if attributed to tumour, and bilirubin <upper limit of normal. Cardiac (left ventricular) ejection fraction (LVEF) <50% determined by multiple-gated acquisition (MUGA) scan (or within normal range for assessing institution); disease-free prior		Grade 4: 1/108 (0.9%) Alopecia: All grades: 47/108 (43.5%) Grade 3: 3/108 (2.8%) Grade 4: 0 (0%) Rash: All grades: 15/108 (13.9%) Grade 3: 2/108 (1.9%) Grade 4: 0 (0%) **Paclitaxel (n = 108)** **Body as a whole** Asthenia: All grades: 36/108 (33.3%) Grade 3: 6 /108 (5.6%) Grade 4: 1/108 (0.9%) Abdominal pain: All grades: 35/108 (32.4%) Grade 3: 7/108 (6.5%) Grade 4: 0 (0%) Fever: All grades: 8/108 (7.4%) Grade 3: 3/108 (2.8%) Grade 4: 0 (0%) Pain: All grades: 24/108 (22.2%) Grade 3: 3/108 (2.8%) Grade 4: 0 (0%) Infection: All grades: 10/108 (9.3%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) Headache: All grades: 13/108 (12.0%) Grade 3: 2/108 (1.9%) Grade 4: 0 (0%) Ascites: All grades: 8/108 (7.4%) Grade 3: 1/108 (0.9%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	malignancies for >5 years with exception of curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix were included. Participants were excluded who were pregnant or breast-feeding; life expectancy <3 months; prior radiation therapy to more than one-third of haematopoietic sites within 30 days prior to first dose of study drug; history of cardiac disease, with New York Heart Association Class II or greater with congestive heart failure; uncontrolled systemic infection; any investigational agent within 30 days of first dose of study drug; prior therapy with PLDH or paclitaxel; prior chemotherapy within 28 days of first dose of study drug (or 42 days if participant had received a nitrosourea or mitomycin); treated with high-dose therapy supported by bone marrow or peripheral stem cell transplantation at any time **Comments about participants** Patients were prospectively stratified based on platinum sensitivity and the presence or absence of bulky disease and were to have been analysed retrospectively for prior anthracycline therapy. Participants who had initially responded to platinum-based therapy and who had a progression-free interval of >6 months off treatment were classified as platinum-sensitive. Participants who		Grade 4: 0 (0%) Backpain: All grades: 14/108 (13%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) **Cardiovascular system** Vasodilatation: All grades: 13/108 (12.0%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) **Digestive system** Nausea: All grades: 47/108 (43.5%) Grade 3: 2/108 (1.9%) Grade 4: 0 (0%) Stomatitis: All grades: 12/108 (11.1%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) Vomiting: All grades: 34/108 (31.5%) Grade 3: 4/108 (3.7%) Grade 4: 0 (0%) Constipation: All grades: 41/108 (38.0%) Grade 3: 5/108 (4.6%) Grade 4: 0 (0%) Diarrhoea: All grades: 24/108 (22.2%) Grade 3: 3/108 (2.8%) Grade 4: 0 (0%) Anorexia: All grades: 11/108 (10.2%) Grade 3: 0 (0%) Grade 4: 0 (0%) Dyspepsia: All grades: 11/108 (10.2%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
	progressed during treatment, or who had stable disease in response to initial platinum-based therapy, or whose disease relapsed within 6 months of cessation of therapy were classified as having platinum-refractory disease. Bulky disease was defined as the presence of a tumour mass that was >5 cm in size		Grade 3: 0 (0%) Grade 4: 0 (0%) **Haemic and lymphatic system** Neutropenia: All grades: 23/108 (21.3%) Grade 3: 10/108 (9.3%) Grade 4: 3/108 (2.8%) Anaemia: All grades: 23/108 (21.3%) Grade 3: 5/108 (4.6%) Grade 4: 0 (0%) Leukopenia: All grades: 21/108 (19.4%) Grade 3: 9/108 (8.3%) Grade 4: 0 (0%) **Metabolic/nutritional disorder** Peripheral oedema: All grades: 15/108 (13.9%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) **Musculoskeletal system** Myalgia: All grades: 31/108 (28.7%) Grade 3: 7/108 (6.5%) Grade 4: 0 (0%) Arthralgia: All grades: 23/108 (21.3%) Grade 3: 2/108 (1.9%) Grade 4: 0 (0%) **Nervous system** Paresthesia: All grades: 47/108 (43.5%) Grade 3: 4/108 (3.7%) Grade 4: 0 (0%) Somnolence: All grades: 17/108 (15.7%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
			Grade 3: 2/108 (1.9%) Grade 4: 0 (0%) **Respiratory system** Dyspnoea: All grades: 15/108 (13.9%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) Pharyngitis: All grades: 18/108 (16.7%) Grade 3: 0 (0%) Grade 4: 0 (0%) **Skin and appendages** Hand–foot syndrome: All grades: 13/108 (12.0%) Grade 3: 0 (0%) Grade 4: 0 (0%) Alopecia: All grades: 94/108 (87.0%) Grade 3: 20/108 (18.5%) Grade 4: 1/108 (0.9%) Rash: All grades: 19/108 (17.6%) Grade 3: 1/108 (0.9%) Grade 4: 0 (0%) **Dosing adjustments** **PLDH (*n* = 108)** Participants with delayed, interrupted or reduced doses: 56/108 (51.9%) Doses delayed, interrupted or reduced: 109 Reason for delay or interruption: Hand–foot syndrome: 21/108 (19.4%) Stomatitis/mucositis: 12/108 (11.1%)	

continued

Study details and design	Participant details	Intervention details	Follow-up/withdrawals and adverse events	Conclusion and comments
			Haematological toxicity: 6/108 (5.6%) Other laboratory toxicity: 0 (0%) Infusion reaction: 10/108 (9.3%) Intercurrent illness: 8/108 (7.4%) Scheduling problem: 2/108 (1.9%) Other/unknown: 22/108 (20.4%) **Paclitaxel (*n* = 108)** Participants with delayed, interrupted or reduced doses: 51 (47.2%) Doses delayed, interrupted or reduced: 76 Reason for delay or interruption: Hand–foot syndrome: 1/108 (0.9%) Stomatitis/mucositis: 1/108 (0.9%) Haematological toxicity: 7/108 (6.5%) Other laboratory toxicity: 1/108 (0.9%) Infusion reaction: 3/108 (2.8%) Intercurrent illness: 9/108 (8.3%) Scheduling problem: 17/108 (15.7%) Other/unknown: 27/108 (25.0%)	

Results

Outcome 1

Outcome: Overall survival (not defined)

PLDH group (I)
Median overall survival: 46.6 weeks (range: 2.3–263.7+)
Number censored: 7.4

Paclitaxel group (C)
Median overall survival: 56.3 weeks (range: 1.4–211.4)
Number censored: 6.5
HR = 0.931 (95% CI: 0.702 to 1.234); (p = 0.618)

Platinum-sensitive disease
PLDH (n = 44)
Median overall survival: 65.4 weeks (range: 3.9–263.7+)
Number censored: 13.6

Paclitaxel (n = 41)
Median overall survival: 57.0 weeks (range: 1.4–172.3)
Number censored: 7.3
HR = 1.051 (95% CI: 0.663 to 1.667); p = 0.833

Platinum-refractory disease
PLDH (n = 64):
Median overall survival: 36.7 weeks (range: 2.3–242.1+)
Number censored: 3.1

Paclitaxel (n = 67):
Median overall survival: 54.3 weeks (range: 1.7–211.4+)
Number censored: 6.0
HR = 0.865 (95% CI: 0.605 to 1.237); (p = 0.427)

Appendix 7

Trials only available in abstract form

Meeting: 2003 ASCO Annual Meeting
Category: Gynecologic Cancer
Subcategory: Gynecologic Cancer

Randomised phase II study of carboplatin (C) versus paclitaxel–carboplatin (PC) in platinum-sensitive (PS) recurrent advanced ovarian carcinoma (AOC) with assessment of quality of life (QoL): a GEICO (Spanish Group for Investigation on Ovarian Carcinoma) study

Abstract No: 1812
Citation: *Proc Am Soc Clin Oncol 2003*; **22**: 451, (abstr 1812)

Authors: AA Gonzalez Martin, E Calvo, I Bover, MJ Rubio, A Arcusa, A Casado, B Ojeda, C Balana, MC Gonzalez, A Herrero, A Pelegri, A Cervantes; Hospital Universitario Ramon y Cajal, Madrid; Hospital Virgen del Rocio, Seville; Hospital Sant Joan, Reus; Hospital Reina Sofia, Cordoba; Hospital de Terrasa, Barcelona; Hospital Clinico San Carlos, Madrid; Hospital Sant Creu i Sant Pau, Barcelona; Hospital Trias i Pujol de Badalona, Barcelona; Hospital Virgen de la Luz, Cuenca, Spain; Hospital Miguel Servet, Zaragoza, Spain

Abstract: The role of platinum (P)-based polychemotherapy (CT) versus monotherapy with P in PS recurrent AOC is not well known because of the small number of randomised clinical trials in this context. Our objective was to determine if PC is superior to C in terms of response rate measured by CT scan and/or CA-125 criteria. Methods: Pts with recurrent AOC, <3 previous CT lines, P-based CT in the last treatment, and a P-free interval (PFI) of more than 6 months (m), were randomised to C AUC = 5 (A) or P 175 mg/m^2 plus C AUC = 5 (B), both every 21 days for 6 cycles. Stratification between 1 or 2 previous lines and 6–12 or >12 m PFI was made. Results: 80 pts have been included from May 2000 and data of the first 77 pts have been analysed (38 A/39 B). 74 pts are valuable for toxicity (38/36). 3 pts randomised to PC did not receive any cycle but had been included in the intent-to-treat analysis. No differences in significant prognostic factors except for more ECOG 2 pts in A (18.4% vs 2.6%; $p = 0.056$). Median PFI was (A/B) 14 m and 13 m. 379 cycles have been administered with a median of 3 in both arms. NCI-CTC haematological toxicities included (% of pts C/PC): anaemia (15.8/5.6), neutropenia (10.5/19.4) and thrombocytopenia (13.1/2.8). NCI-CTC non-haematological toxicity grade 2–4 (% pts C/PC): Carboplatin allergy (5.3/16.6), vomiting (26.3/13.9), mucositis (0/16.7; $p = 0.02$), neurosensory (2.6/19.4; $p = 0.051$), arthralgia–myalgia (7.9/36.1; $p = 0.003$), asthenia (15.7/25). The intent-to-treat overall response rate was 52.6 % with C (21% CR + 31.6% PR) and 74.4% with PC (23.1% CR + 51.3% PR), $p = 0.047$. PD was observed in 31.6% with C and 5.1% with PC ($p = 0.002$). Median time to progression has not been reached with PC. QoL analysis is ongoing. Conclusions: PC polychemotherapy seems superior to C monotherapy in terms of response rate, with an acceptable toxicity profile. Mature survival data and QoL analysis are necessary to consider PC as the treatment of choice in PS recurrent AOC.

Meeting: 2000 ASCO Annual Meeting
Category: Gynecologic Cancer
SubCategory: Gynecologic Cancer

Randomised trial comparing paclitaxel + doxorubicin (AT) versus paclitaxel (T) as second line therapy for advanced ovarian cancer (AOC) patients in early progression after platinum based chemotherapy

Abstract No: 1506

Authors: V Torri, I Floriani, A Tinazzi, P Franco Conte, A Ravaioli, M Grazia Cantù, R Rossi, L Grassi, G Parma, N Colombo; Mario Negri Institute for Pharmacological Research, Milan, Italy; St Chiara Hospital, Division of Medical Oncology, Pisa, Italy; Department of Oncology, Infermi Hospital, Rimini, Italy; San Gerado Hospital of Monza, University of Milano, Italy; Department of Psychology, University of Vermont, Burlington, USA; European Institute of Oncology, Milan, Italy.

Abstract: From October 1994 to June 1999, 234 patients from 35 Italian hospitals have been randomised into a study aimed at evaluating the role of AT (doxorubicin (A): 80 mg/m^2 iv q 21 days × 4–6 cycles; paclitaxel (T): 175 mg/m^2, 3 hours infusion q 21 days × 4–6 cycles) vs. T (paclitaxel (T): 175 mg/m^2, 3 hours infusion q 21 days × 4–6 cycles), as second line therapy for AOC patients. Patients in progressive disease within

12 months from the end of first-line platinum based-therapy, were eligible for the study. At the time of this analysis, 96 out of 118 (81%) patients in AT arm and 90 out of 116 in T arm (78%) are evaluable for the analysis. Platinum-based monochemotherapy was the first-line treatment in 42% patients, while polychemotherapy containing A was the preferred first-line therapy in 26% patients. Median duration of first-line therapy was 4 months, median time from the end of first line therapy to randomisation was 5 months (range 3–12). Seventy-eight percent in T arm and 72% of patients in AT arm received at least 4 cycles of therapy. Treatment was completed without modification in 48% and 28% of T and AT patients respectively. Haematological toxicity was significantly more common in AT patients (grade 3–4 reduction in WBC count: 24% in AT vs. 7% in T arm). Neuropathies were similar in both arms (Sensory: 15% WHO grade 2 or 3, Motor: 4% grade 2 or 3). Objective response was achieved in 54% of patients in T and in 52% of patients in AT arm. At a median follow-up time of 24 months, a total of 150 patients have progressed and 124 have died. Survival analysis showed no evidence of a difference between AT and T (median time to progression: 6.6 and 7.5 months, median survival: 12 and 14 months for AT and T respectively; hazard ratio for mortality of AT vs. T: 1.17 [95% CI 0.82–1.66] $p = 0.39$). AT is not more effective than T in AOC patients refractory to platinum-based chemotherapy.

Meeting: 2001 ASCO Annual Meeting
Category: Gynecologic Cancer
SubCategory: Gynecologic Cancer

Multicenter randomized Phase II study of oxaliplatin (OXA) or topotecan (TOPO) in platinum-pretreated epithelial ovarian cancer (EOC) patients (pts)

Abstract No: 847
Authors: JB Vermorken, M Gore, T Perren, I Vergote, N Colombo, P Harper, G Rustin, A Bonetti, P Zola, N Le Bail, S Brienza; UZ Antwerpen, EDEGEM, Belgium; Royal Marsden Hospital, London, UK; Saint James's University Hospital, Leeds, UK; UZ Gasthuisberg, Leuven, Belgium; Instituto Europeo di Oncologia, Milan, Italy; Guy's Hospital, London, UK; Mount Vernon Hospital, Northwood, UK; Azienda Ospedaliera di Verona, Verona, Italy; Università di Torino, Turin, Italy; Sanofi-Synthélabo Recherche, Paris, France; Debioclinic SA, Charenton le Pont, France

OXA, a new DACH platinum (Pt) with preclinical evidence of partial non cross-resistance with Cisplatin/Carboplatin, has shown in a previous randomized phase II study (JCO, 2000 Mar;18(6):1193–202) similar activity and favorable safety profile when compared to taxol (TAX) in heavily pretreated EOC pts. We conducted a randomized phase II trial to evaluate OXA 130 mg/m^2 day (D)1/q 3 wks vs TOPO 1.5 mg/m^2 D1 to D5/ q 3 weeks. Eligibility criteria included a relapsing progressive EOC, pretreatment with 1 or 2 prior Pt chemotherapy lines (Pt free-interval(PFI) <12 months), bidimensionally measurable disease, WHO performance status (PS) 0–2, adequate hematologic and renal functions. Stratification factors were: institution, PS 0–1 vs 2, PFI 0–6 mos ("refractory" pts) or 6–12 mos ("potentially sensitive" pts), number of prior Pt based regimens (1 vs 2), prior TAX (yes vs no). The primary endpoint was response rate (RR), with time to progression, overall survival, safety and quality of life as secondary endpoints. Efficacy was evaluated by radiological assessment every 6 wks and externally reviewed; responses were confirmed at least 4 wks later. 158 pts were randomized, 156 treated and evaluable for toxicity (78 pts in each arm). Pts characteristics were well balanced between the two arms. Results: the confirmed RR were 11.4% (9/79) for OXA vs 8.9% (7/79) for TOPO. The confirmed RR in Pt-refractory pts were 3.9% (2/51) for OXA and 5.7% (3/53) for TOPO. Discontinuations due to treatment-related adverse events (AE) occurred in 4 pts in each arm. There were no treatment-related deaths with OXA vs 2 with TOPO. Main AEs are shown in the table below. Conclusion: the favorable safety profile combined with the similar activity observed in this study supports the role of OXA in patients failing Pt-based chemotherapy. Final results will be presented at the meeting. Sponsors: Sanofi-Synthelabo Recherche/Debiopharm SA.

Toxicities (NCI-CTC grade 3–4)	OXA ($n = 78$) % pts	TOPO ($n = 78$) % pts
Neutropenia	3.9	94
Febrile neutropenia	0	23
Thrombocytopenia	5.2	43.6
Alopecia	0	24.4
Diarrhea	11,6	3.6
Vomiting	19.2	6.4
Neurosensory	23	3.9

Appendix 8

Economics included studies

Included/excluded studies

Study	Details	Include/exclude
Ojeda, 2003[51]	Cost-minimisation in 2nd line Frequency and cost of adverse events	Include
Neymark, 2002[168]	Cost-effectiveness in 1st line	Exclude
Smith, 2001[226] Abstract[50]	Cost-minimisation 2nd line	Exclude
Fireman, 2000[160]	Review	Exclude
Szucs, 2003[170]	Review	Exclude
Capri, 2003[52]	Cost minimisation in 2nd line Frequency and cost of adverse events	Include
Bodurka-Bevers, 2000[162]	Review Some information about appropriate treatments	Exclude
Young, 2001[178]	Review + model of 1st line Useful information on how to model for 2nd line	Exclude
Smith, 2002[50]	Cost-minimisation (reports results of survival analysis) in 2nd line UK costs and resource use	Include
Girre, 2003[227]	Cost minimisation in 2nd line	Exclude
Karlsson, 2001[86]	Review	Exclude
Prasad, 2004[53]	Cost analysis in 2nd line	Include
Doyle, 2001[156]	Cost analysis in 2nd/3rd line	Exclude
Anonymous, 2001[118]	Review	Exclude
Woronoff-Lemsi, 2001[147] Abstract	Cost minimisation in 1st line	Exclude
Sun, 2002[107]	Review QoL	Exclude
Le, 2004[158]	Review QoL	Exclude
Anon, 2001[167]	Review of drug prices	Exclude
Calhoun, 2000[198] Abstract	Review of toxicity costs	Exclude
Smith, 2001[228] Abstract[50]	Cost-effectiveness of 2nd line	Exclude
Ortega, 1997[69]	Cost–utility of 1st line	Exclude

Review of Smith and colleagues:[50] A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and the UK

Authors	Smith DH, Adams JR, Johnston SR, Gordon A, Drummond MF, Bennett CL.
Date	2002
Type of economic evaluation	Cost-minimisation
Currency used	US$ (UK costs also reported in US$)
Year to which costs apply	2000
Perspective used	Payer in USA and UK
Time frame	In absence of disease progression, treatment continued for up to 1 year
Comparators	PLDH and topotecan
Source(s) of effectiveness data	Gordon *et al*.[22]
Source(s) of resource use data	As above + expert opinion (USA and UK) to estimate the resource use associated with adverse events – method not described. Inpatients' stays due to adverse events were only counted for those experiencing events graded 3 or 4, to account for likely excess of protocol admissions
Source(s) of unit cost data	UK: drug costs from BNF (British Medical Association. *British National Formulary*. Vol. 37. London: BMJ Books; 1999) Blood products from the National Blood Authority, 2000 Tariff (reference not given) Inpatient stays from a national costing database of hospital trusts (NHS Executive. *The New NHS 1999 Reference Costs (CD-ROM)*. Catalogue no. 10756. Leeds: NHS Executive; 1999) Intensive care unit cost from UK study (Edbrooke D, Hibbert C, Kingsley J, Smith S, Bright NM, Quinn JM, *et al*. "The patient-related costs of care for sepsis patients in a United Kingdom adult general intensive care." *Crit Care Med* 1999;**27**:1760–7) Costs of outpatient visits and chemotherapy administration taken from tariffs at a UK cancer centre (reference not given) USA: costs were taken from prior studies looking at costs of cancer care (Stinson TJ, Calhoun E, Yang T, Lurain JR, Bennett CL, *et al.* Cost analysis of second-line therapies for platinum-refractory ovarian cancer: reimbursement dilemmas for Medicare patients. *Cancer Invest* 1999;**17**:559–65)
Modelling approach used	Resource use extrapolated between settings (Europe to USA and vice versa). Ordinary least squares (OLS) regression used to predict patient-specific resource use for specific items Resource use for the 35 patients with missing data was imputed as a zero cost from time of censoring
Summary of effectiveness results	Gordon *et al*.[22]
Summary of cost results	Total cost per person in topotecan was $12,325 higher in North American group and $2909 higher in European group than PLDH. This cost difference was mainly due to increased cost of hospitalisations, management of neutropenia and blood transfusions for topotecan
Summary of cost-effectiveness results	Costs and outcomes not combined
Sensitivity analysis	Some variation in resource use is lost by not using patient-specific estimates, therefore a sensitivity analysis was undertaken using only local patients to estimate resource use. In the North American analysis PLDH was cost saving in all of the bootstrap replicates. In the European analysis PLDH was cost saving in 89% of the bootstrap replicates Given that PLDH was less costly, a sensitivity analysis was undertaken such that all assumptions were in favour of topotecan. In the North American sensitivity analysis PLDH is always cost saving. In the European sensitivity analysis PLDH is cost saving 93% of the time.
Main conclusions	In this clinical trial of second-line ovarian cancer treatments, PLDH in comparison with topotecan was associated with similar clinical outcomes, different toxicity profiles and higher acquisition costs, but lower toxicity management cost, leading to lower overall cost of care Setting also appears to play an important part in assessing costs

Review of Ojeda and colleagues:[51] Cost-minimisation analysis of pegylated liposomal doxorubicin hydrochloride versus topotecan in the treatment of patients with recurrent epithelial ovarian cancer in Spain

Authors	Ojeda B, de Sande LM, Casado A, Merino P, Casado MA
Date	2003
Type of economic evaluation	Cost minimisation
Currency used	Euros
Year to which costs apply	2001
Perspective used	Health service
Time frame	In absence of disease progression treatment continued for up to 1 year
Comparators	PLDH and topotecan
Source(s) of effectiveness data	Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2004;**19**:3312–22 Trial included 474 ovarian cancer patients who had failed first-line therapy with a platinum-based agent (cisplatin or carboplatin) This trial was used to support the fact that there was no significant difference in survival between the two treatments and provide the resource use and adverse events associated with them.
Source(s) of resource use data	As above + expert opinion to estimate the resource use associated with adverse events – methods to derive opinion not described
Source(s) of unit cost data	Costs of drugs from Spanish catalogue of medicinal products Unit costs of procedures and tests from Spanish database of sanitary costs (SOIKOS, *Base de datos de costes sanitarios*, 2001) and published literature (not referenced)
Modelling approach used	No modelling undertaken
Summary of effectiveness results	Overall PFS was 113 for PLDH and 117 for topotecan. Overall response was 19.7% for PLDH and 17% for topotecan. The difference between PLDH and topotecan was more marked in platinum-sensitive patient. Median PFS was 28.9 and 23.3 weeks for PLDH and topotecan, respectively
Summary of cost results	Total costs = differ significantly between PLDH and topotecan: PLDH = 9614 , topotecan = €11,824. This cost difference is mainly due to the increase in adverse events associated with topotecan
Summary of cost-effectiveness results	Not undertaken
Sensitivity analysis	Sensitivity analysis undertaken on length of hospitalisation, total number of cycles given, cost of antiemetics, lower dosage of study drug and assuming application of all changes in favour of topotecan Sensitivity analysis showed results were robust
Main conclusions	Total costs of drug administration per patient do not differ substantially between the two study drugs. However, the total costs show that costs are lower for PLDH. Sensitivity analysis shows that these results are robust There are some limitations, namely data for analysis taken from an efficacy study not designed to look specifically at resource use, adverse event resource use derived from expert opinion, QoL and patients, preferences not considered and indirect costs associated with the regimes have not been included

Review of Capri and Cattaneo:[52] Cost-minimisation analysis of pegylated liposomal doxorubicin versus topotecan for the treatment of ovarian cancer in Italy

Authors	Capri S, Cattaneo G
Date	2003
Type of economic evaluation	Cost minimisation
Currency used	Euros
Year to which costs apply	2002
Perspective used	Italian NHS
Time frame	In absence of disease progression treatment continued for up to 1 year
Comparators	PLDH and topotecan
Source(s) of effectiveness data	Gordon *et al*.[22]
Source(s) of resource use data	As above + expert opinion to estimate the resource use associated with adverse events – Delphi method used to derive estimates from 5 Italian oncologists
Source(s) of unit cost data	Drug costs from the drug formulary (*Drug formulary*. Milan: Masson; 2002) Medical visits and laboratory tests from national charges (Italian Ministry of Health. *National tariffs for tests and ambulatory services*. Rome: Italian Ministry of Health; 2002) Hospitalisations from the Italian DRG's reimbursement rates (Italian Ministry of Health. *National tariffs for hospital stays–DRGs*. Rome: Italian Ministry of Health; 2002)
Modelling approach used	No modelling undertaken
Summary of effectiveness results	Gordon *et al*.[22]
Summary of cost results	Mean total costs per patient were €8812 for PLDH and €15,788 for topotecan. This cost difference is mainly due to the increase in adverse events associated with topotecan
Summary of cost-effectiveness results	Not undertaken
Sensitivity analysis	Sensitivity analysis undertaken on resource use associated with adverse events, using minimum and maximum values (source not specified). Sensitivity analysis showed a broad variation in mean costs per patient for both treatments; however, the conclusion that PLS was less costly did not change
Main conclusions	Present analysis suggests the net cost-saving capability of PLDH which required fewer ambulatory care-centre visits for treatment administration and was associated with fewer severe adverse events than topotecan. The results of this analysis are consistent with those of a previous study using data from the USA and UK

Review of Prasad and colleagues:[53] Costs of treatment and outcomes associated with second-line therapy and greater for relapsed ovarian cancer

Authors	Prasad M, Ben-Porat L, Hoppe B, Aghajanian C, Sabbatini P, Chi DS, Hensley ML
Date	2004
Type of economic evaluation	Cost-effectiveness (?)
Currency used	US$
Year to which costs apply	Not stated
Perspective used	Not stated
Time frame	One course of chemotherapy. Time frame not stated
Comparators	Topotecan and gemcitabine
Source(s) of effectiveness data	Economic evaluation conducted alongside a cohort-study (not randomised) looking at single-agent chemotherapy with topotecan or gemacitabine as 2nd line therapy in patients with recurrent (progression or recurrence within or during 6 months of treatment) platinum- and paclitaxel-resistant ovarian cancer 56 patients received gemacitabine and 51 patients received topotecan. Topotecan was administered for 5 days every 21 days and gemacitabine was administered once a week for 3 weeks (1-week rest) Data on response available for 50/51 topotecan patients
Source(s) of resource use data	Resource use collected alongside the trial 5 patents receiving topotecan were not included in the cost analysis
Source(s) of unit cost data	Direct medical charges for the trial hospital were collected. These were then converted to true costs using institutional, departmental or resource use, category-specific ratios of charges to costs
Modelling approach used	Kaplan–Meier method used to estimate PFS and overall survival. Potential predictors of PFS and overall survival were investigated using the Cox proportional hazards model Multivariate logistic regression used to analyse the covariates associated with clinical benefit
Summary of effectiveness results	13 patients receiving gemacitabine displayed clinical benefit compared with 28 receiving topotecan Median time to progression was 1.8 months for gemacitabine and 3.6 months for topotecan Median overall survival was 8.2 months for gemacitabine compared with 16.8 months for topotecan Potential predictors of response (age, number of prior salvage regimes, time from last prior treatment for recurrent/persistent disease, duration of clinical remission) were evaluated for possible associations with clinical benefit, TTP and overall survival. There were no significant associations
Summary of cost results	Topotecan was significantly more expensive then gemacitabine. The mean patient cost per course was $28,098 for topotecan and $13,937 for gemacitabine. This was mostly due to the chemotherapy drug cost and delivery
Summary of cost-effectiveness results	Costs and outcomes were not combined
Sensitivity analysis	Sensitivity analysis was not undertaken
Main conclusions	The data suggest that topotecan and gemcitabine are both active as single agents and associated with moderate rates of objective clinical response and clinical benefit in heavily pretreated platinum- and paclitaxel-resistant patients

Review of GSK submission:[76] HycamtinT Topotecan Hydrochloride. National Institute for Clinical Excellence: Health Technology Re-appraisal

Author	GlaxoSmithKline
Date	2004
Type of economic evaluation	Cost minimisation
Currency used	UK£
Year to which costs apply	A unique price year was not given
Perspective used	UK NHS
Time frame	Treatment continued for up to 1 year
Comparators	Topotecan and PLDH
Source(s) of effectiveness data	Gordon *et al*.[22] Trial included 474 ovarian cancer patients who had failed first-line therapy with a platinum-based agent (cisplatin or carboplatin) This trial was used to support the fact that there was no significant different in survival between the two treatments and to provide resource use associated with adverse events (except neutropenia)
Source(s) of resource use data	An audit of current practice for relapsed ovarian cancer in UK was used to collect information on resource use. This audit included 9 UK centres and 92 patients receiving topotecan versus 60 patients receiving PLDH Mean drug dosage (for topotecan and PLD), number of treatment cycles, resource use associated to drug administration and management of neutropenia were directly taken from the audit. Resource utilisation associated with other adverse events was taken from the Gordon *et al*.[22] study and adjusted by audit data, assuming that lower drug doses would lead to a reduction in the rate of adverse events
Source(s) of unit cost data	Drug costs, blood products and inpatients stay were taken from the Smith study.[50] In this study the sources of unit costs were the following: Drug costs from BNF (British Medical Association. *British National Formulary*. Vol. 37. London: BMJ Books; 1999) Blood products from the National Blood Authority, 2000 Tariff (reference not given) Inpatient stays from a national costing database of hospital trusts (NHS Executive. *The New NHS 1999 Reference Costs (CD-ROM)*. Catalogue no. 10756. Leeds: NHS Executive; 1999). Outpatients visits, consultations and monitoring tests were instead taken from NHS Reference Costs 2003 and National Tariffs 2004 (reference not given)
Modelling approach used	No modelling undertaken
Summary of effectiveness results	The overall response rate was 19.7% in the PLDH group versus 17% in the topotecan group ($p = 0.39$), and the median PFS was 16.1 weeks versus 17.0 weeks, respectively ($p = 0.095$) and overall survival 60 weeks versus 56.7 weeks, respectively ($p = 0.341$). However, the difference between PLDH and topotecan was more marked in platinum-sensitive patients where the median PFS was 28.9 and 23.3 weeks for PLDH and topotecan, respectively ($p = 0.037$)
Summary of cost results	Total cost per patient was estimated as £7773.03 for topotecan and £8080.43 for PLDH. The higher drug costs for PLDH were only partly offset by lower administration costs and adverse event costs
Summary of cost-effectiveness results	Costs and outcomes not combined
Sensitivity analysis	No sensitivity analyses were performed
Main conclusions	Topotecan and PLDH were similar in terms of both costs and effectiveness data, although some differences in drug toxicity were found. It is inappropriate to recommend PLDH as preferred option and both treatments should be recommended as equal choices for second-line therapies of epithelial ovarian cancer

Review of Schering submission:[23] Caelyx (pegylated liposomal doxorubicin hydrocholoride) in the treatment of recurrent ovarian cancer in the United Kingdom

Author	Schering-Plough Ltd
Date	2004
Type of economic evaluation	Cost minimisation
Currency used	UK£
Year to which costs apply	A unique price year was not given
Perspective used	UK NHS
Time frame	Economic analysis performed on 1-year effectiveness data. Long-term follow-up (3 years) for health outcomes was also conducted.
Comparators	Topotecan and PLD
Source(s) of effectiveness data	Gordon *et al*.[22] Long-term follow-up efficacy analysis based on Gordon AN, Tonda M, Sun S, Rackoff W, Doxil Study 30-49 Investigators. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a Phase 3 randomised study of current and refractory epithelian ovarian cancer. *Gynecol Oncology* 2004;**95**(1)1–8.
Source(s) of resource use data	Drug mean dosage, number of treatment cycles and resource use for drug administration were directly taken from trial data. Expert opinion was used to estimate the resource use associated with adverse events
Source(s) of unit cost data	Drug costs from BNF (British Medical Association. *British National Formulary*. Vol. 37. London: BMJ Books; 1999) Blood products from the National Blood Authority, 2000 Tariff (reference not given) Inpatient stays from the 1999 CIPFA database (Institute of Public Finance. CIPFA/HFM Health Database; 1999) ICU based on literature (Edbrooke D, Hibbert C, Kingsley J, Smith S, Bright N, Quinn J. The patient-related costs of care for sepsis patients in a United Kingdom adult general intensive care. *Crit Care Med* 1999;**27**:1760–7) Outpatient clinical visit from a tariff at a UK cancer centre (no reference given)
Modelling approach used	No modelling undertaken
Summary of effectiveness results	Short-term results for topotecan and PLDH: Gordon *et al*.[22] The median survival times in a 3-year follow-up were 62.7 weeks for PLDH versus 59.7 weeks for topotecan with an HR that almost reached statistical significance ($p = 0.05$). The trend in favour of PLDH was more evident when platinum-sensitive patients were considered. In this group of patients, a statistically significant difference in median survival was found and a higher percentage of patients were alive at 2- and 3-year follow-up
Summary of cost results	Total costs per patient were £9957 for PLDH versus £12,610 for topotecan. This difference was statistically significant. The higher drug cost for PLDH was more than compensated by lower administration costs and lower costs associated with adverse events (in particular for neutropenia)
Summary of cost-effectiveness results	Costs and outcomes not combined
Sensitivity analysis	An extreme analysis favouring topotecan was conducted. PLDH remained statistically less costly than topotecan, showing the robustness of the base-case results
Main conclusions	PLDH was associated with similar clinical outcomes compared to topotecan in the short term but in a 3-year follow-up analysis it demonstrated survival advantage over topotecan. Although PLDH was associated with higher acquisition costs, the lower toxicity management cost and administration costs led to statistically significant lower total per patient costs for PLDH than topotecan. It was concluded that PLDH should be considered as the dominant option, being less costly and more effective

Review of Bristol-Myers Squibb submission:[77] Health technology appraisal of topotecan, pegylated liposomal doxorubicin, and paclitaxel for second-line or subsequent advanced ovarian cancer. A submission to the National Institute for Clinical Excellence

Author	Bristol-Myers Squibb Pharmaceutical Ltd
Date	2004
Type of economic evaluation	Cost-effectiveness
Currency used	UK£
Year to which costs apply	A unique price year was not given
Perspective used	UK NHS
Time frame	3 years
Comparators	Paclitaxel combined with a platinum agent, paclitaxel alone, topotecan and PLDH
Source(s) of effectiveness data	Evidence for paclitaxel/platinum was taken from the ICON4 study.[29] This was a multi-centre RCT including 802 platinum-sensitive ovarian cancer patients (relapsing after 6 months). Evidence for paclitaxel monotherapy and topotecan was taken from a study by ten Bokkel Huinink *et al*.[25] This was a multicentre RCT including 226 ovarian cancer women who had failed a previous platinum-based regimen Evidence for PLDH was taken from Forbes *et al*.,[39] a previous Schering-Plough submission to NICE All these studies were used to collect data on drug effectiveness, drug dosage and administration costs
Source(s) of resource use data	Study drug dosage and drug administration methods were taken from the studies mentioned above The number of treatment cycles for each therapy appears to have been based on the authors' assumptions The dose of carboplatin was based on the literature (Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Bumell M, Boxall RE, *et al*. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* **7**:1748–56) For paclitaxel, premedication therapies were based on product indications
Source(s) of unit cost data	Drug costs from BNF, Vol 47, 2004 Outpatient visit from PSSRU (Netten A, Curtis L. *Unit costs of health and social care*. PSSRU, University of Kent, Canterbury; 2000)
Modelling approach used	A model was constructed in order to calculate the life-years gained over 3 years from clinical trial survival curves. Life-years were estimated averaging the proportion of patients alive between two periods
Summary of effectiveness results	The proportion of patients alive at years 1, 2 and 3 were 78, 43 and 24%, respectively for paclitaxel/platinum, 50, 22 and 15% for paclitaxel alone, 56, 22 and 18% for topotecan and 56, 30 and 18% for PLDH. These survival rates led to 1.83 LYG with paclitaxel/platinum, 1.295 LYG with paclitaxel alone, 1.37 LYG with topotecan and 1.45 LYG with PLDH
Summary of cost results	Total per patient cost over 3 years (at 6% discount rate) was estimated at £25,287.79 for paclitaxel/platinum, £18,998.01 for paclitaxel alone, £30,297.51 for topotecan and £26,992.73 for PLDH
Summary of cost-effectiveness results	Paclitaxel/platinum was dominant compared with topotecan and PLDH, being less costly and associated with more LYG over 3 years. The combined therapy was relatively cost-effective compared with paclitaxel alone with an ICER of £12,120.07 per LYG
Sensitivity analysis	One-way sensitivity analyses were conducted, varying the discount rate for health benefits (from 0 to 6%). The base-case results were confirmed in these analyses. LYG was also varied by 15% but its impact was only assessed on ACERs and not on ICERs
Main conclusions	It was concluded that paclitaxel/platinum should be considered as the preferred option for treatment of platinum-sensitive ovarian cancer patients. It was dominant compared with topotecan and PLDH and cost-effective compared with paclitaxel monotherapy

Quality assessment economics published studies

	Capri and Cattaneo[52]	Prasad et *al.*[53]	Smith et *al.*[50]	Ojeda et *al.*[51]
Study question				
1. Costs and effects examined	× Assumption of equivalence between treatments based on data from a previously reported trial. Main clinical results were reported	✓ Cost-effectiveness results not reported	× Assumption of equivalence between treatments based on data from a previously reported trial. Main clinical results were reported	× Assumption of equivalence between treatments based on data from a previously reported trial. Main clinical results were reported
2. Alternatives compared	✓	✓	✓ PLDH vs topotecan	✓
3. The viewpoint(s)/ perspective of the analysis is clearly stated (e.g. NHS, society)	✓	×	✓	✓
Selection of alternatives				
4. All relevant alternatives are compared (including do nothing if applicable)	× Do nothing not appropriate. However, trial did not include palliative care as an option	× Topotecan not compared with multiple agent regimes	× Do nothing not appropriate. However, trial did not include palliative care as an option	× Do nothing not appropriate However, trial did not include palliative care as an option
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	× Doses not given	✓ Refers back to trial for full details	✓
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	×	✓ As in trial evidence	✓ Based on trial data
Form of evaluation				
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	✓
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	✓ In terms of overall survival; however, there were differences in subgroups of patients	NA	✓ In terms of overall survival; however, there were differences in subgroups of patients	✓ In terms of overall survival; however, there were differences in subgroups of patients

continued

	Capri and Cattaneo[52]	Prasad et *al.*[53]	Smith et *al.*[50]	Ojeda et *al.*[51]
Effectiveness data				
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	✓	✓	✓
10. Effectiveness data from RCT or review of RCTs	✓	× Non-randomised study	✓	✓
11. Potential biases identified (especially if data not from RCTs)	✓	×	✓	✓
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	NA	NA	NA
Costs				
13. All the important and relevant resource use included	× Indirect costs not included	× Indirect costs not included	× Indirect costs not considered	× Indirect costs not included
14. All the important and relevant resource use measured accurately (with methodology)	✓	✓	× Expert panel used to estimate resource use associated with adverse events. Methods used were not described	× Expert panel used to estimate resource use associated with adverse events. Methods used were not described
15. Appropriate unit costs estimated (with methodology)	✓	✓	✓	✓
16. Unit costs reported separately from resource use data	✓	×	✓	✓
17. Productivity costs treated separately from other costs	NA	NA	NA Not included	NA

continued

	Capri and Cattaneo[52]	Prasad et *al.*[53]	Smith et *al.*[50]	Ojeda et *al.*[51]
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	×	✓	✓
Benefit measurement and valuation				
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	NA	✓	✓	✓
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	NA	NA	NA	NA
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	NA	NA	NA
Decision modelling				
22. Details of any decision model used are given (e.g. decision tree, Markov model)	NA	NA	NA	NA
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	NA	NA	NA	NA
24. All model outputs described adequately	NA	NA	NA	NA
Discounting				
25. Discount rate used for both costs and benefits	NA	NA Resource use over 1 cycle of chemotherapy	NA Resource use up to 1 year	NA Resource use collected for up to 1 year

continued

	Capri and Cattaneo[52]	Prasad et *al.*[53]	Smith et *al.*[50]	Ojeda et *al.*[51]
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	NA	NA	NA	NA
Allowance for uncertainty				
Stochastic analysis of patient-level data				
27. Details of statistical tests and CIs are given for stochastic data	× Not undertaken	× Not undertaken	× Not undertaken	× Not undertaken
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	NA	NA	NA	NA
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytical decisions (e.g. methods to handle missing data)	NA	NA	NA	NA
Stochastic analysis of decision models				
30. Are all appropriate input parameters included with uncertainty?	NA	NA	NA	NA
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	NA	NA	NA	NA
32. Are the probability distributions adequately detailed and appropriate?	NA	NA	NA	NA

continued

	Capri and Cattaneo[52]	Prasad et *al.*[53]	Smith et *al.*[50]	Ojeda et *al.*[51]
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytical decisions (e.g. methods to handle missing data)	NA	NA	NA	NA
Deterministic analysis				
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	NA	Sensitivity analysis not undertaken	✓
35. The choice of variables for sensitivity analysis is justified	✓	NA	✓	✓
36. The ranges over which the variables are varied are stated	× Not specified	NA	✓	✓
Presentation of results				
37. Incremental analysis is reported using appropriate decision rules	×	NA	×	×
38. Major outcomes are presented in a disaggregated in addition to aggregated form	✓	✓	✓	✓
39. Applicable to the NHS setting	× Trial in USA. Costs from Italy	× Not directly applicable without adjustment for differences in clinical practice	× Costs in £UK not given	× Trial in US. Costs from Spain

✓, Item properly addressed; ×, item not properly addressed; NA, not clear.

Quality assessment industry-submitted studies

	GSK		Schering-Plough		Bristol-Myers Squibb	
Study question						
1. Costs and effects examined	×	It was assumed equivalence of efficacy between treatments based on results from a previous clinical trial. Few data from the trial were reported	✓		×	It was assumed equivalence of efficacy between treatments based on results from a previous clinical trial. Survival benefit for PLDH in the long term were reported
2. Alternatives compared	✓	PLDH and topotecan	✓	Pacitaxel, paclitaxel/carboplatin, PLDH and topotecan	✓	PLDH and topotecan
3. The viewpoint(s)/ perspective of the analysis is clearly stated (e.g. NHS, society)	✓	NHS	✓	NHS	✓	NHS
Selection of alternatives						
4. All relevant alternatives are compared (including do nothing if applicable)	✓	Do nothing is not an appropriate alternative. Paclitaxel was not considered because of lack of new data since last NICE guidance	✓	Do nothing is not an appropriate alternative	✓	Do nothing is not an appropriate alternative. Placlitaxel was not considered because of lack of new data
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	?	However, for some details the reader is referred to the original trial or the audit	✓		✓	However, for some details the reader is referred to the original trial or the audit
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓		✓		✓	
Form of evaluation						
7. The choice of form of economic evaluation is justified in relation to the questions addressed	×		✓		✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	✓	In terms of overall survival differences were found in subgroup analyses; also different toxicity profiles were found between the two treatments	NA		?	In terms of overall survival, differences were found in subgroup analyses; also different toxicity profiles were found between the two treatments. Survival benefits for PLDH were found in the long-term follow-up

continued

	GSK		Schering-Plough		Bristol-Myers Squibb	
Effectiveness data						
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	×		✓		✓	
10. Effectiveness data from RCT or review of RCTs	✓	The majority of effectiveness data were taken from a trial. However, adverse events rate was obtained from an audit	✓	Effectiveness data are derived from one clinical trial	✓	Effectiveness data are derived from one clinical trial
11. Potential biases identified (especially if data not from RCTs)	×	The potential biases of the audit were not identified and addressed	×	Differences in patient populations in the trial used for obtaining benefit measure were not stated	✓	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓		NA		NA	
Costs						
13. All the important and relevant resource use included	NA	All NHS costs included	×	Resource use associated with adverse events were not included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	?	Some resource use associated with adverse events derived from expert opinion and the methods used were not described (Smith *et al.*[50]). Also, the reduction in the rate of adverse events equal to the reduction in cycles of treatment could be questionable	×	The number of treatment cycles used was not clearly justified	?	Resource utilisation derived from expert opinion for management of adverse events
15. Appropriate unit costs estimated (with methodology)	✓		✓		✓	
16. Unit costs reported separately from resource use data	✓	However, resource use for some adverse events was not reported	✓		✓	
17. Productivity costs treated separately from other costs	NA	Productivity costs not considered	NA	Productivity costs not considered	NA	Productivity costs not considered
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	NA	Unit costs from different price years were used	?	Unit costs from different price years were used	?	Unit costs from different price years were used

continued

	GSK	Schering-Plough	Bristol-Myers Squibb
Benefit measurement and valuation			
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	NA	✓	✓ Life-years gained
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	NA	NA	✓ Area under survival curve
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	NA	NA
Decision modelling			
22. Details of any decision model used are given (e.g. decision tree, Markov model)	NA	NA	NA
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	NA	NA	NA
24. All model outputs described adequately	NA	NA	NA
Discounting			
25. Discount rate used for both costs and benefits	× Resource use up to 1 year	NA Resource use up to 1 year	✓
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	NA	NA	✓ Discount rate as recommended in the previous NICE guidelines (6% for costs; 1.5% for benefits)
Allowance for uncertainty			
Stochastic analysis of patient-level data			
27. Details of statistical tests and CIs are given for stochastic data	NA Deterministic analysis	NA Deterministic analysis	NA Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs).	NA	NA	NA

continued

	GSK	Schering-Plough	Bristol-Myers Squibb
29. Sensitivity analysis used to assess uncertainty in non-stochastical variables (e.g. unit costs, discount rates) and analytical decisions (e.g. methods to handle missing data)	NA	NA	NA
Stochastic analysis of decision models			
30. Are all appropriate input parameters included with uncertainty?	×	NA	NA
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	×	NA	NA
32. Are the probability distributions adequately detailed and appropriate?	×	NA	NA
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytical decisions (e.g. methods to handle missing data)	×	NA	NA
Deterministic analysis			
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	× No sensitivity analyses were performed	✓	✓ Univariate
35. The choice of variables for sensitivity analysis is justified	×	✓ However, sensitivity analyses were not conducted for all relevant parameters	× Sensitivity analyses were not conducted for relevant parameters
36. The ranges over which the variables are varied are stated	×	✓	✓
Presentation of results			
37. Incremental analysis is reported using appropriate decision rules	× No sensitivity analyses were performed	× Cost-minimisation analysis	✓
38. Major outcomes are presented in a disaggregated addition to aggregated form	×	✓	✓
39. Applicable to the NHS setting	×	✓	✓

Appendix 9

Economic review supplementary tables

Mean per-patient cost of adverse events, as estimated by Capri and Cattaneo[52]

Adverse event	Grade	Cost (€)
Nausea/vomiting	1	10
	2	71
	3	81
	4	1001
PPE	1	0
	2	0
	3	37
	4	39
Stomatitis	1	14
	2	28
	3	908
	4	1385
Anaemia	1	21
	2	1370
	3	2351
	4	2943
Neutropenia	1	0
	2	0
	3	284
	4	1554
Diarrhoea	1	10
	2	22
	3	921
	4	1219
Thrombocytopenia	1	0
	2	0
	3	0
	4	1870
Fever	1	3
	2	5
	3	1235
	4	1343
Sepsis	1	0
	2	23
	3	1440
	4	1449

Results from the GSK audit for patients receiving topotecan

Topotecan as line of therapy	Total no. of patients	Mean dose per cycle (mg/m^2) (SD)	No. of cycles (mean)
Second-line	42	1.47 (0.38)	4.19
Third-line	28	1.50 (0.23)	3.57
Fourth-Line	14	1.57 (0.46)	4.31
Fifth-line (and subsequent lines)	8	1.43 (0.12)	2.75
Over all lines	92	1.49	3.88

Results from the GSK audit for patients receiving PLD

PLD as line of chemotherapy	Total no. of patients	Mean dose per cycle mg/m^2 (SD)	No. of cycles (mean)
Second-line	6	50 (0)	3
Third-line	22	48.4 (3.7)	3.6
Forth-line	14	50 (16.3)	3.5
Fifth-line (and subsequent lines)	18	48.9 (7.6)	3.8
Over all lines	60	49.1(11.0)	3.5

Numbers and percentages of patients with maintenance of or improvement in HQL scores at 12 weeks (Study 30-49)

Scales	Caelyx		Topotecan	
	No	%	No.	%
Physical functioning	66/118	56	60/107	56
Role functioning	77/118	65	63/109	58
Emotional functioning	80/119	67	80/108	74
Cognitive functioning	87/119	73	79/108	73
Social functioning	82/119	69	69/108	64
Global QOL	68/117	58	54/104	52
Fatigue	67/118	57	61/109	56
Nausea/vomiting	86/119	72	77/109	71
Pain	76/119	64	88/109	81

Total annual costs per patients for the four chemotherapeutic agents [includes administration costs (£68) plus premedication costs (£2.96)]

Treatment regimen	Cost of study drug (per cycle) (£)	Administration costs (per cycle) (£)	No. of cycles	Total costs (per year) (£)
PLDH	1,626.98	68	6	10,169.88
Topotecan	1,562.50	340	6	11,415.00
Paclitaxel monotherapy	1,122.00	70.96	6	7,157.76
Paclitaxel plus carboplatin	1,516.96	70.96	6	9,527.52

Appendix 10

Utility search strategies

These literature searches were aimed at identifying all studies that include QoL data in ovarian cancer. The search strategies did not include any drug-specific terms.

The literature searches were conducted in May 2004 and were limited to studies published since 1984. There were no limits applied by study design or language of publication. Full details of all databases searched and strategies used are listed below.

This stage of the literature searching retrieved 1321 unique references after deduplication. References were managed using Endnote software version 6.

Databases

Searches were run on the following databases:

MEDLINE
PREMEDLINE
EMBASE
CINAHL
Database of Abstracts of Reviews of Effectiveness (DARE)
NHS Economic Evaluation database (NHS EED)
HTA database
Cochrane Controlled Trials Register
Cochrane Database of Systematic Reviews
Science Citation Index
Index to Scientific and Technical Proceedings
Office of Health Economics Health Economic Evaluations Database (OHE HEED)

Search strategies

Limits:

- Date limits: 1984–date.
- Animal-only studies were excluded where possible.
- Study design: no limits.
- Language: no limits.
- Publication type: letters, comments and editorials were excluded where possible.

MEDLINE (Ovid host) 1984–April 2004

1. exp Ovarian Neoplasms/
2. (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3. (adenexa$ adj4 mass$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4. or/1-3
5. animal/ not (animal/ and human/)
6. 4 not 5
7. exp Life Tables/
8. exp "Quality of Life"/
9. Health Status/
10. exp Health Status Indicators/
11. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
12. (health measurement$ scale$ or health measurement$ questionnaire$).ti,ab.
13. (standard gamble$ or categor$ scal$ or linear scal$ or linear analog$ or visual scal$ or magnitude estmat$).ti,ab.
14. (time trade off$ or rosser$ classif$ or rosser$ matrix or rosser$ distress$ or hrqol).ti,ab.
15. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
16. (rating scale$ or multiattribute$ health ind$ or multi attribute$ health ind$).ti,ab.
17. (health utilit$ index or health utilit$ indices).ti,ab.
18. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
19. (health utilit$ scale$ or classification of illness state$ or 15d or 15 d or 15 dimension).ti,ab.
20. (health state$ utilit$ or 12d or 12 d or 12 dimension).ti,ab.
21. well year$.ti,ab.
22. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
23. health utilit$ scale$.ti,ab.
24. (qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab.

25. (qualy or qaly or qualys or qalys or quality adjusted life year$).ti,ab.
26. life year$ gain$.ti,ab.
27. willingness to pay.ti,ab.
28. (hye or hyes or health$ year$ equivalent$).ti,ab.
29. (person trade off$ or person tradeoff$ or time tradeoff$ or time trade off$).ti,ab.
30. theory utilit$.ti,ab.
31. life table$.ti,ab.
32. health state$.ti,ab.
33. (sf36 or sf 36).ti,ab.
34. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
35. (6d or 6-d or 6 dimension).ti,ab.
36. or/7-35
37. 6 and 36
38. letter.pt.
39. editorial.pt.
40. comment.pt.
41. or/38-40
42. 37 not 41
43. limit 42 to yr=1984 - 2004

PREMEDLINE (Ovid host) 1984–May 2004

1. (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, abstract]
2. (adenexa$ adj4 mass$).mp. [mp=title, abstract]
3. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
4. (health measurement$ scale$ or health measurement$ questionnaire$).ti,ab.
5. (standard gamble$ or categor$ scal$ or linear scal$ or linear analog$ or visual scal$ or magnitude estmat$).ti,ab.
6. (time trade off$ or rosser$ classif$ or rosser$ matrix or rosser$ distress$ or hrqol).ti,ab.
7. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
8. (rating scale$ or multiattribute$ health ind$ or multi attribute$ health ind$).ti,ab.
9. (health utilit$ index or health utilit$ indices).ti,ab.
10. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
11. (health utilit$ scale$ or classification of illness state$ or 15d or 15 d or 15 dimension).ti,ab.
12. (health state$ utilit$ or 12d or 12 d or 12 dimension).ti,ab.
13. well year$.ti,ab.
14. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
15. health utilit$ scale$.ti,ab.
16. (qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab.
17. (qualy or qaly or qualys or qalys or quality adjusted life year$).ti,ab.
18. life year$ gain$.ti,ab.
19. willingness to pay.ti,ab.
20. (hye or hyes or health$ year$ equivalent$).ti,ab.
21. (person trade off$ or person tradeoff$ or time tradeoff$ or time trade off$).ti,ab.
22. theory utilit$.ti,ab.
23. life table$.ti,ab.
24. health state$.ti,ab.
25. (sf36 or sf 36).ti,ab.
26. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
27. (6d or 6-d or 6 dimension).ti,ab.
28. or/1-2
29. or/3-27
30. 28 and 29
31. letter.pt.
32. comment.pt.
33. editorial.pt.
34. or/31-33
35. 30 not 34

EMBASE (Ovid host) 1984–May 2004

1. exp Ovary Cancer/
2. (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
3. (adenexa$ adj4 mass$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. exp "Quality of Life"/
5. Health Status/
6. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
7. (health measurement$ scale$ or health measurement$ questionnaire$).ti,ab.
8. (standard gamble$ or categor$ scal$ or linear scal$ or linear analog$ or visual scal$ or magnitude estmat$).ti,ab.
9. (time trade off$ or rosser$ classif$ or

rosser$ matrix or rosser$ distress$ or hrqol).ti,ab.
10. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
11. (rating scale$ or multiattribute$ health ind$ or multi attribute$ health ind$).ti,ab.
12. (health utilit$ index or health utilit$ indices).ti,ab.
13. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
14. (health utilit$ scale$ or classification of illness state$ or 15d or 15 d or 15 dimension).ti,ab.
15. (health state$ utilit$ or 12d or 12 d or 12 dimension).ti,ab.
16. well year$.ti,ab.
17. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
18. health utilit$ scale$.ti,ab.
19. (qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab.
20. (qualy or qaly or qualys or qalys or quality adjusted life year$).ti,ab.
21. life year$ gain$.ti,ab.
22. willingness to pay.ti,ab.
23. (hye or hyes or health$ year$ equivalent$).ti,ab.
24. (person trade off$ or person tradeoff$ or time tradeoff$ or time trade off$).ti,ab.
25. theory utilit$.ti,ab.
26. life table$.ti,ab.
27. health state$.ti,ab.
28. (sf36 or sf 36).ti,ab.
29. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
30. (6d or 6-d or 6 dimension).ti,ab.
31. life table/
32. health survey/
33. or/1-3
34. or/4-32
35. 33 and 34
36. animal/ or nonhuman/
37. human/
38. 36 not (36 and 37)
39. 35 not 38
40. (editorial or letter).pt.
41. 39 not 40
42. 41
43. limit 42 to yr=1984 - 2004

CINAHL (Ovid host) 1984–April 2004

1. exp Ovarian Neoplasms/
2. (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
3. (adenexa$ adj4 mass$).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
4. or/1-3
5. exp "Quality of Life"/
6. Health Status/
7. exp Health Status Indicators/
8. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
9. (health measurement$ scale$ or health measurement$ questionnaire$).ti,ab.
10. (standard gamble$ or categor$ scal$ or linear scal$ or linear analog$ or visual scal$ or magnitude estmat$).ti,ab.
11. (time trade off$ or rosser$ classif$ or rosser$ matrix or rosser$ distress$ or hrqol).ti,ab.
12. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
13. (rating scale$ or multiattribute$ health ind$ or multi attribute$ health ind$).ti,ab.
14. (health utilit$ index or health utilit$ indices).ti,ab.
15. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
16. (health utilit$ scale$ or classification of illness state$ or 15d or 15 d or 15 dimension).ti,ab.
17. (health state$ utilit$ or 12d or 12 d or 12 dimension).ti,ab.
18. well year$.ti,ab.
19. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
20. health utilit$ scale$.ti,ab.
21. (qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab.
22. (qualy or qaly or qualys or qalys or quality adjusted life year$).ti,ab.
23. life year$ gain$.ti,ab.
24. willingness to pay.ti,ab.
25. (hye or hyes or health$ year$ equivalent$).ti,ab.
26. (person trade off$ or person tradeoff$ or time tradeoff$ or time trade off$).ti,ab.
27. theory utilit$.ti,ab.
28. life table$.ti,ab.
29. health state$.ti,ab.
30. (sf36 or sf 36).ti,ab.
31. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
32. (6d or 6-d or 6 dimension).ti,ab.
33. letter.pt.
34. editorial.pt.

35. comment.pt.
36. or/33-35
37. Life Table Method/
38. or/5-37
39. 4 and 38
40. letter.pt.
41. editorial.pt.
42. or/40-41
43. 39 not 42

DARE
NHS EED
HTA database (http://www.york.ac.uk/inst/crd/crddatabases.htm)
1984–April 2004

s ovar$(4w)(cancer$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)
s adenexa$(4w)mass$
s s1 or s2
s health(w)status
s utilit$(w)approach$ or health(w)gain or hui or hui2 or hui(w)2 or hui3 or hui(w)3
s health(w)measurement$(w)scale$ or health(w)measurement$(w)questionnaire$
s standard(w)gamble$ or categor$(w)scal$ or linear(w)scal$ or linear(w)analog$ or visual(w)scal$ or magnitude(w)estmat$
s time(w)trade(w)off$ or rosser$(w)classif$ or rosser$(w)matrix or rosser$(w)distress$ or hrqol
s index(2w)wellbeing or quality(2w)wellbeing or qwb
s rating(w)scale$ or multiattribute$(w)health(w)ind$ or multi(w)attribute$(w)health(w)ind$
s health(w)utilit$(w)index or health(w)utilit$(w)indices
s multiattribute$(w)theor$ or multi(w)attribute$(w)theor$ or multiattribute$(w)analys$ or multi(w)attribute$(w)analys$
s health(w)utilit$(w)scale$ or classification(2w)illness(w)state$ or 15d or 15(w)d or 15(w)dimension
s health(w)state$(w)utilit$ or 12d or 12(w)d or 12(w)dimension
s well(w)year$
s multiattribute$(w)utilit$ or multi(w)attribute$(w)utilit$
s health(w)utilit$(w)scale$
s qol or 5d or 5(w)d or 5(w)dimension or quality(2w)life or eq(w)5d or eq5d or euroqol
s qualy or qaly or qualys or qalys or quality(w)adjusted(w)life(w)year$
s life(w)year$(w)gain$
s willingness(w)to(w)pay
s hye or hyes or health$(w)year$(w)equivalent$
s person(w)trade(w)off$ or person(w)tradeoff$ or time(w)tradeoff$ or time(w)trade(w)off$
s theory(w)utilit$
s life(w)table$
s health(w)state$
s sf36 or sf(w)36
s short(w)form(w)36 or shortform(w)36 or sf(w)thirtysix or sf(w)thirty(w)six or shortform(w)thirtysix or shortform(w)thirty(w)six or short(w)form(w)thirtysix or short(w)form(w)thirty(w)six
s 6d or 6(w)d or 6(w)dimension
s s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29
s s3 and s30

Cochrane Controlled Trials Register
Cochrane Database of Systematic Reviews
(The Cochrane Library)
1984–Issue 2, 2004

#1. OVARIAN NEOPLASMS explode all trees (MeSH)
#2. (ovar* near cancer*)
#3. (ovar* near tumor*)
#4. (ovar* near tumour*)
#5. (ovar* near malignan*)
#6. (ovar* near oncolog*)
#7. (ovar* near carcinoma)
#8. (ovar* near neoplas*)
#9. (ovar* near mass*)
#10. (ovar* near growth*)
#11. (ovar* near cyst*)
#12. (adenexa* near mass*)
#13. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
#14. LIFE TABLES explode all trees (MeSH)
#15. QUALITY OF LIFE explode all trees (MeSH)
#16. ((utilit* next approach*) or (health next gain) or hui or hui2 or hui-2 or hui3 or hui-3)
#17. ((health next measurement* next scale*) or (health next measurement* next questionnaire*))
#18. ((standard next gamble*) or (categor* next scal*) or (linear next scal*) or (linear next analog*) or (visual next scal*) or (magnitude next estmat*))
#19. ((time next trade next off*) or (rosser* next classif*) or (rosser* next matrix) or (rosser* next distress*) or hrqol)
#20. ((index next wellbeing) or (quality next wellbeing) or qwb)
#21. ((rating next scale*) or (multiattribute* next health next ind*) or (multi next attribute* next health next ind*))

#22. ((health next utilit* next index) or (health next utilit* next indices))
#23. ((multiattribute* next theor*) or (multi next attribute* next theor*) or (multiattribute* next analys*) or (multi next attribute* next analys*))
#24. ((health next utilit* next scale*) or (classification next illness next state*) or 15d or 15-d or 15-dimension)
#25. ((health next state* next utilit*) or 12d or 12-d or 12-dimension)
#26. (well next year*)
#27. ((multiattribute* next utilit*) or (multi next attribute* next utilit*))
#28. (health next utilit* next scale*)
#29. (qol or 5d or 5-d or 5-dimension or (quality next life) or eq-5d or eq5d or eq-5d or euroqol)
#30. (qualy or qaly or qualys or qalys or (quality next adjusted next life next year*))
#31. (life next year* next gain*)
#32. (willingness next pay)
#33. (hye or hyes or (health* next year* next equivalent*))
#34. ((person next trade next off*) or (person next tradeoff*) or (time next tradeoff*) or (time next trade next off*))
#35. (theory next utilit*)
#36. (life next table*)
#37. (sf36 or sf-36)
#38. ((short next form-36) or shortform-36 or (sf next thirtysix) or (sf next thirty next six) or (shortform next thirtysix) or (shortform next thirty next six) or (short next form next thirtysix) or (short next form next thirty next six))
#39. (6d or 6-d or 6-dimension)
#40. (health next status)
#41. (#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
#42. (#13 and #41)
#43. #42 (1984 to current date)

Science Citation Index
Index to Scientific and Technical Proceedings
(Web of Knowledge)
1984–May 2004 (Science Citation Index)
1992–May 2004 (Index to Scientific and Technical Proceedings)

(ovar* same (cancer* or tumo?r* or malignan* or oncolog* or carcinoma* or neoplas* or mass* or growth* or cyst*)) or (adenexa* same mass*)

and

Health Status or utilit* approach* or health gain or hui or hui2 or hui 2 or hui3 or hui 3 or health measurement* scale* or health measurement* questionnaire* or standard gamble* or categor* scal* or linear scal* or linear analog* or visual scal* or magnitude estmat* or time trade off* or rosser* classif* or rosser* matrix or rosser* distress* or hrqol or index of wellbeing or quality of wellbeing or qwb

or

rating scale* or multiattribute* health ind* or multi attribute* health ind* or health utilit* index or health utilit* indices or multiattribute* theor* or multi attribute* theor* or multiattribute* analys* or multi attribute* analys* or health utilit* scale* or classification of illness state* or 15d or 15 d or 15 dimension or health state* utilit* or 12d or 12 d or 12 dimension or well year* or multiattribute* utilit* or multi attribute* utilit* or health utilit* scale*

or

qol or 5d or 5 d or 5 dimension or quality of life or eq 5d or eq5d or euroqol or qualy or qaly or qualys or qalys or quality adjusted life year* or life year* gain* or willingness to pay or hye or hyes or health* year* equivalent* or person trade off* or person tradeoff* or time tradeoff*

or

time trade off* or theory utilit* or life table* or health state* or sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or 6d or 6 d or 6 dimension

OHE HEED
(CD-ROM)
1984–May 2004

ovarian or ovary or ovaries

and

cancer* or tumor* or tumour* or malignan* or oncolog* or carcinoma* or neoplas* or mass* or growth* or cyst*

Appendix 11

WinBUGS code

Analysis 1: Base-case

Below is the WinBUGS code used to estimate PFS and overall survival for the base-case analysis.

```
#Estimates overall survival for topotecan,
paclitaxel and caelyx, and uses topotecan baseline
from 30-49
#Topotecan=a, paclitaxel=b, PLDH=c

model {
#priors for basic parameters
dab ~ dnorm(0,.001)     #LHR a vs B
dac ~ dnorm(0,.001)     # LHR A vs C
la ~ dnorm(0,.001)      # Log hazard rate for A
                          (overall baseline)
psla ~ dnorm(0,.001)    # Log hazard for a
                          (platinum sensitive
                          baseline)
prla ~ dnorm(0,.001)    # Log hazard for a
                          (platinum
                          resistant/refractory
                          baseline)

#OVERALL POPULATION
# define absolute hazards on log scale
ltopo ~ dnorm(la,ptopo)
lb <- la - dab
lc <- la - dac

# define absolute hazards PER WEEK on natural
scale
log(a) <- la
log(b) <- lb
log(c) <- lc

# convert to mean survival
OSa <- 1/a
OSb <- 1/b
OSc <- 1/c

#PLATINUM SENSITIVE POPULATION
# define platinum sensitive baseline
psltopo ~ dnorm(psla,psptopo)
# define absolute hazards for platinum sensitive
pslb <- psla - dab
pslc <- psla - dac

# define absolute hazards PER WEEK on natural
scale
log(psa) <- psla
log(psb) <- pslb
log(psc) <- pslc

# convert to mean survival
psOSa <- 1/psa
psOSb <- 1/psb
psOSc <- 1/psc

#PLATINUM RESISTANT/REFRACTORY
POPULATION
# define platinum resistant/refractory baseline
prltopo ~ dnorm(prla,prptopo)

# define absolute hazards for platinum
resistant/refractory
prlb <- prla - dab
prlc <- prla - dac

# define absolute hazards PER WEEK on natural
scale
log(pra) <- prla
log(prb) <- prlb
log(prc) <- prlc

# convert to mean survival
prOSa <- 1/pra
prOSb <- 1/prb
prOSc <- 1/prc

#likelihood
yab ~ dnorm(dab,pab)
yac ~ dnorm(dac,pac)

data list
list(yab=-0.0899,yac=0.1956,
        # from 039, 30-49
pab=44.4520,pac=100.6718,
        # precision=1/variance. SD = 95CI/3.92
ltopo= -4.4558,  ptopo=114.9304,
        #from 30-49
psltopo=-4.6164, psptopo=52.9206,
prltopo=-4.1066, prptopo=59.4225)

the log baseline (topo) rate is log(-log(0.5) / 59.7)
= -4.455845
precision (=1/variance),
variance=hazard^2/#events

initial values
```

```
list(dac=.01, dab=.01,la=.01,psla=.01,prla=.01)

#Estimates progression-free survival for
topotecan, paclitaxel and caelyx, using only 039
and 30-49, and uses topotecan baseline from 30-
49#

model {
#priors for basic parameters
dab ~ dnorm(0,.001)    #LHR a vs B
dac ~ dnorm(0,.001)    # LHR A vs C
la ~ dnorm(0,.001)     # Log hazard rate for A
(overall baseline)
psla ~ dnorm(0,.001)   # Log hazard rate for A
                         (plat sens baseline)
prla ~ dnorm(0,.001)   # Log hazard rate for A
                         (plat ref/resis baseline)

#OVERALL POPULATION
# define absolute hazards on log scale
ltopo ~ dnorm(la,ptopo)
lb <- la - dab
lc <- la - dac

# define absolute hazards PER WEEK on natural
scale
log(a) <- la
log(b) <- lb
log(c) <- lc

# convert to mean survival
PFSa <- 1/a
PFSb <- 1/b
PFSc <- 1/c

#PLATINUM SENSITIVE POPULATION
# define platinum sensitive baseline
psltopo ~ dnorm(psla,psptopo)
# define absolute hazards for platinum sensitive
pslb <- psla - dab
pslc <- psla - dac

# define absolute hazards PER WEEK on natural
scale
log(psa) <- psla
log(psb) <- pslb
log(psc) <- pslc

# convert to mean survival
psPFSa <- 1/psa
psPFSb <- 1/psb
psPFSc <- 1/psc

#PLATINUM RESISTANT/REFRACTORY
POPULATION
# define platinum resistant/refractory baseline
prltopo ~ dnorm(prla,prptopo)
# define absolute hazards for platinum
resistant/refractory
prlb <- prla - dab
prlc <- prla - dac

# define absolute hazards PER WEEK on natural
scale
log(pra) <- prla
log(prb) <- prlb
log(prc) <- prlc

# convert to mean survival
prPFSa <- 1/pra
prPFSb <- 1/prb
prPFSc <- 1/prc

#likelihood
yab ~ dnorm(dab,pab)
yac ~ dnorm(dac,pac)

data list
list(yab=-0.2095,yac=0.1115,
        # from 039, 30-49
pab=43.5733,pac=110.6824,
        # precision=1/variance. SD = 95CI/3.92
ltopo= -3.1938,  ptopo=114.9304,
        #from 30-49
psltopo=-3.4889, psptopo=52.9206,
prltopo=-2.9766, prptopo=59.4225)

initial values
list(dac=.01, dab=.01,la=.01,psla=.01,prla=.01)
```

Analysis 1: including trial 30-57

Below is the WinBUGS code used to estimate overall survival for sensitivity analysis including trial 30-57.

```
#Estimates overall survival for topotecan,
paclitaxel and caelyx, and uses topotecan baseline
from 30-49. Also incorporates comparison
between paclitaxel and PLDH from trial 30-57
#Topotecan=a, paclitaxel=b, PLDH=c
model {
#priors for basic parameters
#LHR a vs B
dab ~ dnorm(0,.001)
# LHR A vs C
dac ~ dnorm(0,.001)
# Log hazard rate for A (overall baseline
la ~ dnorm(0,.001)       )
# Log hazard for a (platinum sensitive baseline)
psla ~ dnorm(0,.001)
# Log hazard for a (platinum resistant/refractory
baseline)
```

```
prla ~ dnorm(0,.001)

#define functional parameters
dbc <- dac - dab

#OVERALL POPULATION
# define absolute hazards on log scale
ltopo ~ dnorm(la,ptopo)
lb <- la - dab
lc <- la - dac

# define absolute hazards PER WEEK on natural
scale
log(a) <- la
log(b) <- lb
log(c) <- lc

# convert to mean survival
OSa <- 1/a
OSb <- 1/b
OSc <- 1/c

#PLATINUM SENSITIVE POPULATION
# define platinum sensitive baseline
psltopo ~ dnorm(psla,psptopo)
# define absolute hazards for platinum sensitive
pslb <- psla - dab
pslc <- psla - dac

# define absolute hazards PER WEEK on natural
scale
log(psa) <- psla
log(psb) <- pslb
log(psc) <- pslc

# convert to mean survival
psOSa <- 1/psa
psOSb <- 1/psb
psOSc <- 1/psc

#PLATINUM RESISTANT/REFRACTORY
POPULATION
# define platinum resis/refrac baseline
prltopo ~ dnorm(prla,prptopo)
# define absolute hazards for platinum resis/refrac
prlb <- prla - dab
prlc <- prla - dac

# define absolute hazards PER WEEK on natural
scale
log(pra) <- prla
log(prb) <- prlb
log(prc) <- prlc

# convert to mean survival
prOSa <- 1/pra
prOSb <- 1/prb
prOSc <- 1/prc

#likelihood
yab ~ dnorm(dab,pab)
yac ~ dnorm(dac,pac)
ybc ~ dnorm(dbc,pbc)

}

data list
# from 039, 30-49, 30-57
list(yab=-0.0899,yac=0.1956,ybc=-.0715,
# precision=1/variance. I got sd as 95CI/3.92
pab=44.4520,pac=100.6718,pbc=48.2933,
#from 30-49
ltopo= -4.4558,  ptopo=114.9304,
psltopo=-4.6164, psptopo=52.9206,
prltopo=-4.1066, prptopo=59.4225)

the log baseline (topo) rate is log(-log(0.5) / 59.7)
= -4.455845
precision (=1/variance),
variance=hazard^2/#events

initial values
list(dac=.01, dab=.01,la=.01,psla=.01,prla=.01)
```

Analysis 2

Below is the WinBUGS code used to estimate PFS and overall survival for analysis 2.
Estimates overall survival for topotecan, paclitaxel, caelyx, paclitaxel+pt and pt, and uses topotecan baseline from 30-49. This is so PFS can be estimated on same population as OS (no data is available on PFS in platinum sensitive from 039).

```
#Topotecan=a, paclitaxel=b, PLDH=c, paclitaxel
combination=d, platinum=e, CAP=f

model
#priors for basic parameters
dab ~ dnorm(0,.001)    # LHR A vs B
dac ~ dnorm(0,.001)    # LHR A vs C
dbf ~ dnorm(0,.001)    # LHR B vs F
la ~ dnorm(0,.001)     # Log hazard rate for A
                         (baseline)
ld ~ dnorm(0,.001)     # Log hazard rate for D
le ~ dnorm(0,.001)     # Log hazard rate for E

#define functional parameters
daf <- dab + dbf
dad <- la-ld
dae <- la-le

# define absolute hazards on log scale topotecan
```

```
ltopo ~ dnorm(la,ptopo)
# absolute hazard on log scale pacpt
lpacpt ~ dnorm(ld,ppacpt)
# absolute hazard on log scale pt
lpt ~ dnorm(le,ppt)

lb <- la - dab
lc <- la - dac
lf <- la - daf

# define absolute hazards PER WEEK on natural
scale
log(a) <- la
log(b) <- lb
log(c) <- lc
log(d) <- ld
log(e) <- le
log(f) <- lf

# convert to mean survival
OSa_2 <- 1/a
OSb_2 <- 1/b
OSc_2 <- 1/c
OSd_2 <- 1/d
OSe_2 <- 1/e
OSf_2 <- 1/f

#likelihood
yab ~ dnorm(dab,pab)
yac ~ dnorm(dac,pac)
ybf ~ dnorm(dbf,pbf)

data list
list(yab=0.0100, yac=0.3591,ybf=.5447,
        #039, 30-49, cantu
pab=21.6019,pac=44.1477,pbf=13.7121,
        # precision=1/variance. SD = 95CI/3.92
ltopo= -4.6164,  ptopo=52.9206,
        #from 30-49
lpacpt= -5.2028, ppacpt=193.4339,
        #from ICON4
lpt=-5.0205, ppt=202.4341)
        #from ICON 4

initial values
list(dab=.01,dac=.01,dbf=.01,la=.01,ld=.01,le=.
01)

#Estimates progression-free survival for
topotecan, paclitaxel, caelyx, paclitaxel+pt and pt,
and uses topotecan baseline from 30-49. This is so
PFS can be estimated on same population as OS
(no data is available on PFS in platinum sensitive
from 039).

model {
#priors for basic parameters
dab ~ dnorm(0,.001)    # LHR A vs B
dac ~ dnorm(0,.001)    # LHR A vs C
dbf ~ dnorm(0,.001)    # LHR B vs F
la ~ dnorm(0,.001)     # Log hazard rate for A
(baseline)
ld ~ dnorm(0,.001)     # Log hazard rate for D
le ~ dnorm(0,.001)     # Log hazard rate for E

#define functional parameters
daf <- dab + dbf
dad <- la-ld
dae <- la-le

# define absolute hazards on log scale topotecan
ltopo ~ dnorm(la,ptopo)
# absolute hazard on log scale pacpt
lpacpt ~ dnorm(ld,ppacpt)
# absolute hazard on log scale pt
lpt ~ dnorm(le,ppt)

lb <- la - dab
lc <- la - dac
lf <- la - daf

# define absolute hazards PER WEEK on natural
scale
log(a) <- la
log(b) <- lb
log(c) <- lc
log(d) <- ld
log(e) <- le
log(f) <- lf

# convert into mean survival
PFSa_2 <- 1/a
PFSb_2 <- 1/b
PFSc_2 <- 1/c
PFSd_2 <- 1/d
PFSe_2 <- 1/e
PFSf_2 <- 1/f
#likelihood
yab ~ dnorm(dab,pab)
yac ~ dnorm(dac,pac)
ybf ~ dnorm(dbf,pbf)

data list
list(yab=-0.1948,yac=0.2523,ybf=.5108,
        #039, 30-49, Cantu
pab=21.1785,pac=50.7314,pbf=16.5426,
        # precision=1/variance. I got sd as
        95CI/3.92
ltopo= -3.4889,  ptopo=52.9206,
        #from 30-49
lpacpt= -4.4096, ppacpt=193.4339,
        #from ICON4
lpt=-4.1507, ppt=202.4341)
        #from ICON 4
```

initial values
list(dab=.01,dac=.01,dbf=.01,la=.01,ld=.01,le=.01)

Adverse events (Analysis 1)

Below is the WinBUGS code used to estimate the probabilities of adverse events for Analysis 1.

```
#Probability of Adverse events (model 1, including 039, 30-49 and 30-57)
model{

######neutropenia grade 3(t.n3)

for (j in 1:2) { delta.n3[j] ~ dnorm(0.0,0.0001) }
m.rn3~dnorm(0.0,0.001)
t.rn3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rn3[j]~dnorm(m.rn3,t.rn3) }

for (i in 1:6){ logit(p.n3[i])<-mu.rn3[study.n3[i]]
+ equals(treat.n3[i],2) * delta.n3[1] +
equals(treat.n3[i],3) * delta.n3[2]}

for (i in 1:6){ r.n3[i]~dbin(p.n3[i],n.n3[i]) }

logit(t.n3[1]) <- m.rn3
for (j in 2: 3) { logit(t.n3[j]) <- m.rn3 + delta.n3[j-1] }

######neutropenia grade 4 (t.n4)

for (j in 1:2) { delta.n4[j] ~ dnorm(0.0,0.0001) }
m.rn4~dnorm(0.0,0.001)
t.rn4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rn4[j]~dnorm(m.rn4,t.rn4) }

for (i in 1:6){ logit(p.n4[i])<-mu.rn4[study.n4[i]]
+ equals(treat.n4[i],2) * delta.n4[1] +
equals(treat.n4[i],3) * delta.n4[2]}

for (i in 1:6){ r.n4[i]~dbin(p.n4[i],n.n4[i]) }

logit(t.n4[1]) <- m.rn4
for (j in 2: 3) { logit(t.n4[j]) <- m.rn4 + delta.n4[j-1] }

######thrombocytopenia grade 3 (t.t3)

for (j in 1:2) { delta.t3[j] ~ dnorm(0.0,0.0001) }
m.rt3~dnorm(0.0,0.001)
t.rt3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rt3[j]~dnorm(m.rt3,t.rt3) }

for (i in 1:6){ logit(p.t3[i])<-mu.rt3[study.t3[i]] +
equals(treat.t3[i],2) * delta.t3[1] +
equals(treat.t3[i],3) * delta.t3[2]}

for (i in 1:6){ r.t3[i]~dbin(p.t3[i],n.t3[i]) }

logit(t.t3[1]) <- m.rt3
for (j in 2: 3) { logit(t.t3[j]) <- m.rt3 + delta.t3[j-1] }


######thrombocytopenia grade 4 (t.t4)

for (j in 1:2) { delta.t4[j] ~ dnorm(0.0,0.0001) }
m.rt4~dnorm(0.0,0.001)
t.rt4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rt4[j]~dnorm(m.rt4,t.rt4) }

for (i in 1:6){ logit(p.t4[i])<-mu.rt4[study.t4[i]] +
equals(treat.t4[i],2) * delta.t4[1] +
equals(treat.t4[i],3) * delta.t4[2]}

for (i in 1:6){ r.t4[i]~dbin(p.t4[i],n.t4[i]) }

logit(t.t4[1]) <- m.rt4
for (j in 2: 3) { logit(t.t4[j]) <- m.rt4 + delta.t4[j-1] }


######anemia grade 3 (t.a3)

for (j in 1:2) { delta.a3[j] ~ dnorm(0.0,0.0001) }
m.ra3~dnorm(0.0,0.001)
t.ra3~dgamma(0.01,0.01)
for (j in 1:3){ mu.ra3[j]~dnorm(m.ra3,t.ra3) }

for (i in 1:6){ logit(p.a3[i])<-mu.ra3[study.a3[i]] +
equals(treat.a3[i],2) * delta.a3[1] +
equals(treat.a3[i],3) * delta.a3[2]}

for (i in 1:6){ r.a3[i]~dbin(p.a3[i],n.a3[i]) }

logit(t.a3[1]) <- m.ra3
for (j in 2: 3) { logit(t.a3[j]) <- m.ra3 + delta.a3[j-1] }

######anemia grade 4 (t.a4)

for (j in 1:2) { delta.a4[j] ~ dnorm(0.0,0.0001) }
m.ra4~dnorm(0.0,0.001)
t.ra4~dgamma(0.01,0.01)
for (j in 1:3){ mu.ra4[j]~dnorm(m.ra4,t.ra4) }

for (i in 1:6){ logit(p.a4[i])<-mu.ra4[study.a4[i]] +
equals(treat.a4[i],2) * delta.a4[1] +
equals(treat.a4[i],3) * delta.a4[2]}

for (i in 1:6){ r.a4[i]~dbin(p.a4[i],n.a4[i]) }
```

```
logit(t.a4[1]) <- m.ra4
for (j in 2: 3) { logit(t.a4[j]) <- m.ra4 + delta.a4[j-1] }


######PPE grade 3 (t.p3)

for (j in 1:2) { delta.p3[j] ~ dnorm(0.0,0.0001) }
m.rp3~dnorm(0.0,0.001)
t.rp3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rp3[j]~dnorm(m.rp3,t.rp3) }

for (i in 1:6){ logit(p.p3[i])<-mu.rp3[study.p3[i]]
+ equals(treat.p3[i],2) * delta.p3[1] +
equals(treat.p3[i],3) * delta.p3[2]}

for (i in 1:6){ r.p3[i]~dbin(p.p3[i],n.p3[i]) }

logit(t.p3[1]) <- m.rp3
for (j in 2: 3) { logit(t.p3[j]) <- m.rp3 +
delta.p3[j-1] }


######PPE grade 4 (t.p4)

for (j in 1:2) { delta.p4[j] ~ dnorm(0.0,0.0001) }
m.rp4~dnorm(0.0,0.001)
t.rp4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rp4[j]~dnorm(m.rp4,t.rp4) }

for (i in 1:6){ logit(p.p4[i])<-mu.rp4[study.p4[i]]
+ equals(treat.p4[i],2) * delta.p4[1] +
equals(treat.p4[i],3) * delta.p4[2]}

for (i in 1:6){ r.p4[i]~dbin(p.p4[i],n.p4[i]) }

logit(t.p4[1]) <- m.rp4
for (j in 2: 3) { logit(t.p4[j]) <- m.rp4 +
delta.p4[j-1] }


######stomatitis/pharyngitis grade 3 (t.s3)
for (j in 1:2) { delta.s3[j] ~ dnorm(0.0,0.0001) }
m.rs3~dnorm(0.0,0.001)
t.rs3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rs3[j]~dnorm(m.rs3,t.rs3) }

for (i in 1:6){ logit(p.s3[i])<-mu.rs3[study.s3[i]] +
equals(treat.s3[i],2) * delta.s3[1] +
equals(treat.s3[i],3) * delta.s3[2]}

for (i in 1:6){ r.s3[i]~dbin(p.s3[i],n.s3[i]) }

logit(t.s3[1]) <- m.rs3
for (j in 2: 3) { logit(t.s3[j]) <- m.rs3 + delta.s3[j-1] }


######stomatitis/pharyngitis grade 4 (t.s4)
for (j in 1:2) { delta.s4[j] ~ dnorm(0.0,0.0001) }
m.rs4~dnorm(0.0,0.001)
t.rs4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rs4[j]~dnorm(m.rs4,t.rs4) }

for (i in 1:6){ logit(p.s4[i])<-mu.rs4[study.s4[i]] +
equals(treat.s4[i],2) * delta.s4[1] +
equals(treat.s4[i],3) * delta.s4[2]}

for (i in 1:6){ r.s4[i]~dbin(p.s4[i],n.s4[i]) }

logit(t.s4[1]) <- m.rs4
for (j in 2: 3) { logit(t.s4[j]) <- m.rs4 + delta.s4[j-1] }


######diarrhoea grade 3 (t.d3)
for (j in 1:2) { delta.d3[j] ~ dnorm(0.0,0.0001) }
m.rd3~dnorm(0.0,0.001)
t.rd3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rd3[j]~dnorm(m.rd3,t.rd3) }

for (i in 1:6){ logit(p.d3[i])<-mu.rd3[study.d3[i]] +
equals(treat.d3[i],2) * delta.d3[1] +
equals(treat.d3[i],3) * delta.d3[2]}

for (i in 1:6){ r.d3[i]~dbin(p.d3[i],n.d3[i]) }

logit(t.d3[1]) <- m.rd3
for (j in 2: 3) { logit(t.d3[j]) <- m.rd3 + delta.d3[j-1] }


######diarrhoea grade 4 (t.d4)
for (j in 1:2) { delta.d4[j] ~ dnorm(0.0,0.0001) }
m.rd4~dnorm(0.0,0.001)
t.rd4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rd4[j]~dnorm(m.rd4,t.rd4) }

for (i in 1:6){ logit(p.d4[i])<-mu.rd4[study.d4[i]] +
equals(treat.d4[i],2) * delta.d4[1] +
equals(treat.d4[i],3) * delta.d4[2]}

for (i in 1:6){ r.d4[i]~dbin(p.d4[i],n.d4[i]) }

logit(t.d4[1]) <- m.rd4
for (j in 2: 3) { logit(t.d4[j]) <- m.rd4 + delta.d4[j-1] }


######nausea/vomiting grade 3 (t.nv3)
for (j in 1:2) { delta.nv3[j] ~ dnorm(0.0,0.0001) }
m.rnv3~dnorm(0.0,0.001)
t.rnv3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rnv3[j]~dnorm(m.rnv3,t.rnv3) }

for (i in 1:6){ logit(p.nv3[i])<-
mu.rnv3[study.nv3[i]] + equals(treat.nv3[i],2) *
delta.nv3[1] + equals(treat.nv3[i],3) *
```

```
delta.nv3[2]}

for (i in 1:6){ r.nv3[i]~dbin(p.nv3[i],n.nv3[i]) }

logit(t.nv3[1]) <- m.rnv3
for (j in 2: 3) { logit(t.nv3[j]) <- m.rnv3 +
delta.nv3[j-1] }

######nausea/vomiting grade 4 (t.nv4)
for (j in 1:2) { delta.nv4[j] ~ dnorm(0.0,0.0001) }
m.rnv4~dnorm(0.0,0.001)
t.rnv4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rnv4[j]~dnorm(m.rnv4,t.rnv4) }

for (i in 1:6){ logit(p.nv4[i])<-
mu.rnv4[study.nv4[i]] + equals(treat.nv4[i],2) *
delta.nv4[1] + equals(treat.nv4[i],3) *
delta.nv4[2]}

for (i in 1:6){ r.nv4[i]~dbin(p.nv4[i],n.nv4[i]) }

logit(t.nv4[1]) <- m.rnv4
for (j in 2: 3) { logit(t.nv4[j]) <- m.rnv4 +
delta.nv4[j-1] }

######sepsis grade 3 (t.se3)
for (j in 1:2) { delta.se3[j] ~ dnorm(0.0,0.0001) }
m.rse3~dnorm(0.0,0.001)
t.rse3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rse3[j]~dnorm(m.rse3,t.rse3) }

for (i in 1:6){ logit(p.se3[i])<-mu.rse3[study.se3[i]]
+ equals(treat.se3[i],2) * delta.se3[1] +
equals(treat.se3[i],3) * delta.se3[2]}

for (i in 1:6){ r.se3[i]~dbin(p.se3[i],n.se3[i]) }

logit(t.se3[1]) <- m.rse3
for (j in 2: 3) { logit(t.se3[j]) <- m.rse3 +
delta.se3[j-1] }

######sepsis grade 4 (t.se4)
for (j in 1:2) { delta.se4[j] ~ dnorm(0.0,0.0001) }
m.rse4~dnorm(0.0,0.001)
t.rse4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rse4[j]~dnorm(m.rse4,t.rse4) }

for (i in 1:6){ logit(p.se4[i])<-mu.rse4[study.se4[i]]
+ equals(treat.se4[i],2) * delta.se4[1] +
equals(treat.se4[i],3) * delta.se4[2]}

for (i in 1:6){ r.se4[i]~dbin(p.se4[i],n.se4[i]) }

logit(t.se4[1]) <- m.rse4
for (j in 2: 3) { logit(t.se4[j]) <- m.rse4 +
delta.se4[j-1] }

#########fever grade 3 (t.f3)
for (j in 1:2) { delta.f3[j] ~ dnorm(0.0,0.0001) }
m.rf3~dnorm(0.0,0.001)
t.rf3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rf3[j]~dnorm(m.rf3,t.rf3) }

for (i in 1:6){ logit(p.f3[i])<-mu.rf3[study.f3[i]] +
equals(treat.f3[i],2) * delta.f3[1] +
equals(treat.f3[i],3) * delta.f3[2]}

for (i in 1:6){ r.f3[i]~dbin(p.f3[i],n.f3[i]) }

logit(t.f3[1]) <- m.rf3
for (j in 2: 3) { logit(t.f3[j]) <- m.rf3 + delta.f3[j-
1] }


##########fever grade 4 (t.f4)
for (j in 1:2) { delta.f4[j] ~ dnorm(0.0,0.0001) }
m.rf4~dnorm(0.0,0.001)
t.rf4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rf4[j]~dnorm(m.rf4,t.rf4) }

for (i in 1:6){ logit(p.f4[i])<-mu.rf4[study.f4[i]] +
equals(treat.f4[i],2) * delta.f4[1] +
equals(treat.f4[i],3) * delta.f4[2]}

for (i in 1:6){ r.f4[i]~dbin(p.f4[i],n.f4[i]) }

logit(t.f4[1]) <- m.rf4
for (j in 2: 3) { logit(t.f4[j]) <- m.rf4 + delta.f4[j-
1] }

}


# data

list(r.n3 =c(33,19,17,34,10,6),(r.n4 =
c(146,10,89,24,3,1),
(r.t3=c(40,3,25,2,0.5,0.5),
(r.t4=c(40,0.5,30,3,0.5,0.5),
(r.a3=c(59,13,42,4,5,3),
(r.a4=c(10,1,4,3,0.5,0.5),
(r.p3=c(0.5,55,0.5,0.5,0.5,16),
(r.p4=c(0.5,2,0.5,0.5,0.5,1), (r.s3=c(2,19,1,1,1,11),
(r.s4=c(0.5,1,0.5,0.5,0.5,0.5), (r.d3=c(9,5,6,1,3,3),
(r.d4=c(1,1,1,0.5,0.5,0.5),
(r.nv3=c(34,29,17,4,6,16), (r.nv4=c(8,3,5,1,0.5,3),
(r.se3=c(1,0.5,2,2,0.5,0.5),
(r.se4=c(1,0.5,2,0.5,0.5,0.5), (r.f3=c(8,2,1,1,3,7),
(r.f4=c(5,0.5,0.5,0.5,0.5,0.5),

n.n3=c(235,239,112,114,108,108),
n.n4=c(235,239,112,114,108,108),
n.t3=c(235,239,112,114,108.5,108.5),
n.t4=c(235,239.5,112,114,108.5,108.5),
```

```
n.a3=c(235,239,112,114,108,108),
n.a4=c(235,239,112,114,108.5,108.5),
n.p3=c(235.5,239,112.5,114.5,108.5,108),
n.p4=c(235.5,239,112.5,114.5,108.5,108),
n.s3=c(235,239,112,114,108,108),
n.s4=c(235.5,239,112.5,114.5,108.5,108.5),
n.d3=c(235,239,112,114,108,108),
n.d4=c(235,239,112,114.5,108.5,108.5),
n.nv3=c(235,239,112,114,108,108),
n.nv4=c(235,239,112,114,108.5,108),
n.se3=c(235,239.5,112,114,108.5,108.5),
n.se4=c(235,239.5,112,114.5,108.5,108.5),
n.f3=c(235,239,112,114,108,108),
n.f4=c(235,239.5,112.5,114.5,108.5,108.5),

study.n3=c(1,1,2,2,3,3),
study.n4=c(1,1,2,2,3,3),
study.t3=c(1,1,2,2,3,3),
study.t4=c(1,1,2,2,3,3),
study.a3=c(1,1,2,2,3,3),
study.a4=c(1,1,2,2,3,3),
study.p3=c(1,1,2,2,3,3),
study.p4=c(1,1,2,2,3,3),
study.s3=c(1,1,2,2,3,3),
study.s4=c(1,1,2,2,3,3),
study.d3=c(1,1,2,2,3,3),
study.d4=c(1,1,2,2,3,3),
study.nv3=c(1,1,2,2,3,3),
study.nv4=c(1,1,2,2,3,3),
study.se3=c(1,1,2,2,3,3),
study.se4=c(1,1,2,2,3,3),
study.f3=c(1,1,2,2,3,3),
study.f4=c(1,1,2,2,3,3),

treat.n3=c(1,3,1,2,2,3),
treat.n4=c(1,3,1,2,2,3),
treat.t3=c(1,3,1,2,2,3),
treat.t4=c(1,3,1,2,2,3),
treat.a3=c(1,3,1,2,2,3),
treat.a4=c(1,3,1,2,2,3),
treat.p3=c(1,3,1,2,2,3),
treat.p4=c(1,3,1,2,2,3),
treat.s3=c(1,3,1,2,2,3),
treat.s4=c(1,3,1,2,2,3),
treat.d3=c(1,3,1,2,2,3),
treat.d4=c(1,3,1,2,2,3),
treat.nv3=c(1,3,1,2,2,3),
treat.nv4=c(1,3,1,2,2,3),
treat.se3=c(1,3,1,2,2,3),
treat.se4=c(1,3,1,2,2,3),
treat.f3=c(1,3,1,2,2,3),
treat.f4=c(1,3,1,2,2,3))


# initial
list(m.rn3=0,
t.rn3=1, m.rn4=0,t.rn4=1,m.rt3=0, t.rt3=1,
m.rt4=0, t.rt4=1,m.ra3=0,t.ra3=1,
m.ra4=0,t.ra4=1, m.rp3=0,t.rp3=1,
m.rp4=0,t.rp4=1, m.rs3=0,t.rs3=1,
m.rs4=0,t.rs4=1, m.rd3=0,t.rd3=1,
m.rd4=0,t.rd4=1, m.rnv3=0, t.rnv3=1,
m.rnv4=0,t.rnv4=1, m.rse3=0, t.rse3=1,
m.rse4=0, t.rse4=1, m.rf3=0, t.rf3=1, m.rf4=0,
t.rf4=1)
```

Adverse events (Analysis 2)

Below is the WinBUGS code used to estimate the probabilities of adverse events, using data from the 30-49, 039, 30-57, Cantu, ICON4 and Bolis trials.

```
#Probability of Adverse events (model 1, including
039, 30-49 and 30-57)

#If all 6 trials included then: treatment 1 =
topotecan, treatment 2 = paclitaxel, treatment 3
= PLD, treatment 4 = CAP, treatment 5=
paclitaxel combination, treatment 6 =
carboplatin/cisplatin, treatment 7 =
carboplatin+enoxiparin. Trial 1 = 039, trial 2 =
30-49, trial 3 = 30-57, trial 4 = cantu, trial 5 =
ICON4 and trial 6 = Bolis

model{

######neutropenia grade 3(t.n3)
#incorporates Cantu data as well as 3 original
trials
for (j in 1:3) { delta.n3[j] ~ dnorm(0.0,0.0001) }
m.rn3~dnorm(0.0,0.001)
t.rn3~dgamma(0.01,0.01)
for (j in 1:4){ mu.rn3[j]~dnorm(m.rn3,t.rn3) }

for (i in 1:8){ logit(p.n3[i])<-mu.rn3[study.n3[i]]
+ equals(treat.n3[i],2) * delta.n3[1] +
equals(treat.n3[i],3) * delta.n3[2] +
equals(treat.n3[i],4) * delta.n3[3]}

for (i in 1:8){ r.n3[i]~dbin(p.n3[i],n.n3[i]) }

logit(t.n3[1]) <- m.rn3
for (j in 2: 4) { logit(t.n3[j]) <- m.rn3 + delta.n3[j-
1] }


######neutropenia grade 4 (t.n4)
#incorporates Cantu data as well as 3 original
trials
for (j in 1:3) { delta.n4[j] ~ dnorm(0.0,0.0001) }
m.rn4~dnorm(0.0,0.001)
```

```
t.rn4~dgamma(0.01,0.01)
for (j in 1:4){ mu.rn4[j]~dnorm(m.rn4,t.rn4) }

for (i in 1:8){ logit(p.n4[i])<-mu.rn4[study.n4[i]]
+ equals(treat.n4[i],2) * delta.n4[1] +
equals(treat.n4[i],3) * delta.n4[2] +
equals(treat.n4[i],4) * delta.n4[3]}

for (i in 1:8){ r.n4[i]~dbin(p.n4[i],n.n4[i]) }

logit(t.n4[1]) <- m.rn4
for (j in 2: 4) { logit(t.n4[j]) <- m.rn4 + delta.n4[j-
1] }

######thrombocytopenia grade 3 (t.t3)
#Treatment 5 = carboplatin/cisplatin, treatment
6= carboplatin+enoxiparin
#incorporates Cantu and Bolis data
for (j in 1:5) { delta.t3[j] ~ dnorm(0.0,0.0001) }
m.rt3~dnorm(0.0,0.001)
t.rt3~dgamma(0.01,0.01)
for (j in 1:6){ mu.rt3[j]~dnorm(m.rt3,t.rt3) }

for (i in 1:10){ logit(p.t3[i])<-mu.rt3[study.t3[i]] +
equals(treat.t3[i],2) * delta.t3[1] +
equals(treat.t3[i],3) * delta.t3[2] +
equals(treat.t3[i],4) * delta.t3[3] +
equals(treat.t3[i],5) * delta.t3[4] +
equals(treat.t3[i],6) * delta.t3[5]}

for (i in 1:10){ r.t3[i]~dbin(p.t3[i],n.t3[i]) }

logit(t.t3[1]) <- m.rt3
for (j in 2: 6) { logit(t.t3[j]) <- m.rt3 + delta.t3[j-
1] }


######thrombocytopenia grade 4 (t.t4)
#Treatment 5 = carboplatin/cisplatin, treatment
6= carboplatin+enoxiparin
#incorporates Cantu and Bolis data
for (j in 1:5) { delta.t4[j] ~ dnorm(0.0,0.0001) }
m.rt4~dnorm(0.0,0.001)
t.rt4~dgamma(0.01,0.01)
for (j in 1:6){ mu.rt4[j]~dnorm(m.rt4,t.rt4) }

for (i in 1:10){ logit(p.t4[i])<-mu.rt4[study.t4[i]] +
equals(treat.t4[i],2) * delta.t4[1] +
equals(treat.t4[i],3) * delta.t4[2] +
equals(treat.t4[i],4) * delta.t4[3] +
equals(treat.t4[i],5) * delta.t4[4] +
equals(treat.t4[i],6) * delta.t4[5]}

for (i in 1:10){ r.t4[i]~dbin(p.t4[i],n.t4[i]) }

logit(t.t4[1]) <- m.rt4
for (j in 2: 6) { logit(t.t4[j]) <- m.rt4 + delta.t4[j-
1] }


######anemia grade 3 (t.a3)
#treatment 4 = carboplatin/cisplatin, treatment 5
= carboplatin+enoxaparin
#incorporates Bolis data
for (j in 1:4) { delta.a3[j] ~ dnorm(0.0,0.0001) }
m.ra3~dnorm(0.0,0.001)
t.ra3~dgamma(0.01,0.01)
for (j in 1:5){ mu.ra3[j]~dnorm(m.ra3,t.ra3) }

for (i in 1:8){ logit(p.a3[i])<-mu.ra3[study.a3[i]] +
equals(treat.a3[i],2) * delta.a3[1] +
equals(treat.a3[i],3) * delta.a3[2] +
equals(treat.a3[i],4) * delta.a3[3] +
equals(treat.a3[i],5) * delta.a3[4]}

for (i in 1:8){ r.a3[i]~dbin(p.a3[i],n.a3[i]) }

logit(t.a3[1]) <- m.ra3
for (j in 2: 5) { logit(t.a3[j]) <- m.ra3 + delta.a3[j-
1] }

######anemia grade 4 (t.a4)
#treatment 4 = carboplatin/cisplatin, treatment 5
= carboplatin+enoxaparin
#incorporates Bolis data
for (j in 1:4) { delta.a4[j] ~ dnorm(0.0,0.0001) }
m.ra4~dnorm(0.0,0.001)
t.ra4~dgamma(0.01,0.01)
for (j in 1:5){ mu.ra4[j]~dnorm(m.ra4,t.ra4) }

for (i in 1:8){ logit(p.a4[i])<-mu.ra4[study.a4[i]] +
equals(treat.a4[i],2) * delta.a4[1] +
equals(treat.a4[i],3) * delta.a4[2] +
equals(treat.a4[i],4) * delta.a4[3] +
equals(treat.a4[i],5) * delta.a4[4]}

for (i in 1:8){ r.a4[i]~dbin(p.a4[i],n.a4[i]) }

logit(t.a4[1]) <- m.ra4
for (j in 2: 5) { logit(t.a4[j]) <- m.ra4 + delta.a4[j-
1] }


######PPE grade 3 (t.p3)

for (j in 1:2) { delta.p3[j] ~ dnorm(0.0,0.0001) }
m.rp3~dnorm(0.0,0.001)
t.rp3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rp3[j]~dnorm(m.rp3,t.rp3) }

for (i in 1:6){ logit(p.p3[i])<-mu.rp3[study.p3[i]]
+ equals(treat.p3[i],2) * delta.p3[1] +
equals(treat.p3[i],3) * delta.p3[2]}
```

```
for (i in 1:6){ r.p3[i]~dbin(p.p3[i],n.p3[i]) }

logit(t.p3[1]) <- m.rp3
for (j in 2: 3) { logit(t.p3[j]) <- m.rp3 +
delta.p3[j-1] }


######PPE grade 4 (t.p4)

for (j in 1:2) { delta.p4[j] ~ dnorm(0.0,0.0001) }
m.rp4~dnorm(0.0,0.001)
t.rp4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rp4[j]~dnorm(m.rp4,t.rp4) }

for (i in 1:6){ logit(p.p4[i])<-mu.rp4[study.p4[i]]
+ equals(treat.p4[i],2) * delta.p4[1] +
equals(treat.p4[i],3) * delta.p4[2]}

for (i in 1:6){ r.p4[i]~dbin(p.p4[i],n.p4[i]) }

logit(t.p4[1]) <- m.rp4
for (j in 2: 3) { logit(t.p4[j]) <- m.rp4 +
delta.p4[j-1] }


######stomatitis/pharyngitis grade 3 (t.s3)
#treatment 5 = carboplatin/cisplatin, treatment
6= carboplatin+enoxiparin
# incorporates Bolis data and assumed number of
events from Cantu
for (j in 1:5) { delta.s3[j] ~ dnorm(0.0,0.0001) }
m.rs3~dnorm(0.0,0.001)
t.rs3~dgamma(0.01,0.01)
for (j in 1:6){ mu.rs3[j]~dnorm(m.rs3,t.rs3) }

for (i in 1:10){ logit(p.s3[i])<-mu.rs3[study.s3[i]] +
equals(treat.s3[i],2) * delta.s3[1] +
equals(treat.s3[i],3) * delta.s3[2] +
equals(treat.s3[i],4) * delta.s3[3] +
equals(treat.s3[i],5) * delta.s3[4] +
equals(treat.s3[i],6) * delta.s3[5]}

for (i in 1:10){ r.s3[i]~dbin(p.s3[i],n.s3[i]) }

logit(t.s3[1]) <- m.rs3
for (j in 2: 6) { logit(t.s3[j]) <- m.rs3 + delta.s3[j-
1] }

######stomatitis/pharyngitis grade 4 (t.s4)
# incorporates Bolis data and assumed number of
events from Cantu
for (j in 1:5) { delta.s4[j] ~ dnorm(0.0,0.0001) }
m.rs4~dnorm(0.0,0.001)
t.rs4~dgamma(0.01,0.01)
for (j in 1:6){ mu.rs4[j]~dnorm(m.rs4,t.rs4) }

for (i in 1:10){ logit(p.s4[i])<-mu.rs4[study.s4[i]] +
equals(treat.s4[i],2) * delta.s4[1] +
equals(treat.s4[i],3) * delta.s4[2] +
equals(treat.s4[i],4) * delta.s4[3] +
equals(treat.s4[i],5) * delta.s4[4] +
equals(treat.s4[i],6) * delta.s4[5]}

for (i in 1:10){ r.s4[i]~dbin(p.s4[i],n.s4[i]) }

logit(t.s4[1]) <- m.rs4
for (j in 2: 6) { logit(t.s4[j]) <- m.rs4 + delta.s4[j-
1] }

######diarrhoea grade 3 (t.d3)
for (j in 1:2) { delta.d3[j] ~ dnorm(0.0,0.0001) }
m.rd3~dnorm(0.0,0.001)
t.rd3~dgamma(0.01,0.01)
for (j in 1:3){ mu.rd3[j]~dnorm(m.rd3,t.rd3) }

for (i in 1:6){ logit(p.d3[i])<-mu.rd3[study.d3[i]] +
equals(treat.d3[i],2) * delta.d3[1] +
equals(treat.d3[i],3) * delta.d3[2]}

for (i in 1:6){ r.d3[i]~dbin(p.d3[i],n.d3[i]) }

logit(t.d3[1]) <- m.rd3
for (j in 2: 3) { logit(t.d3[j]) <- m.rd3 + delta.d3[j-
1] }

######diarrhoea grade 4 (t.d4)
for (j in 1:2) { delta.d4[j] ~ dnorm(0.0,0.0001) }
m.rd4~dnorm(0.0,0.001)
t.rd4~dgamma(0.01,0.01)
for (j in 1:3){ mu.rd4[j]~dnorm(m.rd4,t.rd4) }

for (i in 1:6){ logit(p.d4[i])<-mu.rd4[study.d4[i]] +
equals(treat.d4[i],2) * delta.d4[1] +
equals(treat.d4[i],3) * delta.d4[2]}

for (i in 1:6){ r.d4[i]~dbin(p.d4[i],n.d4[i]) }

logit(t.d4[1]) <- m.rd4
for (j in 2: 3) { logit(t.d4[j]) <- m.rd4 + delta.d4[j-
1] }

######nausea/vomiting grade 3 (t.nv3)
#incorporates ICON4, Cantu and Bolis data
for (j in 1:6) { delta.nv3[j] ~ dnorm(0.0,0.0001) }
m.rnv3~dnorm(0.0,0.001)
t.rnv3~dgamma(0.01,0.01)
for (j in 1:7){ mu.rnv3[j]~dnorm(m.rnv3,t.rnv3) }

for (i in 1:12){ logit(p.nv3[i])<-
mu.rnv3[study.nv3[i]] + equals(treat.nv3[i],2) *
delta.nv3[1] + equals(treat.nv3[i],3) * delta.nv3[2]
+ equals(treat.nv3[i],4) * delta.nv3[3] +
equals(treat.nv3[i],5) * delta.nv3[4] +
equals(treat.nv3[i],6) * delta.nv3[5] +
```

```
equals(treat.nv3[i],7) * delta.nv3[6]}

for (i in 1:12){ r.nv3[i]~dbin(p.nv3[i],n.nv3[i]) }

logit(t.nv3[1]) <- m.rnv3
for (j in 2: 7) { logit(t.nv3[j]) <- m.rnv3 +
delta.nv3[j-1] }

######nausea/vomiting grade 4 (t.nv4)
##no info from Cantu available for grade 4,
therefore T[4] is paclitaxel combination, T[5] is
carboplatin/cisplatin # no grade 4 info from Bolis

for (j in 1:4) { delta.nv4[j] ~ dnorm(0.0,0.0001) }
m.rnv4~dnorm(0.0,0.001)
t.rnv4~dgamma(0.01,0.01)
for (j in 1:5){ mu.rnv4[j]~dnorm(m.rnv4,t.rnv4) }

for (i in 1:8){ logit(p.nv4[i])<-
mu.rnv4[study.nv4[i]] + equals(treat.nv4[i],2) *
delta.nv4[1] + equals(treat.nv4[i],3) * delta.nv4[2]
+ equals(treat.nv4[i],4) * delta.nv4[3] +
equals(treat.nv4[i],5) * delta.nv4[4] }

for (i in 1:8){ r.nv4[i]~dbin(p.nv4[i],n.nv4[i]) }

logit(t.nv4[1]) <- m.rnv4
for (j in 2: 5) { logit(t.nv4[j]) <- m.rnv4 +
delta.nv4[j-1] }

######sepsis grade 3 (t.se3)
#T[4] is carboplatin and T[5] is carboplatin +
enoxiparin
#incorporates data from Bolis
for (j in 1:4) { delta.se3[j] ~ dnorm(0.0,0.0001) }
m.rse3~dnorm(0.0,0.001)
t.rse3~dgamma(0.01,0.01)
for (j in 1:5){ mu.rse3[j]~dnorm(m.rse3,t.rse3) }

for (i in 1:8){ logit(p.se3[i])<-mu.rse3[study.se3[i]]
+ equals(treat.se3[i],2) * delta.se3[1] +
equals(treat.se3[i],3) * delta.se3[2] +
equals(treat.se3[i],4) * delta.se3[3] +
equals(treat.se3[i],5) * delta.se3[4]}

for (i in 1:8){ r.se3[i]~dbin(p.se3[i],n.se3[i]) }

logit(t.se3[1]) <- m.rse3
for (j in 2: 5) { logit(t.se3[j]) <- m.rse3 +
delta.se3[j-1] }

######sepsis grade 4 (t.se4)
#T[4] is carboplatin and T[5] is carboplatin +
enoxiparin
#incorporates data from Bolis
for (j in 1:4) { delta.se4[j] ~ dnorm(0.0,0.0001) }
m.rse4~dnorm(0.0,0.001)
t.rse4~dgamma(0.01,0.01)
for (j in 1:5){ mu.rse4[j]~dnorm(m.rse4,t.rse4) }

for (i in 1:8){ logit(p.se4[i])<-mu.rse4[study.se4[i]]
+ equals(treat.se4[i],2) * delta.se4[1] +
equals(treat.se4[i],3) * delta.se4[2] +
equals(treat.se4[i],4) * delta.se4[3] +
equals(treat.se4[i],5) * delta.se4[4]}

for (i in 1:8){ r.se4[i]~dbin(p.se4[i],n.se4[i]) }

logit(t.se4[1]) <- m.rse4
for (j in 2: 5) { logit(t.se4[j]) <- m.rse4 +
delta.se4[j-1] }

#########fever grade 3 (t.f3)
#T[4] is carboplatin and T[5] is carboplatin +
enoxiparin
#incorporates data from Bolis
for (j in 1:4) { delta.f3[j] ~ dnorm(0.0,0.0001) }
m.rf3~dnorm(0.0,0.001)
t.rf3~dgamma(0.01,0.01)
for (j in 1:5){ mu.rf3[j]~dnorm(m.rf3,t.rf3) }

for (i in 1:8){ logit(p.f3[i])<-mu.rf3[study.f3[i]] +
equals(treat.f3[i],2) * delta.f3[1] +
equals(treat.f3[i],3) * delta.f3[2] +
equals(treat.f3[i],4) * delta.f3[3] +
equals(treat.f3[i],5) * delta.f3[4]}

for (i in 1:8){ r.f3[i]~dbin(p.f3[i],n.f3[i]) }

logit(t.f3[1]) <- m.rf3
for (j in 2: 5) { logit(t.f3[j]) <- m.rf3 + delta.f3[j-
1] }


#########fever grade 4 (t.f4)
#T[4] is carboplatin and T[5] is carboplatin +
enoxiparin
#incorporates data from Bolis
for (j in 1:4) { delta.f4[j] ~ dnorm(0.0,0.0001) }
m.rf4~dnorm(0.0,0.001)
t.rf4~dgamma(0.01,0.01)
for (j in 1:5){ mu.rf4[j]~dnorm(m.rf4,t.rf4) }

for (i in 1:8){ logit(p.f4[i])<-mu.rf4[study.f4[i]] +
equals(treat.f4[i],2) * delta.f4[1] +
equals(treat.f4[i],3) * delta.f4[2] +
equals(treat.f4[i],4) * delta.f4[3] +
equals(treat.f4[i],5) * delta.f4[4] }

for (i in 1:8){ r.f4[i]~dbin(p.f4[i],n.f4[i]) }

logit(t.f4[1]) <- m.rf4
for (j in 2: 5) { logit(t.f4[j]) <- m.rf4 + delta.f4[j-
1] }
```

```
}

# data

list(r.n3 =c(33,19,17,34,10,6,5,8,3,12),(r.n4 =
c(146,10,89,24,3,1,1,9),
(r.t3=c(40,3,25,2,0.5,0.5,0.5,5,11,31),
(r.t4=c(40,0.5,30,3,0.5,0.5,0.5,1,8,29),
(r.a3=c(59,13,42,4,5,3,5,18),
(r.a4=c(10,1,4,3,0.5,0.5,4,5),
(r.p3=c(0.5,55,0.5,0.5,0.5,16),
(r.p4=c(0.5,2,0.5,0.5,0.5,1),
(r.s3=c(2,19,1,1,1,11,0.5,0.5,0.5,3),
(r.s4=c(0.5,1,0.5,0.5,0.5,0.5,0.5,1,0.5,1),
(r.d3=c(9,5,6,1,3,3), (r.d4=c(1,1,1,0.5,0.5,0.5),
(r.nv3=c(34,29,17,4,6,16,0.5,2,37,47,3,12),
(r.nv4=c(8,3,5,1,0.5,3,2,6),
(r.se3=c(1,0.5,2,2,0.5,0.5,0.5,0.5),
(r.se4=c(1,0.5,2,0.5,0.5,0.5,0.5,0.5),
(r.f3=c(8,2,1,1,3,7,0.5,0.5),
(r.f4=c(5,0.5,0.5,0.5,0.5,0.5,0.5,0.5),

n.n3=c(235,239,112,114,108,108,47,47),
n.n4=c(235,239,112,114,108,108,47,47),
n.t3=c(235,239,112,114,108.5,108.5,47.5,47,95,95
),
n.t4=c(235,239.5,112,114,108.5,108.5,47.5,47,95,
95),
n.a3=c(235,239,112,114,108,108,95,95),
n.a4=c(235,239,112,114,108.5,108.5,95,95),
n.p3=c(235.5,239,112.5,114.5,108.5,108),
n.p4=c(235.5,239,112.5,114.5,108.5,108),
n.s3=c(235,239,112,114,108,108,47.5,47.5,95.5,95
),
n.s4=c(235.5,239,112.5,114.5,108.5,108.5,47.5,47,
95.5,95),
n.d3=c(235,239,112,114,108,108),
n.d4=c(235,239,112,114.5,108.5,108.5),,
n.nv3=c(235,239,112,114,108,108,47.5,47,392,41
0,95,95),
n.nv4=c(235,239,112,114,108.5,108,392,410),
n.se3=c(235,239.5,112,114,108.5,108.5,95.5,95.5),
n.se4=c(235,239.5,112,114.5,108.5,108.5,95.5,95.
5),
n.f3=c(235,239,112,114,108,108,95.5,95.5),
n.f4=c(235,239.5,112.5,114.5,108.5,108.5,95.5,95.
5),

study.n3=c(1,1,2,2,3,3,4,4),
study.n4=c(1,1,2,2,3,3,4,4),
study.t3=c(1,1,2,2,3,3,4,4,5,5),
study.t4=c(1,1,2,2,3,3,4,4,5,5),
study.a3=c(1,1,2,2,3,3,4,4),
study.a4=c(1,1,2,2,3,3,4,4),
study.p3=c(1,1,2,2,3,3),
study.p4=c(1,1,2,2,3,3),
study.s3=c(1,1,2,2,3,3,4,4,5,5),
study.s4=c(1,1,2,2,3,3,4,4,5,5),
study.d3=c(1,1,2,2,3,3),
study.d4=c(1,1,2,2,3,3),
study.nv3=c(1,1,2,2,3,3,4,4,5,5,6,6),
study.nv4=c(1,1,2,2,3,3,4,4),
study.se3=c(1,1,2,2,3,3,4,4),
study.se4=c(1,1,2,2,3,3,4,4),
study.f3=c(1,1,2,2,3,3,4,4),
study.f4=c(1,1,2,2,3,3,4,4),

treat.n3=c(1,3,1,2,2,3,2,4),
treat.n4=c(1,3,1,2,2,3,2,4),
treat.t3=c(1,3,1,2,2,3,2,4,5,6),
treat.t4=c(1,3,1,2,2,3,2,4,5,6),
treat.a3=c(1,3,1,2,2,3,4,5),
treat.a4=c(1,3,1,2,2,3,4,5),
treat.p3=c(1,3,1,2,2,3),
treat.p4=c(1,3,1,2,2,3),
treat.s3=c(1,3,1,2,2,3,2,4,5,6),
treat.s4=c(1,3,1,2,2,3,2,4,5,6),
treat.d3=c(1,3,1,2,2,3),
treat.d4=c(1,3,1,2,2,3),
treat.nv3=c(1,3,1,2,2,3,2,4,5,6,6,7),
treat.nv4=c(1,3,1,2,2,3,4,5),
treat.se3=c(1,3,1,2,2,3,4,5),
treat.se4=c(1,3,1,2,2,3,4,5),
treat.f3=c(1,3,1,2,2,3,4,5),
treat.f4=c(1,3,1,2,2,3,4,5))

# initial
list(m.rn3=0,
t.rn3=1, m.rn4=0,t.rn4=1,m.rt3=0, t.rt3=1,
m.rt4=0, t.rt4=1,m.ra3=0,t.ra3=1,
m.ra4=0,t.ra4=1, m.rp3=0,t.rp3=1,
m.rp4=0,t.rp4=1, m.rs3=0,t.rs3=1,
m.rs4=0,t.rs4=1, m.rd3=0,t.rd3=1,
m.rd4=0,t.rd4=1, m.rnv3=0, t.rnv3=1,
m.rnv4=0,t.rnv4=1, m.rse3=0, t.rse3=1,
m.rse4=0, t.rse4=1, m.rf3=0, t.rf3=1, m.rf4=0,
t.rf4=1)
```

Appendix 12

Details of the economic model

Survival data used in the sensitivity analysis (values in parentheses are ranges)

		Name	Overall trial population	Platinum sensitive	Platinum resistant/refractory	Source trial
Sensitivity analysis including trial 30-57 overall survival data	Overall survival hazards	Topotecan 'v' paclitaxel	0.914 (0.681, 1.226)	1.01 (0.663, 1.541)	0.738 (0.498, 1.093)	039
		Topotecan 'v' PLDH	1.216 (1, 1.478)	1.432 (1.066, 1.923)	1.069 (0.823, 1.387)	30-49
		PLDH 'v' paclitaxel	0.93 (0.70, 1.23)	1.05 (0.66, 1.67)	0.87 (0.61, 1.24)	30-57
	PFS hazards	Topotecan 'v' paclitaxel	0.811 (0.603, 1.092)	0.823 (0.538, 1.261)	0.749 (0.501, 1.121)	039
		Topotecan 'v' PLDH	1.118 (0.928, 1.347)	1.287 (0.977, 1.694)	0.992 (0.77, 1.279)	30-49
		PLDH 'v' paclitaxel	–	–	–	
Sensitivity analysis using subgroup treatment effects	Overall survival hazards	Topotecan 'v' paclitaxel	–	1.01 (0.663, 1.541)	0.738 (0.498,1.093)	
		Topotecan 'v' PLDH	–	1.432 (1.066, 1.923)	1.069 (0.823, 1.387)	
		PLDH 'v' paclitaxel	–	1.05 (0.66, 1.67)	0.87 (0.61, 1.24)	
	PFS survival hazards	Topotecan 'v' paclitaxel	–	0.823 (0.538, 1.261)	0.749 (0.501, 1.121)	
		Topotecan 'v' PLDH	–	1.287 (0.977, 1.694)	0.992 (0.77, 1.279)	
		PLDH 'v' paclitaxel	–			
Other sensitivity analysis on Analysis 1 did not involve changing any of the survival estimates.						

Resource use associated with adverse events (taken from Schering-Plough submission[23]

Adverse event	Resource use item	Cost per item (£)	Distribution
Stomatitis/pharyngitis grade 3	Outpatient visit	90	Triangular (0, 1.5, 2)
	Paracetamol mouthwash	1	Fixed
	Sulcralfate	0.37	Triangular (7, 8.5, 10)
	Oramorph	4.62	Fixed
Stomatitis/pharyngitis grade 4	Inpatient stay	293	Uniform (5, 7)
	Fluconzole i.v.	204.96	Fixed
	Saline	42	Fixed
	Paracetamol mouthwash	1	Fixed
	Sulcrafate	0.37	Triangular (7, 8.5, 10)
	Oramorph	4.62	Fixed
PPE grade 3	Outpatient visit	90	Fixed
	Paracetamol	3.09	Fixed
	Pyridoxine	0.29	Fixed
PPE grade 4	Inpatient stay	293	Triangular (5, 7, 14)
	Flucoxacillin i.v.	57.12	Fixed
	Saline	42	Fixed
	Paracetamol	3.09	Fixed
	Pyridoxine	0.29	Fixed
Neutropenia grade 3	Outpatient visit	90	Uniform (0, 1)
	Ciprofloxacin	1.50	Uniform (5, 7)
Neutropenia grade 4	Inpatient stay	293	Uniform (2, 5)
	Ciprofloxacin	1.50	Uniform (5, 7)
	G-CSF	77.03	Uniform (3, 7)
Thrombocytopenia grade 3	–	–	–
Thrombocytopenia grade 4	Day-case admission	293	Fixed
	Platelet transfusion	705	Fixed
	Type and cross	18	Fixed
Anaemia grade 3	Day-case admission	293	Fixed
	Blood transfusion	78.80	Fixed
	Type and cross	18	Fixed
Anaemia grade 4	Inpatient stay	293	Uniform (3, 6)
	Blood transfusion	78.80	Fixed
	Type and cross	18	Fixed
Diarrhoea grade 3	Inpatient stay	1465	Fixed
	Buscopan	1.39	Fixed
	Ciprofloxacin	1.50	Uniform (5, 7)
	Codeine	0.33	Fixed
	Loperamide	0.08	Uniform (2, 3)
Diarrhoea grade 4	Inpatient stay	1465	Fixed
	Buscopan	1.39	Fixed
	Ciprofloxacin	1.50	Uniform (5, 7)
	Codeine	0.33	Fixed
	Loperamide	0.08	Uniform (2, 3)
Nausea/vomiting grade 3	Outpatient visit	90	Fixed
	Dexamethasone	0.51	Uniform (5, 7)
	Granisetron	383.95	Fixed

continued

Adverse event	Resource use item	Cost per item (£)	Distribution
Nausea/vomiting grade 4	Inpatient stay	1465	Fixed
	Saline	42	Fixed
	Dexamethasone i.v.	6.60	Fixed
	Granisetron i.v.	360	Fixed
	Cyclizine	8.55	Fixed
Sepsis grade 3	Inpatient stay	293	Uniform (3, 6)
	Gentamicin	61.25	Fixed
	Tazocin	368.48	Fixed
Sepsis grade 4	Inpatient stay	293	Triangular (3.5, 5, 7)
	Intensive care unit	558	Triangular (3.5, 5, 7)
	Gentamicin	61.25	Fixed
	Tazocin	368.48	Fixed
	Saline	42	Fixed
	Fluconzole i.v.	204.96	Fixed
Fever grade 3	Inpatient stay	293	Uniform (3, 6)
	Gentamicin	61.25	Fixed
	Tazocin	368.48	Fixed
Fever grade 4	Inpatient stay	293	Triangular (3.5, 5, 7)
	Intensive care unit	558	Triangular (3.5, 5, 7)
	Gentamicin	61.25	Fixed
	Tazocin	368.48	Fixed
	Saline	42	Fixed
	Fluconzole i.v.	204.96	Fixed

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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