All pts had received prior treatment with platinum containing combination chemotherapy.

Results: The median P dose/week received for P70 (57 pts) was 42 (24–52.5) mg/m²/wk, for P50 (35 pts) it was 32 (20.6–37.5) mg/m²/wk. The WBC nadirs were median 1 85 (0.64–8.9) × 10^9/l and 2 1 (0.75–4.9) × 10^9/l and the Plts nadirs were median 67 (8–193) × 10^9/l and 127 (11–320) × 10^9/l, respectively. 5 P70 pts had nephrotoxicity grade 2. Neurotoxicity grade 2 was observed in 4 P70 pts and 3 P50 pts. The response rate according to the PFI is shown in the table.

Response	PFI < 3 m N = 22	PFI 3–6 m N = 14	PFI 6–12 m N = 21	PFI > 12 m N = 35
CR	18%	22%	33%	57%
PR	18%	57%	62%	34%
Overall RR	36%	79%	95%	91%

The response duration for the patients with a PFI of <1 year was median 10 m, range (4–29⁺)m and for pts with a PFI ot of >1 year median 14 m, range (3.5–29⁺)m.

Conclusion: Salvage therapy with weekly cisplatin and oral vepesid is highly active Combination chemotherapy with weekly cisplatin should be tested in first-line.

530 ORAL

Efficacy of a combination of irinotecan (CPT-11) with mitomycin-C (MMC) for clear cell carcinoma of the ovary (OCCA) which is intrinsically platinum-resistant

Y. Shimizu[1], S. Umezawa[1], K. Hasumi[1], K. Yamauchi[1], S.G. Silverberg[2].
[1]*Department of Gynecology, Cancer Institute Hospital, Tokyo, Japan;*
[2]*Department of Pathology, University of Maryland Medical System, USA*

Purpose: To assess the efficacy of a combination of CPT-11 with MMC for OCCA which is intrinsically platinum-refractory.

Methods: Eligible patients (pts) had histologically-confirmed pure OCCA progressed during platinum-based chemotherapy (CTX) or relapsed within 6 months after the end of this CTX, measurable lesions, WHO PS ≤ 3, age ≤75, adequate hematopoietic, liver and renal functions, and written informed consent.

Protocol: CPT-11 (140 mg/m², IV infused over 4 hours on day 1, 15, and 29) and MMC (7 mg/m², IP injection through a reservoir on day 1, 15, and 29). The course was repeated every 3 weeks.

Results: To date 24 pts with OCCA were entered, of whom 7 had failed to respond to prior CPT-11 alone subsequent to platinum-based CTX. The median age was 53 (40–69). Among total 73 courses, grade 3 diarrhea was observed in 8 courses. Other toxic signs were acceptable. The responses by tumor size were 2 CR, 2 PR, and 1 NC for ≤2 cm in diameter, and 2 CR, 5 PR, 9 NC, and 3 PD for >2 cm. Eleven responders have showed a significantly longer survival compared with 13 non-responders (median survival after the start of CTX: 21 months vs 8 months, p < 0.001 for Log-rank test).

Conclusion: CPT-11 plus MMC was the first regimen to demonstrate a significant activity with survival benefit for intrinsically platinum-resistant OCCA. Further studies with this regimen are warranted in previously untreated pts with OCCA.

531 ORAL

Cisplatin/paclitaxel vs carboplatin/paclitaxel: Optimizing of treatment in advanced ovarian cancer

V. Möbus[1], C. Jackisch, H.-J. Lück, W. Meier, T. Bauknecht, S. Costa, B. Richter, U. Nitz, A. du Bois. *For the AGO Study Group Ovarian Cancer;*
[1]*Department of Gynecology and Obstetric of the University of Ulm, Germany*

Purpose: Recently, it has become evident that in advanced ovarian cancer primary chemotherapy with Paclitaxel/Cisplatin is more effective than the combination Cyclophosphamide/Cisplatin. An issue that has to be addressed is to decrease the severity of side effects by substituting the nonneurotoxic analogue carboplatin for cisplatin.

Methods: Patients FIGO stage IIb–IV were randomised to two treatment arms receiving either Paclitaxel 185 mg/m² plus Carboplatin AUC = 6 mg/ml/min (Arm A) or Paclitaxel 185 mg/m² plus Cisplatin 75 mg/m² (Arm B). 6 cycles were administered every 3 weeks. Patients followed stratification of <1 cm vs. >1 cm residual tumor.

Results: After 12 months 382 patients were enrolled in the ongoing study protocol Hematological toxicity occurred more frequently in Arm A, febrile neutropenie > grade 2 was not observed. G-CSF, antibiotics or red blood cells were given in less than 4% of courses in both arms. Treatment delay ≥7 d was observed in 13% and 7% in Arm A and Arm B, dose reduction was necessary in less than 5% of courses in both arms. Grade II neuropathy occurred in 17% and 33% of pts. in Arm A and Arm B, respectively.

Conclusion: Accrual is still going on. Except for alopecia, non-hematological toxicity occurred more frequently in Arm B.

532 ORAL

Long term survivors from a European-Canadian trial of paclitaxel in platinum-pretreated ovarian cancer (OVCA)

E. Eisenhauer[1], M. Bacon[1], W. Walsh[1], C. McDaniel[2], R. Canetta[2], N. Onetto[2], B. Zee[1]. [1]*NCIC Clinical Trials Group, Queen's University, Kingston, Canada;* [2]*Bristol-Myers Squibb, Wallingford, USA; Bristol-Myers Squibb, Brussels, Belgium*

In a randomized European-Canadian study, 2nd or 3rd line paclitaxel (P) was given to 391 pts with recurrent OVCA. Results of the trial comparing two doses and schedules of P have been reported (JCO 12: 2654, 1994). Long term data indicate 65 pts lived >2 yrs after receiving P. In order to determine if pt characteristics at study entry were related to likelihood of long survival (LTS), both groups were compared with respect to 23 baseline variables Univariate results are shown:

	>2 yr survivors (n = 65)	<2 yr survivors (n = 326)	p value
Mean age (yrs)	53.1	56.7	0.018
Performance status 0	60%	37%	0.001
Histology serious	66%	55%	0.095
Mean size largest lesion (cm)	6.6	7.8	0.029
≤2 sites of disease	82%	53%	0.001
CR to first-line chemo	46%	30%	0.013
Days since diagnosis (mean)	993	647	0.0003
Days since last chemo (mean)	406	215	0.0003

Following stepwise logistic regression, 4 factors remained significant at p < 0.05: age, number of disease sites, time since last chemo and performance status. Since all pts received P, no conclusion can be drawn regarding its impact on LTS, but these data suggest pt and disease characteristics at the time of initiation of 2nd or 3rd line OVCA treatment have an important effect.

533 POSTER

Independent radiological review of a phase III study of topotecan versus paclitaxel as second-line therapy in advanced epithelial ovarian cancer

S.J. Gwyther[1], M. Gore[2], W. ten Bokkel Huinink[2], S.Z. Fields[3], I. Hudson[3].
[1]*Dept of Radiology, East Surrey Hospital, Redhill;* [2]*On behalf of The International Topotecan Study Group;* [3]*SmithKline Beecham Pharmaceuticals, UK*

Purpose: To independently review claimed responses in a randomised, multicentre trial of topotecan (T) vs. paclitaxel (P) for advanced epithelial ovarian cancer (AEOC).

Methods: 226 patients (pts) with bidimensionally measurable AEOC, who had failed prior platinum-based therapy, were randomized to receive either T (1.5 mg/m²/d × 5 as a 30 min. inf. q 21 d) or P (175 mg/m²/d as a 3 h inf. q21 d). Pts who progressed or whose best response was stable disease after 6 courses were eligible to receive the alternate regimen. Radiographs or scans for claimed responses were reviewed by an independent radiologist.

Results:

Randomised Treatment	Topotecan		Paclitaxel	
	No. randomised	No. Switched to P	No. randomised	No. Switched to T
No. of pts	112	60	114	48
Claimed responses	38 (37.9%)	6 (10%)	28 (24.6%)	2 (4.2%)
Confirmed responses	23 (37.9%)	6 (10%)	16 (14.0%)	2 (4.2%)
No. rejected	15	0	12	0
% Rejected of claimed	39.5%	0%	42.9%	0%

Independent radiological review rejected 35% of responses; reasons for rejection included misinterpretation of normal structures & measurement errors.

Conclusions: T is an active agent in AEOC & although independent radiological review reduces the response rate it verifies the accuracy and

allows for reproducibility of results. We recommend that independent review should be standard in positive phase II & III studies.

534 POSTER

A phase II study of primary intraperitoneal paclitaxel combined with CBDCA/cytoxan (CC) in primary OC

P.H.B. Willemse, L. Hofstra, J.H. Beijnen[1], E.G.E. de Vries, A.G.J. van der Zee, W.T.A. van der Graaf, H. Boonstra, D.Th. Sleijfer, D.A. Piers[2], N.H. Mulder. *Depts of Medical & Gynecological Oncology; [2]Nuclear Med. University Hospital Groningen; [1]Dept of Pharmacy, Slotervaart Hospital, The Netherlands*

Methods: Twenty pts with primary stage III ovarian cancer (OC) received intraperitoneal Paclitaxel (PCL) and IV Carboplatin/Cyclophosphamide (PCC). Pharmacokinetic studies were done on IV and IP PCL levels by HPLC. GI toxicity was tolerable: Grade III abdominal pain in one, nausea and vomiting (N/V) Grade III in 15%. Leucopenia WHO Grade III and IV was 75% for PCC without infections. Thrombocytopenia Grade III and IV was 15% without bleeding episodes. Pharmacokinetics: Median plasma $T_{1/2}$ was 9.1 h (range 6.5–13 h). The IP-PCL levels decayed slowly after instillation. The C_{max} IP/IV ratio ranged from 780–1255.

Conclusions: IP-PCL mimics a 24 hrs IV infusion, reaching high drug levels in the peritoneal cavity. Combination with full-dose CC is feasible.

535 POSTER

Topotecan: A "compassionate use" study in patients with advanced epithelial ovarian cancer refractory to other therapies

T. Bauknecht[1], H.-J. Lueck[2], H. Calvert[3], R. Kreienberg[4], R. Pastovic[5]. *[1]Universitätsfrauenklinik, Freiburg; [2]Frauenklinik der MHH, Hannover; [4]Universitätsfrauenklinik, Ulm; [5]SmithKline Beecham Pharma, Munich, Germany; [3]Newcastle General Hospital, UK*

Purpose: To evaluate safety and efficacy of i.v. Topotecan in patients with advanced epithelial ovarian cancer with very poor prognosis refractory to other therapies.

Method: 1.25 mg/m^2 Topotecan was given i.v. on five consecutive days, cycle repetition every 3 weeks. Patients must have received two or more prior chemotherapies containing platin derivates and/or paclitaxel. The study focused on safety with efficacy analysis performed in patients with indicator lesions.

Results: The analysis included 109 patients from Germany, UK and Austria, 24 are still ongoing. 108 patients were evaluable for safety and 83 for efficacy. The median age was 56 (range 24–79). 25% of the patients had a performance status >1. Patients had up to 7 previous chemotherapie regimens with a median of 3. Fortynine % of patients received 4 or more courses of topotecan (range 1–12) with a total of 406 courses. In 10% of patients partial response and in 36% stable disease were observed. Time to progression was 13 weeks (10–30), in the range of previously reported results. Serious Adverse Experiences related to topotecan (17/56) were all based on myelosupressive activity, particularly neutropenia.

Conclusion: Topotecan proved to be efficacious in this heavily pretreated patient group with managable myelo- and little nonhematological toxicity.

536 POSTER

Pooled analysis of patients (PTS) treated with topotecan (T) after progression or failure on platinum (PLAT) and paclitaxel (P)

A. Gordon[1], M. Bookman[2], W. ten Bokkel Huinink[3], M. Gore[4], H. Malmstrom[5], J.B. Krebs[6], S.Z. Fields[6]. *[1]Texas Oncology PA, Dallas, Texas; [6]SmithKline Beecham Pharmaceuticals, Collegeville, PA, USA; [2]Fox Chase Cancer Center; [3]Netherlands Cancer Institute, Amsterdam, The Netherlands; [4]Royal Marsden NHS Trust, London, UK; [5]University Hospital, Linkoping, Sweden*

Purpose: T is a new agent for the treatment of women with recurrent ovarian cancer (ROC) after failure of initial or subsequent chemotherapy. We performed an analysis of pooled data from two multicenter studies in which 200 pts received T after progressing or failing first-line (62 pts) or second-line (138 pts) therapies which included Plat and P.

Methods: T was administered as a 30-min infusion at an initial dose of 1.5 mg/m^2 daily times 5 q 21 days. Responses were confirmed by independent radiological review. Data presented are for the intent-to-treat population.

Results: A total of 1124 courses (crs) were administered (median 4/pt; range: 1–27). Mean age was 56.8 y (range: 20–82 y). Median performance status was 1 (range: 0–3). The response rate was 13.5% (95% CI 8.8–18.2%; 1 CR, 26 PR). Median time to response was 11 wks (range: 3–32 wks). Median duration of response was 24 wks (range: 12–70 wks). Median time to progression was 11 wks (range: 0.7–83 wks). Median survival was 45 wks (range: 1.3–126 wks). One year survival was 42%. Hematologic toxicity was reversible, non-cumulative, and generally not associated with significant sequelae. Gr 4 neutropenia was reported in 82% of crs, with infection or gr 2 fever in 4% of crs. Gr 4 thrombocytopenia and gr 3–4 anemia occurred in 9% and 17% of crs, respectively. Non-hematologic toxicities were generally mild.

Conclusion: Topotecan is a valuable new agent with a manageable toxicity profile in pts with ROC who relapsed after first- or second-line Plat and P. (Supported by SmithKline Beecham.)

537 POSTER

A phase II study of topotecan given as a continuous 21-day infusion every 28 days in platinum pre-treated ovarian carcinoma

S. Johnson[1], L. Pyle[1], K. King[2], M. Gore[1]. *[1]The Royal Marsden Hospital, Fulham Rd, London, SW3 6JJ; [2]SmithKline Beecham Pharmaceuticals, Harlow, UK*

Purpose: Topotecan (TOP) has proven activity in second-line ovarian cancer (OC) when given at 1.5 mg/m^2/d × 5 as a 30 minute infusion q 21 days (d). The aim of this study was to evaluate the efficacy of TOP given by continuous infusion.

Methods: TOP 0.4 mg/m^2/d was given as a continuous 21-d intravenous infusion every 28 d in patients (pts) with advanced epithelial OC.Dose escalation or reduction was permitted and patients could remain on treatment until disease progression. All responses were confirmed by independent radiological review.

Results: 19 pts were recruited and 78 courses (cse) were given (1–10 courses per pt), 2 pts escalated TOP to 0.5 mg/m^2/d and no patient required a dosage reduction. All pts had relapsed after platinum based therapy. 2pts (10.5%) responded and 3 patients (15.8%) had stable disease. One of the responders had refractory disease (progressed on first line carboplatin) and the other had relapsed after a platinum free interval of 26 weeks (wks). In the 2 responding pts response duration was 39.1 and 16 wks. Survival in both pts was >45 wks. Haematological toxicities were reversible, non-cumulative and manageable. Grade 3/4 neutropenia, thrombocytopenia and anaemia were seen in 33/78, 13/78 and 30/78 of cse respectively. Growth factor support was not required but 11 pts in 24 cse required red blood cell transfusion and 1 pt in 1 course required a platelet transfusion. Non-haematological toxicities were generally mild and included nausea, fatigue, diarrhoea and alopecia.

Conclusion: Topotecan given by 21-day infusion has activity in ovarian cancer.

538 POSTER

Activity of Gemcitabine in stage 3 or 4 ovarian cancer: Patients previously treated with cisplatin (CP)-containing regimens

M. Friedlander[1], A. De Gramont[2], M.J. Millward[3], D. Bell[4], R. Bugat[5], P. Harnett[6], J.A. Moreno[7], L. Campbell[8], V. Ripoche[9], L. Kayitalire[9]. *[1]Prince of Wales Hosp., Randwick; [3]Peter Maccallum Cancer Institute, East Melbourne; [8]Lilly, Australia; [2]Hôpital Saint-Antoine, Paris; [5]Centre Claudius Régaud, Toulouse; [4]Royal North Shore Hosp., St Leonards; [9]Lilly, France; [7]Hosp. Universitario Virgen del Rocio, Sevilla, Spain; [6]Westmead Hosp., Westmead,*

Purpose: GEMZAR® (Gemcitabine, GEM) is a nucleoside analogue active against a variety of solid tumours. In a phase II study a 19% response rate was observed in 42 evaluable and CP-resistant ovarian cancers (Lund et al. JNCI, 1994; 86: 1530–1533).

Methods: From December 93 to March 95, we investigated the efficacy and the safety profile of GEM in stage 3 or 4 ovarian cancer. Major inclusion criteria were: previous CP-containing regimens, measurable disease, adequate renal, hepatic and bone marrow functions. GEM (1200 mg/m^2) was administered as a 30 min infusion on days 1, 8, 15 of a 28 day cycle.

Results: 38 pts were enrolled. Mean age was 58 years, median Karnofsky Score was 90 (60–100), FIGO stage at entry was 3 for 13 pts, 4 for 25 pts. 4 pts were ineligible (1 pt for diagnosis not confirmed and 3 pts for insufficient therapy) and 2 pts were lost to follow-up before evaluation. With