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Product name: **HYCAMTIN**
Procedure No. **EMEA/H/C/123/II/38**

SCIENTIFIC DISCUSSION

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Introduction

Topotecan was authorised in the European Union (EU) through the centralised procedure in 1996 and is also registered in 59 other countries around the world for the treatment of relapsed ovarian cancer following platinum-based therapy. In addition, topotecan is registered in the EU and 39 other countries around the world for the treatment of relapsed small cell lung cancer (SCLC). Approximately 230,000 patients have been treated with topotecan (this represents approximately 1,000,000 courses of therapy) since its first market launch in May 1996.

This is an application to add an additional clinical indication, treatment in combination with cisplatin of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IV-B disease, thereby varying the existing marketing authorisation for topotecan hydrochloride.

Topotecan is a cytotoxic anti-cancer agent, semisynthetic analogue of the alkaloid camptothecin. Topotecan is exerting its activity by the inhibition of the nuclear enzyme topoisomerase I that is involved in DNA replication. The inhibition is due to stabilisation of the intermediate covalent complex of enzyme and strand-cleaved DNA. As a result, DNA damage induces apoptotic cell death predominantly in replicating cells such as tumour cells.

Cervical cancer remains the second most common cancer in women worldwide and in many countries, the leading cause of cancer related deaths among women. Globally, approximately 493,000 women are diagnosed with invasive cervical cancer each year and each year approximately 273,000 will die as a direct consequence of the disease. The incidence rates around the world vary considerably with an estimated 80% of new cases occurring in less developed countries.

In countries with efficient screening for cervical cancer, advanced disease is relatively rare, but overall there are about 38,000 new cases of cervical cancer a year within the EU and about 17,000 associated deaths. Vaccination is expected to further reduce the incidence of the disease.

Approximately 90% of cervical cancers are squamous cell carcinomas. In the EU, most patients are diagnosed with early disease (FIGO I-IIa) and surgery is curative. In more advanced, non-metastatic disease, radio- and radiochemotherapy is administered with curative intent. In case of persistent, recurrent or metastatic disease, treatment is in most cases administered with palliative intent. There is no universally accepted standard chemotherapy for advanced and incurable disease, but cisplatin 50 mg/m^2 every three weeks may be regarded as a reasonable reference regimen for comparative trials.

New indication: Treatment, in combination with cisplatin, of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IV-B disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination (see section 5.1 of the SPC).

New posology: The recommended dose of topotecan is 0.75 mg/m^2/day administered as a 30-minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2/day and following the topotecan dose. This treatment schedule is repeated every 21 days for 6 courses or until progressive disease.

In addition, new information on the pharmacokinetics of topotecan in combination with cisplatin has been included in sections 4.5 and 5.2.

Clinical aspects

Clinical Pharmacology

The dose and schedule of topotecan in combination with cisplatin for cervical cancer has been determined on the basis of safety and tolerability and the pharmacokinetics of 0.75 mg/m^2/day of topotecan as a 3-day regimen in combination with cisplatin 50 mg/m^2 on day 1 in patients with cervical cancer has not been investigated. However, a previous study in ovarian cancer patients investigated the pharmacokinetics of 0.75 mg/m^2/day topotecan in a 5-day regimen in combination with cisplatin 60 mg/m^2 on day 1. This study was submitted in support of the current variation together with a study investigating the pharmacokinetics of a topotecan + cisplatin + paclitaxel regimen in patients with ovarian carcinoma.

Study 096

The objective of the study was to determine the effect of a single IV infusion of cisplatin on the pharmacokinetics of intravenous topotecan. Cisplatin 60 mg/m^2 was given as an infusion on Day 1 only. Topotecan 0.75 mg/m^2/day was given as a 30-minute infusion for 5 consecutive days. The first dose of topotecan was given directly after cisplatin. Blood sampling for topotecan lactone and total topotecan concentrations were drawn on Days 1 and 5 and for cisplatin concentrations on Day 1.

Compared to Day 1, mean systemic exposure of topotecan lactone (C_{max} and AUC) on Day 5 was increased by approximately 29% and 16%, respectively, and mean exposure of total topotecan was increased by 23% and 12%, respectively. One subject had unusually high C_{max} values for both total topotecan and topotecan lactone. Removal of this subject reduced the mean increase in C_{max} values to 16% and 11%, respectively. The mean terminal elimination half life increased on Day 5 compared to Day 1 from 1.96 h to 2.46 h for topotecan lactone and 2.02 h to 2.20 h for total topotecan. Mean CL and Vss values of total topotecan were slightly reduced on Day 5 compared to Day 1 (19.1 L/h/m2 versus 21.3 L/h/m^2 and 54.5 L/m^2 versus 59.0 L/m^2, respectively). A similar pattern was observed for topotecan lactone (35.6 L/h/m^2 versus 40.8 L/h/m^2 (CL) and 103 L/m^2 versus 107 L/m^2 (Vss)). The mean maximum plasma concentration of free platinum following intravenous infusion of cisplatin was similar to other reported values.

Study 100

This was a phase I study, designed to determine the maximum tolerated doses of paclitaxel, cisplatin, and topotecan administered intravenously every 21 days as first-line therapy in patients with advanced ovarian cancer. Paclitaxel (110 mg/m^2) was administered as a 24 h IV infusion on Day 1, followed by cisplatin (50 mg/m^2) as a 3-h infusion on Day 2, followed by topotecan (0.3 mg/m^2) as a 30-minute infusion daily on Days 2, 3, 4, 5, 6. The pharmacokinetic determinations were made during course 1; paclitaxel samples were obtained on Day 1, and cisplatin and topotecan (total and lactone) samples on Day 2. One additional daily sample (2.5 h after the start of the infusion) was obtained on Days 3-6 for topotecan (total and lactone).

Mean topotecan lactone and total topotecan CL and Vss values were 47.5 L/h/m^2 and 19.3 L/h/m^2, respectively and 84.9 L/m^2 and 49.5 L/m^2, respectively. These values were similar to those observed in Study 096. Mean concentrations 2.5 h after start of infusion were slightly higher 22% (topotecan lactone) and 19% (total topotecan) on Days 3-6 compared to Day 2. Mean percent topotecan dose excreted in urine was calculated in this study; mean values were lower on Days 3 (43%), 4 (45%), and 5 (45%) than Day 2 (50%). CV% ranged between 41 and 50 (mean 45) across days.
The pharmacokinetics of paclitaxel and cisplatin were similar to previously reported values, although the half-life of cisplatin was somewhat longer than previously reported.

Discussion on Clinical Pharmacology

As previous data has not indicated a change in topotecan pharmacokinetics over time at repeated administration over 5 days, the results of studies 096 and 100 might suggest that cisplatin decreases

the (renal) clearance of topotecan. However, firm conclusions cannot be drawn, as there was no comparison of topotecan concentrations with and without cisplatin on day 1. Topotecan is predominantly cleared renally, and there is some limited biliary excretion. Topotecan undergoes very little metabolism, although a demethylated metabolite has been identified in plasma, urine and faeces in humans. A possible explanation might be a hydration prior to cisplatin infusion and cisplatin-induced (transient) reduction in kidney function. Appropriate information in this regard has been added to sections 4.5 and 5.2 of the SPC.

Topotecan as monotherapy in ovarian cancer is dosed at an initial dose of 1.5 mg/m^2 per day for 5 consecutive days every 3 weeks. The dosing recommendations for patients with compromised renal or liver function as described in the current SPC are considered appropriate also for the regimen recommended for cervical cancer. The Hycamtin SPC makes reference to the product information of cisplatin regarding e.g. special population recommendations for cisplatin, which is appropriate.

Clinical Efficacy

Topotecan monotherapy

Summary data from two topotecan monotherapy, phase II GOG studies are presented below.

Phase II data: Topotecan monotherapy in advanced cervical cancer

Study	Phase	Patient Population	N	Regimen	Efficacy	Principal Toxicity
GOG-127	II	2nd-line Squamous cell carcinoma of the cervix; Measurable Disease	41	1.5mg/m2/ day Dx5 q 21 days	Primary: Response rate: 12.5% Secondary: Stable Disease: 38% Median PFS: 2.1 months Median Survival: 6.6 months	Haematological Grade 4 Neutropenia 68% pts No treated related deaths
GOG-76-U	II	Chemotherapy naïve, Incurable cervical cancer. Measurable disease	43	1.5mg/m2/ day Dx5 q 28 days	Primary: Response rate: 18.6% Secondary: Stable Disease: 33% Median PFS: 2.4 months Median Survival: 6.4 months	Haematological Grade 4 Neutropenia 68% pts 1 treated related deaths

Combination therapy cisplatin + topotecan

Supportive Phase II study - GSK-CRT-234

This was a single arm phase II trial designed to investigate the safety and efficacy of topotecan and cisplatin combinations in patients with persistent or recurrent squamous and non-squamous cell carcinomas of the cervix.

Eligible patients had bidimensionally measurable persistent or recurrent histologically confirmed squamous cell or non squamous cell cervical cancer, adequate bone marrow, renal, and hepatic function GOG PS ≤3 and failed or considered incurable with local therapeutic measures.

Patients were randomized to receive Cisplatin 50 mg/m² IV over 1h (Day 1) and Topotecan 0.75 mg/m² IV over 30 minutes (Days 1, 2 and 3) every 21 days.

35 patients were enrolled into the trial.

Primary efficacy endpoint

- Overall survival: (all-cause mortality) was expressed as the time from randomization until death in the intent-to-treat (ITT) population.

Secondary efficacy endpoints

- Progression-free survival: the time from randomization until death or relapse in the ITT population.
- Response rate: the percentage of all eligible patients responding to treatment; i.e., patients with complete response or partial response divided by the total number of patients in each group in the ITT population. The overall best response categories were categorized as follows:
Complete response (CR): complete disappearance of all gross evidence for at least 4 weeks.
Partial response (PR): at least a 50% decrease in the cross-product dimensions of each tumor compared to the cross-product dimensions reported on the first course of therapy for at least 4 weeks.
Progressive Disease: at least 50% increase in the cross-product dimensions of any tumor compared to the cross-product dimensions reported on the first course of therapy and occurring within 8 weeks of study entry or the appearance of any new lesion within 8 weeks of study entry.
Stable Disease: disease not meeting any of the above 3 response criteria.

RESULTS

Overall response rate was 9/32 (evaluable patients out of a total of 35 patients) with a reported median survival of 10 months. The regimen was considered tolerable.

Pivotal Phase III study - GOG-0179

This was a randomised, open-label, three-arm, comparator controlled phase III study of cisplatin versus cisplatin plus topotecan versus methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) in stage IVB, recurrent or persistent carcinoma of the cervix. It was a multicentre (47, all US) trial conceived, designed and conducted by the GOG (Gynecologic Oncology Group) between Aug 1999 and Dec 2002.

The third arm "MVAC" (methotrexate, vinblastine, doxorubicin, cisplatin) was closed by the Data Safety Monitoring Board (DSMB) due to too high toxicity (four treatment related deaths in 63 patients).

Methods

Primary efficacy endpoint:
- Overall survival

Secondary efficacy endpoints:
- Response rate (RR) WHO,
- Progression Free Survival (PFS),
- Quality of Live (QoL)

Main inclusion criteria:
- Histologically proven stage IVB (i.e. disseminated disease) or recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix not amenable to curative treatment with surgery and/or radiation therapy (RT).
- Measurable disease
- Adequate haematological, renal and hepatic function.
- GOG performance status of 0, 1, or 2.
- Patients must have recovered from the effects of surgery, RT, or chemoradiotherapy. At least 6 weeks must have elapsed from the last administration of chemoradiotherapy, and at least 3 weeks must have elapsed from the last administration of RT alone.

Main exclusion criteria:
- Bilateral hydronephrosis not alleviated by ureteral stents or percutaneous drainage.
- Prior chemotherapy except when used concurrently with RT.

Regimen I: Cisplatin 50 mg/m2 IV on day 1 every 3 weeks for 6 courses or until disease progression or unacceptable adverse effects.

Regimen II: Topotecan 0.75 mg/m2 infused over 30 minutes on days 1, 2, and 3 followed by cisplatin 50 mg/m2 IV on day 1. The regimen was repeated every 3 weeks for 6 courses or until disease progression or unacceptable adverse effects.

Methodology:

- ITT population: all randomized patients, excluding ineligible patients
- Randomized population: all randomized patients, including the ineligible subjects.
- Treated population: included all patients who were randomized and treated in the topotecan/cisplatin and cisplatin alone treatment groups.

Central randomisation was used and no stratification. There was one interim analysis, final nominal p-value 0.044. The following parameters were collected, analyzed and reported:
- Disease characteristics: primary vs. recurrent, location of lesion(s) and previous treatment.
- Host characteristics: age, performance status and race.

The trial was conducted in accordance with National Cancer Institute (NCI) Standard Operation Procedures encompassing the principles of GCP.

Baseline characteristics, ITT

	Cisplatin	Topotecan/cisplatin
Number of Patients	146	147
Performance Status	n (%)	n (%)
0	68 (47)	69 (47)
1	66 (45)	66 (45)
2	12 (8)	12 (8)
3	NA	NA
Histological Cell Type		
Squamous	121 (83)	128 (87)
Total Non-squamous	25 (17)	19 (13)
Adenosquamous	11 (8)	5 (3)
Adenocarcinoma	9 (6)	9 (6)
Mucinous	0 (0)	4 (3)
Clear Cell	2 (1)	0 (0)
Endometrioid	3 (2)	0 (0)
Villoglandular	0 (0)	1 (1)
Tumour Grade		
1 Well differentiated	9 (6)	8 (5)
2 Moderately differentiated	81 (55)	84 (57)
3 Poorly differentiated	52 (36)	52 (35)
Not Graded	4 (3)	3 (2)
Stage		
IVB	16(11)	14 (10)
Persistent	12 (8)	20 (14)
Recurrent	118 (81)	113 (77)
Prior Radiotherapy		
No Prior Radiotherapy	20 (14)	18 (12)
Prior Radiotherapy	------	-----
Prior radiotherapy, no prior sensitisation	37 (25)	37 (25)
Prior cisplatin radiation sensitiser	82 (56)	83 (56)
Prior non-cisplatin radiation sensitiser	7 (5)	9 (6)

Patient disposition

Reason for Study Conclusion	Cisplatin (n = 146)		Topotecan/Cisplatin (n = 147)	
	n	(%)	N	(%)
Completed Study[a]	21	(14)	29	(20)
Withdrawal reason				
Disease progression	81	(55)	62	(42)
Refused further study treatment	8	(5)	13	(9)
Toxicity	15	(10)	15	(10)
Death	9	(6)	11	(7)
Patient off study for other disease	4	(3)	7	(5)
Other	8	(5)	10	(7)
Total Withdrawn	125	(86)	118	(80)

a. Completed as defined by completing 6 courses of treatment as described in the protocol.

RESULTS

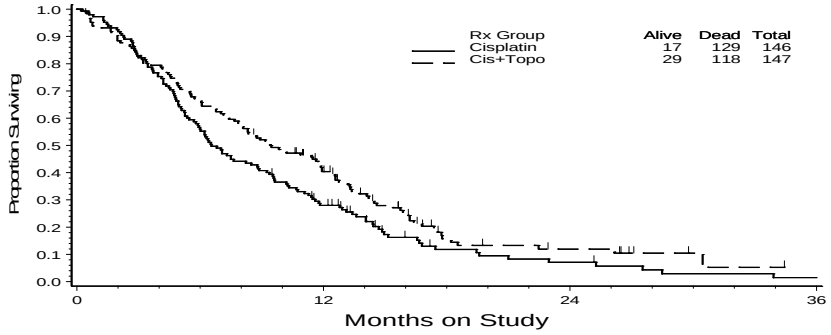
Overall Survival, ITT Population

	Cisplatin	Topotecan/Cisplatin
	(N = 146)	(N = 147)
Overall Survival Time (months)		
Median (95% C.I.)	6.5 (5.8, 8.8)	9.4 (7.9, 11.9)
Log-rank p-value[1]	0.033	
*Hazard Ratio (95% C.I.)	0.76 (0.59, 0.98)	
1 Year Survival Rate (%) (95% C.I.)	28.0 (20.6, 35.4)	40.4 (32.3, 48.5)
2 Year Survival Rate (%) (95% C.I.)	7.1 (2.0, 12.2)	11.9 (5.5, 18.3)
Range	0.3 – 39.0	0.2 – 34.4
Observed events	129 (88%)	118 (80%)
Censored events	17 (12%)	29 (20%)

1 Log-rank p-value was significant (<0.044 adjusted significance level).

After adjusting for covariates of age, performance status and disease status at study entry, the hazard ratio was 0.76 (95% C.I., 0.59 to 0.98; p=0.033) favouring the combination arm.

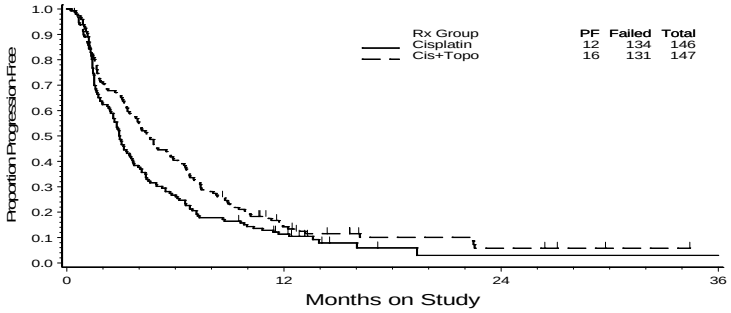
Figure 1.1
Kaplan Meier Plot of survival
Cisplatin versus topotecan plus Cisplatin in stage IVB, recurrent or persistent carcinoma of the cervix (GOG 0179).
ITT (intent to treat) subjects.



The survival results were similar in the "all randomised population" (p=0.04).
No appreciable differences were observed between the treatment arms with respect to the use of post-study (salvage) therapy. Approximately 44% of topotecan/cisplatin and 42% of cisplatin patients received at least one post-study chemotherapy regimen.

Progression-Free Survival Following Treatment, ITT Population

Figure 2.1
Kaplan Meier Plot of progression free survival
Cisplatin versus topotecan plus Cisplatin in stage IVB, recurrent or persistent carcinoma of the cervix (GOG 0179).
ITT (intent to treat) subjects.



	Cisplatin	Topotecan/Cisplatin
PFS (months)	(N = 146)	(N = 147)
Median (95% C.I.)	2.9 (2.6, 3.5)	4.6 (3.5, 5.7)
Log-rank p-value	0.026	
[a]Hazard Ratio (95% C.I.)	0.76 (0.60, 0.97)	
Range	0.3 – 39.0	0.2 – 34.4
Observed Events (%)	134 (92)	131 (89)
Censored Events (%)	12 (8)	16 (11)

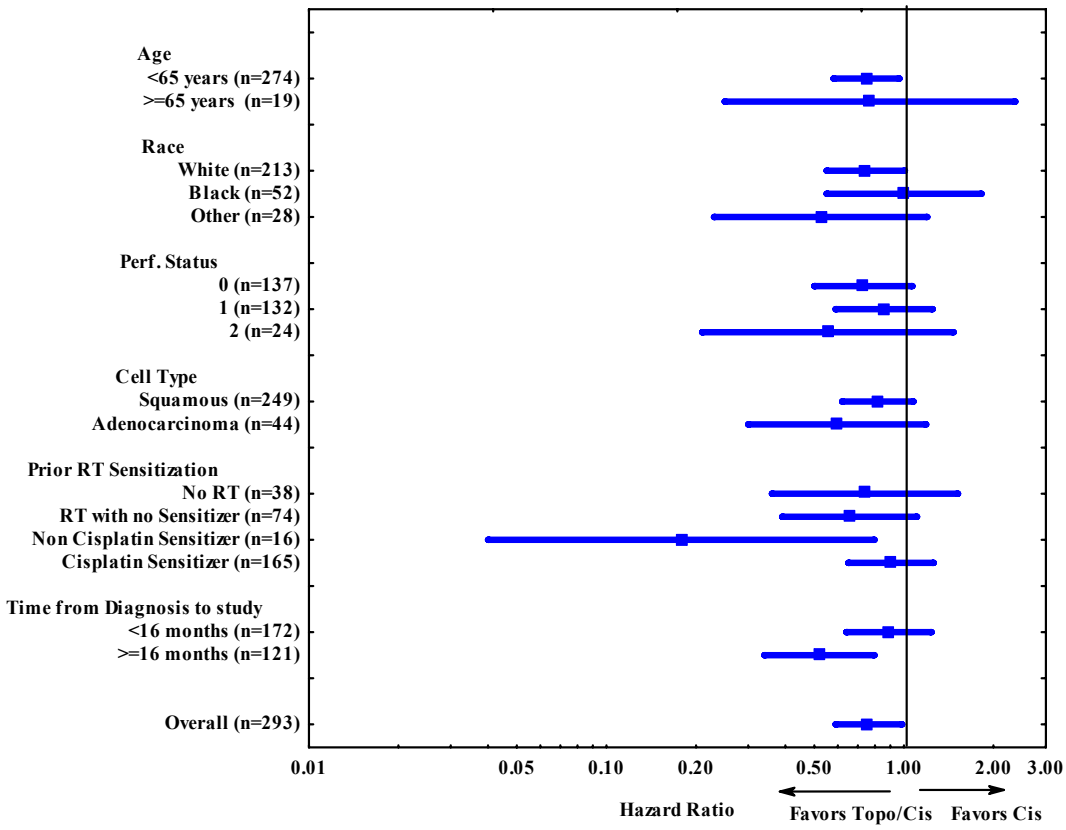
a. Unadjusted

Best response Following Treatment, ITT Population

	Cisplatin (n = 146)		Topotecan/ Cisplatin/ (n = 147)	
Response to Treatment	**n**	**(%)**	**N**	**(%)**
Responders				
Complete response (CR)	4	(3)	14	(10)
Partial response (PR)	14	(10)	22	(15)
Total (CR+PR)	18	(12)	36	(24)
Non-Responders				
Stable disease	70	(48)	61	(41)
Progressive disease (PD)	51	(35)	38	(26)
Inevaluable (IE)	7	(5)	12	(8)
Total (Stable disease+PD+IE)	128	(88)	111	(76)
Pearson Chi-square Test p-value[a]	0.0073			

a. p-value is a comparison of topotecan/cisplatin versus cisplatin for responders versus non-responders.

Range Plots of 95%C.I. of Hazard Ratios for Survival in Subgroups



Patients with Recurrent Disease by Prior History of Cisplatin Use as a Radiation Sensitizer

Patients with Prior Cisplatin Chemoradiotherapy		
	Cisplatin	Topotecan/Cisplatin
Survival (months)	(n= 72)	(n = 69)
Median (95% C.I.)	5.9 (4.7, 8.8)	7.9 (5.5, 10.9)
Hazard ratio (95% C.I.)	0.85 (0.59, 1.21)	
PFS (months) (95% C.I.)	2.7 (1.7, 3.3)	3.8 (3.1, 4.5)
Hazard ratio (95% C.I.)	0.97 (0.69; 1.38)	
Response Rate	9.7%	14.5%
Patients without Prior Cisplatin Chemoradiotherapy		
	Cisplatin	Topotecan/Cisplatin
Survival (months)	(n= 46)	(n = 44)
Median (95% C.I.)	8.8 (6.4, 11.5)	15.7 (11.9, 17.7)
Hazard ratio (95% C.I.)	0.51 (0.31, 0.82)	
PFS (months) (95% C.I.)	3.2 (2.4, 5.3)	7.0 (5.7, 10.2)
Hazard ratio (95% C.I.)	0.46 (0.29; 0.74)	
Response Rate	17.4%	38.6%

Data were further explored through unplanned sub-set analyses in an attempt to reduce the level of heterogeneity and gain understanding but the size of the respective sub-sets greatly limits if not precludes any meaningful comparisons or conclusions.

Efficacy analysis by TTP from Prior Cisplatin Chemoradiation

	TTP from prior chemo <180 days		TTP from prior chemo ≥180 days	
	Topo/Cisplatin (n=20)	**Cisplatin (n=19)**	**Topo/Cisplatin (n=49)**	**Cisplatin (n=53)**
Median survival in months (95% C.I.)	4.6 (2.6, 6.1)	4.5 (2.9, 9.6)	9.9 (7, 12.6)	6.3 (4.9, 9.5)
Hazard Ratio for survival (95% C.I.)	1.15 (0.59, 2.23)		0.75 (0.49, 1.16)	
Response Rate n (%)	2 (10)	2 (11)	8 (16)	5 (9)
Median PFS in months (95% C.I.)	1.5 (0.9, 4.0)	1.4 (1.2, 4.3)	4.1 (3.3, 4.9)	2.8 (2.3, 3.5)

Efficacy Data for Patients with Recurrent or Stage IVB Carcinoma of the Cervix

	Recurrent		Stage IVB	
	Topo/ Cisplatin (n=113)	**Cisplatin (n=118)**	**Topo/ Cisplatin (n=14)**	**Cisplatin (n=16)**
Median survival in months (95% C.I.)	10.2 (8.3, 12.6)	6.5 (5.8, 9.2)	9.9 (4.1, 22.5)	7.1 (5.3, 12.9)
Hazard Ratio for survival (95% C.I.)	0.68 (0.51, 0.91)		0.84 (0.38, 1.87)	
Response Rate n (%)	27 (24)	15 (13)	7 (50)	2 (13)
Median PFS in months (95% C.I.)	4.6 (3.5, 5.8)	2.9 (2.4, 3.4)	5.8 (1.8, 11.7)	2.7 (1.6, 6.0)

Quality of Life
QoL was assessed using several instruments (FACT-Cx, FACT-NTX, BPI and UNISCALE). Overall no differences between treatment groups were detected in this open label study.

Irrespective of instrument, less affected QoL at baseline predicted for longer time on study, i.e. a better prognosis.

Discussion on Clinical Efficacy

Study GSK-CRT-234 (Phase II)

Study GSK-CRT-234 was a single-arm phase II study in patients with incurable cervical cancer. The same regimen of cisplatin + topotecan as in the pivotal study was investigated. The overall response rate was 9/32 (evaluable patients out of a total of 35 patients). The regimen was considered tolerable.

Topotecan and cisplatin show essentially non-overlapping toxicities and both have shown monotherapy activity in cervical cancer. This constitutes a reasonable rationale to study this doublet in the treatment of cervical cancer.

The topotecan dose/schedule in study GSK-CRT-234 is less dose-intensive than in other combination regimens used for the treatment of solid tumours. The rationale for this, prior pelvic radiotherapy, is considered reasonable as haematotoxicity is dose limiting for topotecan. The cisplatin dose is "standard" in advanced cervical cancer.
Phase II activity and tolerability for the experimental arm to be used in the main study has been demonstrated.

GOG-0179 (Phase III)

Overall the design of the pivotal study GOG-0179 is considered acceptable from a clinical perspective. Locally persistent and recurrent disease, however, is likely to respond differently to chemotherapy. Open label is unavoidable due to differences in haematotoxicity. Survival was the primary endpoint, however, physical examination plays an important role in clinical practice response evaluations. Nevertheless, the supportive value of data on RR and PFS is reduced since no external, blinded review of tumour response and progression data was undertaken.
Closing of the MVAC arm is not considered to constitute a problem from a methodological perspective.

Approximately half of the patients in the pivotal study were previously treated with cisplatin containing chemo-radiotherapy. This probably reflects that the study was run between 1999 and 2002, while today chemoradiotherapy is considered standard.
Patients with recurrent tumour constitute the main group of patients. With respect to patients with metastatic disease this is probably no major issue, taking the rarity of the condition into account, as the sensitivity to chemotherapy is not hampered by prior radio- or chemoradiotherapy. Persistent disease after (chemo)-radiotherapy, however, is likely to be predictive of resistance to chemotherapy.
As expected patients with good performance status predicted a better outcome.

Altogether 31% in the topotecan-cisplatin arm and 24% in the cisplatin arm were withdrawn from study therapy for other reasons than progression or death. In the protocol it is stated:

- Each patient will continue on study for six courses or until disease progression or toxicity prohibits further therapy. Patients in continued response may continue on study with consent of the Study Chair but must be reported using GOG forms.
- Patient should be followed until death.
- Report all therapies and toxicities on GOG forms even if the patient is taken off protocol therapy until progression is documented.

Most patients taken off therapy were followed for PFS as only 8 and 11% of the patients were censored in the PFS analysis, cisplatin and topotecan-cisplatin, respectively.

Study data are mature with a low percentage of censored patients. The treatment effect in terms of overall survival, however, is of borderline statistical significance and has to be scrutinised as regards consistency in relation to reasonably defined treatment subgroups and in relation to secondary endpoints and safety.

Irrespective of outcome measure, the prognosis is worse in patients with a history of prior cisplatin chemoradiotherapy. Furthermore, the added value of topotecan to cisplatin is clearly smaller. Prior cisplatin therapy thus appears to increase the likelihood of resistance to subsequent chemotherapy; cisplatin as well as the combination cisplatin and topotecan. This is considered as a critical finding, as cisplatin chemoradiotherapy is considered standard today.

With respect to time from diagnosis, submitted data are less detailed. As shown in the range plots of 95% C.I. of Hazard Ratios for Survival in Subgroups, the hazard ratio topotecan-cisplatin/cisplatin alone was more favourable in patients with more than 16 months since the original diagnosis although it did favour the combination in both subgroups. In ovarian cancer recurrence within 6 (to 12) months after end of cisplatin-based chemotherapy is considered as a poor prognostic factor and the tumour is considered platinum resistant.

With reference to Quality of Life, due to the open label nature of the study it can only be concluded that major differences between treatment groups are unlikely.

Clinical safety

Patient exposure

All in all, 35 patients in the phase II trial and 140 patients in the confirmatory phase III trial were exposed to the cisplatin-topotecan combination. This report focuses on the confirmatory study. The median number of cisplatin-topotecan courses was 4 with a range of 1 to 20 and 567/628 of the courses were administered at the protocol defined starting dose.

Adverse events

The reported added events for the combination cisplatin-topotecan compared with cisplatin monotherapy were those expected, i.e. essentially events related to myelosuppression. Therefore, haematotoxicity is detailed first below, followed by a general overview.

Summary of Maximum Haematological Toxicities (patient incidence)

Toxicity and Grade		Cisplatin N=144	Topotecan/Cisplatin N=140
		n (%)	n (%)
Neutropenia			
	Grade 1	16 (11)	8 (6)
	Grade 2	10 (7)	14 (10)
	Grade 3	1 (1)	36 (26)
	Grade 4	1 (1)	67 (48)
	Total[1]	28 (19)	125 (89)
Thrombocytopenia			
	Grade 1	12 (8)	33 (24)
	Grade 2	4 (3)	25 (18)
	Grade 3	5 (3)	36 (26)
	Grade 4	0 (0)	10 (7)
	Total[1]	21 (15)	104 (74)
Anaemia			
	Grade 1	44 (31)	21 (15)
	Grade 2	53 (37)	54 (39)
	Grade 3	28 (19)	47 (34)
	Grade 4	5 (3)	9 (6)
	Total[1]	130 (90)	131 (94)

n = Number of treated patients who reported a grade 1, grade 2, grade 3 or grade 4 event

1. Total = Total number of treated patients who reported a grade 1, grade 2, grade 3 or grade 4 event

Summary of Therapeutic Interventions: Study GOG-0179

	Cisplatin Patients (N = 144)		Topotecan/ Cisplatin Patients (N = 140)	
Intervention	N	(%)	n	(%)
G-CSF	5	(3.5)	37	(26.4)
Platelet Transfusion	1	(0.7)	16	(11.4)
RBC Transfusion	49	(34.0)	68	(48.6)
Erythropoietin	38	(26.4)	51	(36.4)

Summary of Nadir ANC, CTC Grades Per Course Calculated from Raw Laboratory Data

Topotecan/Cisplatin

Course	N	Grade 1	Grade 2	Grade 3	Grade 4
Baseline	139/140	1 (1%)	0 (0%)	1 (1%)	0 (0%)
1	126/140	11 (9%)	15 (12%)	39 (31%)	46 (37%)
2	119/126	14 (12%)	22 (18%)	31 (26%)	20 (17%)
3	88/92	12 (14%)	12 (14%)	21 (24%)	17 (19%)
4	78/83	12 (15%)	12 (15%)	22 (28%)	17 (22%)
5	61/66	5 (8%)	13 (21%)	13 (21%)	17 (28%)
6	52/57	5 (10%)	6 (12%)	12 (23%)	17 (33%)
7	19/20	1 (5%)	3 (16%)	5 (26%)	5 (26%)
8	15/15	3 (20%)	2 (13%)	4 (27%)	3 (20%)

Summary of Infection and Associated Events

Regimen	**Cisplatin (N=144)**					**Topotecan/Cisplatin (N=140)**				
	n (%)					**n (%)**				
Grade	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**
Febrile neutropenia	0 (0)	15 (10)	**11 (8)**	**0 (0)**	26 (18)	1 (1)	12 (9)	**21 (15)**	**5 (4)**	39 (28)
AE of Febrile neutropenia leading to withdrawal	0 (0)					1 (0.7)				
SAE of Urinary Tract Infection (UTI)	3 (2.1)					0 (0)				
SAE of Sepsis, Pneumonia, and Cellulitis	1 (0.7)					0 (0)				
Topotecan dose reductions due to neutropenic fever	Not applicable					**15 (10.7)**				

Platelet CTC Grades Per Course Calculated from Raw Laboratory Data

CTCv2.0 Toxicity Grade (Platelets)
Cisplatin

Course	n	Grade 1	Grade 2	Grade 3	Grade 4
Baseline	143/144	1 (1%)	0 (0%)	0 (0%)	0 (0%)
1	134/144	4 (3%)	2 (1%)	3 (2%)	0 (0%)
2	119/127	3 (3%)	1 (1%)	1 (1%)	1 (1%)
3	77/85	3 (4%)	0 (0%)	0 (0%)	0 (0%)
4	65/68	2 (3%)	2 (3%)	0 (0%)	0 (0%)

CTCv2.0 Toxicity Grade (Platelets)
Topotecan/Cisplatin

Course	n	Grade 1	Grade 2	Grade 3	Grade 4
Baseline	139/140	2 (1%)	0 (0%)	0 (0%)	0 (0%)
1	125/140	30 (24%)	17 (14%)	23 (18%)	1 (1%)
2	116/126	28 (24%)	12 (10%)	13 (11%)	0 (0%)
3	87/92	29 (33%)	10 (11%)	10 (11%)	2 (2%)
4	78/83	16 (21%)	12 (15%)	15 (19%)	3 (4%)
5	64/66	17 (27%)	11 (17%)	13 (20%)	0 (0%)
6	52/57	11 (21%)	10 (19%)	6 (12%)	2 (4%)
7	19/20	2 (11%)	5 (26%)	4 (21%)	0 (0%)
8	15/15	4 (27%)	3 (20%)	2 (13%)	0 (0%)

Summary of Bleeding Complications

	Cisplatin					Topotecan/Cisplatin				
	N=144					N=140				
	n (%)					n[2] (%)				
Toxicity Grade	1	2	3	4	Total	1	2	3	4	Total
Hemorrhage	11 (8)	5 (3)	3 (2)	1 (1)	20 (14)	7 (5)	5 (4)	8 (6)	1 (1)	21 (15)

Fatal haemorrhage is a well known complication of cervical cancer, both treated and untreated. The submitted safety database supporting the use of combination topotecan and cisplatin in patients with cervical cancer reported one case of grade 5 haemorrhage. This patient treated with combination therapy died as a result of hemorrhagic complications related to tumour bleeding and severe thrombocytopenia.

Summary of Worst Grade Non-haematological Toxicities by Patient: Study GOG-0179

	Cisplatin (N=144)					Topotecan/Cisplatin (N=140)				
CTC Grade	1	2	3	4+	Total	1	2	3	4+	Total
CTC Category	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Constitutional Symptoms	32 (22)	40 (28)	17 (12)	0 (0)	89 (62)	28 (20)	57 (41)	11 (8)	0 (0)	96 (69)
Other Gastrointestinal (GI)	39 (27)	26 (18)	12 (8)	3 (2)	80 (56)	32 (23)	36 (26)	16 (11)	4 (3)	88 (63)
Pain	16 (11)	33 (23)	18 (13)	5 (3)	72 (50)	17 (12)	34 (24)	28 (20)	3 (2)	82 (59)
Nausea	36 (25)	30 (21)	13 (9)	0 (0)	79 (55)	29 (21)	28 (20)	18 (13)	2 (1)	77 (55)
Dermatologic	19 (13)	10 (7)	0 (0)	0 (0)	29 (20)	22 (16)	44 (31)	1 (1)	0 (0)	67 (48)
Vomiting	13 (9)	27 (19)	13 (9)	0 (0)	53 (37)	16 (11)	18 (13)	20 (14)	2 (1)	56 (40)
Metabolic – Laboratory	17 (12)	12 (8)	14 (10)	1 (1)	44 (31)	22 (16)	13 (9)	13 (9)	7 (5)	55 (39)
Genitourinary	20 (14)	15 (10)	7 (5)	7 (5)	49 (34)	16 (11)	17 (12)	9 (6)	9 (6)	51 (36)
Other neurologic	26 (18)	8 (6)	7 (5)	2 (1)	43 (30)	29 (21)	16 (11)	3 (2)	1 (1)	49 (35)
Infection – Febrile Neutropenia	0 (0)	15 (10)	11 (8)	0 (0)	26 (18)	1 (1)	12 (9)	21 (15)	5 (4)	39 (28)
Other cardiovascular	7 (5)	4 (3)	7 (5)	3 (2)	21 (15)	10 (7)	12 (9)	7 (5)	6 (4)	35 (25)
Other haematological	6 (4)	8 (6)	16 (11)	2 (1)	32 (22)	4 (3)	10 (7)	17 (12)	4 (3)	35 (25)
Hepatic	19 (13)	2 (1)	2 (1)	0 (0)	23 (16)	22 (16)	5 (4)	5 (4)	2 (1)	34 (24)
Pulmonary	1 (1)	14 (10)	5 (3)	3 (2)	23 (16)	7 (5)	13 (9)	4 (3)	2 (1)	26 (19)
Haemorrhage	11 (8)	5 (3)	3 (2)	1 (1)	20 (14)	7 (5)	5 (4)	8 (6)	2 (1)	22 (16)
Musculoskeletal	3 (2)	2 (1)	1 (1)	1 (1)	7 (5)	7 (5)	9 (6)	3 (2)	0 (0)	19 (14)
Lymphatics	7 (5)	1 (1)	0 (0)	0 (0)	8 (6)	7 (5)	3 (2)	0 (0)	0 (0)	10 (7)
Allergy/Immunology	2 (1)	1 (1)	0 (0)	1 (1)	4 (3)	1 (1)	4 (3)	2 (1)	1 (1)	8 (6)
Auditory	3 (2)	5 (3)	0 (0)	0 (0)	8 (6)	5 (4)	3 (2)	0 (0)	0 (0)	8 (6)
Coagulation	2 (1)	1 (1)	7 (5)	0 (0)	10 (7)	0 (0)	1 (1)	4 (3)	3 (2)	8 (6)
Endocrine	1 (1)	1 (1)	2 (1)	0 (0)	4 (3)	6 (4)	2 (1)	0 (0)	0 (0)	8 (6)
Stomatitis and pharyngitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	6 (4)	1 (1)	0 (0)	8 (6)
Ocular/visual	2 (1)	4 (3)	1 (1)	0 (0)	7 (5)	3 (2)	4 (3)	0 (0)	0 (0)	7 (5)
Sexual/reproductive function	4 (3)	5 (3)	1 (1)	0 (0)	10 (7)	3 (2)	4 (3)	0 (0)	0 (0)	7 (5)
Neuropathy	2 (1)	0 (0)	1 (1)	0 (0)	3 (2)	3 (2)	0 (0)	1 (1)	0 (0)	4 (3)
Other (hernia)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ventricular function	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

In **bold** entries where the absolute difference between treatment arms was >5%.

Reasons for Dose Reduction

Treatment Group	Drug	Reasons for Dose Reduction	Courses n (%)
Cisplatin	Cisplatin	Haematological Toxicity	1 (0.3)
		TOTAL	1 (0.3)
Topotecan/Cisplatin	Cisplatin	GI Toxicity	4 (0.8)
		Neurologic/Ototoxicity	2 (0.4)
		Renal Toxicity	3 (0.6)
		TOTAL	9 (1.8)
	Topotecan	GI Toxicity	8 (1.6)
		Haematological Toxicity	12 (2.5)
		Hepatic Toxicity	2 (0.4)
		Missing	1 (0.2)
		Neurologic/Ototoxicity	1 (0.2)
		Neutropenic fever	22 (4.5)
		Unknown	4 (0.8)
		TOTAL	50 (10.2)

Summary Dose Reductions through Course 10: Study GOG-0179

	Number of Patients Treated		Patients with Dose Reductions-		
			Cisplatin	Topotecan/Cisplatin	
Course	Cisplatin	Topotecan/Cisplatin	Cisplatin	Topotecan	Cisplatin
			n (%)	n (%)	n (%)
2	127	126	0 (0)	15 (12)	1 (1)
3	85	92	0 (0)	9 (10)	0 (0)
4	68	83	0 (0)	8 (10)	1 (1)
5	51	66	1 (2)	7 (11)	1 (2)
6	40	57	0 (0)	5 (9)	2 (4)
7	13	20	0 (0)	3 (15)	2 (10)
8	12	15	0 (0)	1 (7)	1 (7)
9	5	7	0 (0)	1 (14)	0 (0)
10	3	4	0 (0)	0 (0)	1 (25)
Overall	144	140	1 (1)	24 (17)	5 (4)

Summary of Dose Delays through Course 10: Study GOG-0179

	Number of Patients Treated		Patients with Dose Delays-	
			Cisplatin	Topotecan/Cisplatin
Course	Cisplatin	Topotecan/Cisplatin	n (%)	N (%)
2	127	126	9 (7)	40 (32)
3	85	92	7 (8)	31 (34)
4	68	83	7 (10)	31 (37)
5	51	66	5 (10)	32 (48)
6	40	57	4 (10)	23 (40)
7	13	20	1 (8)	12 (60)
8	12	15	1 (8)	7 (47)
9	5	7	0 (0)	4 (57)
10	3	4	0 (0)	3 (75)
Overall	144	140	26 (18)	78 (56)

Summary of Deaths ≤ 30 days Start of Last Medication by Cause

	Cisplatin (N=144)		Topotecan/Cisplatin (N=140)	
Cause of Death	n	(%)	N	(%)
Deaths ≤ 30 Days				
Treatment-related	0	(0)	4	(3)
Disease-related	9	(6)	7	(5)
Other (myocardial infarction)	1	(1)	0	(0)

Possibly treatment-related deaths

- Massive vaginal bleeding primarily due to tumour progression aggravated by drug-related grade IV thrombocytopenia.
- Comatose at time of pancytopenia without signs of intracerebral bleeding.
- Ileus, bowel resection, cardiac arrest, pleura effusion.
- Respiratory infection at time of grade IV neutropenia, pulmonary embolism, ARDS.

Discussion on Clinical Safety

Severe bleeding complications at the time of profound thrombocytopenia are expected to occur especially in relation to tumour tissue such as in the case reported. Treatment cannot be excluded as a potential contributing factor to the fatalities related to haematological toxicities among the patients treated with topotecan/cisplatin (none in the cisplatin treatment arm).

The differences in the number of haemorrhagic events between the treatment arms may not be significant and the reported fatal haemorrhage unique, but inconsistency in the way in which the clinical data are reported makes it difficult to judge undisputedly whether the reported deaths were treatment related or not. The reported 'patient incidence' of grade 3/4 thrombocytopenia was 33% in the combination arm (vs. 3%).

Haematotoxicity was also the most common reason for treatment delay (118/187).
Although the haematotoxicity of the combination regimen is rather profound for a treatment administered with palliative intent, toxicity was manageable and the adverse event profile for topotecan when given in combination with cisplatin is consistent with that seen with topotecan monotherapy.

The SPC already states that full blood count, including platelets, should be monitored regularly. In addition, sections 4.4 and 4.8 of the SPC have been revised to state the fact that thrombocytopenia is a common adverse effect of the combination therapy and has the potential of leading to fatal complications/bleeding and, furthermore, that the risk of haemorrhage should also kept in mind when choosing patients who will undergo the treatment.

Further, the MAH will collect data on haemorrhagic events as part of the routine global clinical safety Pharmacovigilance program and will be reviewed as part of the next PSUR.

Close to 50% of the patients experienced grade 4 neutropenia. The highest incidence was seen in cycle 1 as expected. There were no signs of obvious cumulative toxicity. Duration of grade 4 neutropenia was not reported.
Altogether 19% grade 3/4 neutropenic fever (vs. 8%) is considered high for a treatment administered with palliative intent.

With respect to "Other gastrointestinal" the difference between treatment groups is explained by mucositis/pharyngitis in the combination group.

The dose intensity as measured by need for dose reductions is clearly much lower in the monotherapy arm, also if haematotoxicity/neutropenic fever is not taken into account.

Benefit-risk assessment

Topotecan as add-on to a standard cisplatin regimen has been demonstrated to result in a borderline significant (p=0.03) prolongation of overall survival (Hazard Ratio (HR) 0.76, median survival 6.5 and 9.4 months, respectively) to be weighed against a non-trivial increase in toxicity, especially haematotoxicity. Whether benefit-risk in the whole study population has been shown to be favourable or not might be disputed. More importantly, however, the study population is heterogeneous and not considered to be fully representative of current clinical practice.

In patients with recurrent disease after cisplatin-radiotherapy, the prognosis was overall worse and the added benefit small (HR 0.85, median 5.9 and 7.9 months), compared with patients not administered prior chemoradiotherapy (HR 0.51, median 8.8 and 15.7 months). In patients not administered cisplatin containing chemoradiotherapy, treatment benefit is considered robust both from a statistical and clinical perspective. In this group of patients, data as such indicate that benefit-risk is favourable. This subgroup analysis is not considered hypothesis generating as intensity of prior therapy is likely to affect activity of later lines of therapy.

It cannot be excluded that these findings partly reflect a bias in the choice of primary therapy. Patients perceived to have a worse prognosis might have been administered chemoradiotherapy more frequently as this study was conducted between 1999 and 2002, i.e. during a transitional phase before chemoradiotherapy became standard. However, it is considered more likely that the add-on of cisplatin to radiotherapy increases the risk of resistance to next-line chemotherapy and it is well known that early recurrence after cisplatin-based therapy in patients with, e.g. ovarian carcinoma is associated with poor prognosis and platinum resistance.
Therefore, “persistent disease” after (chemo)radiotherapy was considered highly unlikely to respond to cisplatin/topotecan and the number of individuals was much too small for a proper benefit-risk assessment based on study data.

Today, cisplatin-containing chemoradiotherapy is considered standard therapy, but the uptake varies. It would therefore be inappropriate to reject the indication altogether.

In patients with disease resistant to chemo-radiotherapy the likelihood of meaningful activity of chemotherapy is low. Study data supports this notion.

Study data as such are sparse in patients with stage IVB disease, but there are no good reasons to assume that the add-on value of topotecan is substantially diminished in this treatment naïve population. In terms of response rate, actual data are compatible with this notion.

From an efficacy perspective the CHMP therefore considers a restricted indication appropriate:

“Treatment, in combination with cisplatin, of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IV-B disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination (see section 5.1 of the SPC).”

The reported benefit in this group of patients (prior radiotherapy: median survival 16 months versus 9 months, hazard ratio 0.51, 95% CI 0.31; 0.82) is considered to outweigh the increased risk of severe haematological side effects when topotecan is added to a standard cisplatin regimen.
The SPC has been amended accordingly to reflect this message.

IV. CONCLUSION

On 19 October 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.