Title	AGO 10 - Randomized Phase II AGO-Study comparing Combined liposomal-encapsulated doxorubicin citrate (Myocet®) and Gemcitabine (Gemzar) with liposomal-encapsulated doxorubicin citrate (Myocet®) Monotherapy in Platinum-Refractory and Platinum-Resistant Epithelial Cancer of the Ovary, Fallopian Tube, and the Peritoneum
Background	Platinum-resistance is a significant problem in patients with ovarian cancer. In this situation, patients usually carry significant tumor-related symptoms, chemotherapy is only moderately active, and the median survival lies between 6 and 11 months (1,2). New active drugs and drug combinations with limited toxicity are particularly needed for this patient population. Single agent liposomal doxorubicin (L-DXR) and gemcitabine (GEM) have different mechanisms of action (3, 18). In addition, some studies have indicated a possible synergistic antiproliferative activity between L-DXR and GEM in vitro (4). A phase II trial by the Austrian AGO in which pegylated liposomal doxorubicin (PEG-L-DXR) 30 mg/m2 on day 1 and GEM 650 mg/m2 on days 1 and 8 were administered at 4-weekly intervals revealed a favorable therapeutic index in patients with platinum-resistant ovarian cancer (5). Currently, no standard exists with regard to the treatment of **platinum-resistant** ovarian cancer. Topotecan administered for 5 days every 3 weeks has shown similar efficacy as PEG-L-DXR monotherapy administered once per month in a randomized phase III study. However, topotecan at the schedule administered resulted in significant hematotoxicity. PEG-L-DXR monotherapy exerted only few hematotoxicity. On the other hand, hand foot syndrome was more prevalent in the PEG-L-DXR arm (grades 3 or 4 in 23%)(6). Thus, worldwide many groups regard PEG-L-DXR therapy as the current standard in platinum-resistant ovarian cancer. Since survival is poor in platinum-resistant disease, developments in this field are urgently needed. In a phase II study of the AGO using combined PEG-L-DXR and gemcitabine, one quarter of patients developed grade 3 or 4 neutropenia but none developed febrile neutropenia. Palmoplantar erythrodysesthesia (PPE) grades 2 and 3 occurred in 13% and 3% only, respectively, and no grade 4 PPE was observed. Grade 1 to 3 stomatitis was found in 58% of patients with 10% being classified as grade 3. In the present study, the combination of liposomal-encapsulated doxorubicin citrate (Myocet®) and gemcitabine is compared to liposomal-encapsulated doxorubicin citrate (Myocet®) monotherapy. Since liposomal doxorubicin is widely regarded as the chemotherapy standard in platinum-resistant ovarian cancer. The main objectives of this study are the remission rates and the quality of life exerted by the two regimens. Since liposomal-encapsulated doxorubicin citrate (Myocet®) is associated with comparable activity as PEG-L-DXR (7) and does not exert palmoplantar erythrodysesthesia, the AGO Austria has chosen this drug for investigation within a randomized phase II

	study.
Main objective	To assess, if the response rate for the combination of liposomal-encapsulated doxorubicin citrate (Myocet®) and gemcitabine is favourable over single agent cytotoxic therapy with liposomal-encapsulated doxorubicin citrate (Myocet®)
Trial design	Randomized Phase II multicenter trial
Treatment	**ARM 1:** Liposomal encapsulated doxorubicin citrate (Myocet®) 60mg/m2 – day 1 Gemcitabine 650mg/m2 – days 1 and 8 Every 21 days (q21) **ARM 2:** liposomal-encapsulated doxorubicin citrate (Myocet®) 60mg/m2 - day 1 Every 21 days (q21)
Number of patients	154 patients (77 patients per each treatment arm)
Inclusion criteria	• Histologically confirmed epithelial cancer of the ovary, the fallopian tube or the primary peritoneum. • Patients must have received first-line platinum-based chemotherapy. • Progression or recurrence during first-line platinum-based chemotherapy (= **platinum-refractory disease**) or progression/recurrence during the first 6 months following the end of the last platinum-containing chemotherapy (= day 21 or day 28) = **platinum-resistant disease**. • Age ≥ 18 years. • Karnofsky performance status ≥ 70. • Life expectancy ≥ 3 months. • **Measurable** metastatic disease on CT or MRI or ultrasound, or chest X-ray and/**or** • **Evaluable** disease on CT/MRI (e.g. ascites, pleural effusion) or chest X-ray (e.g. pleural effusion) and/or • Tumor marker progression (CA-125) according to the criteria by Rustin. **Increasing CA-125 levels** according to Rustin et al. ([i]): **CA-125 ≥ 2x UNL** (upper normal limit) or **CA-125 > 2x nadir value** on two occasions. The date of progressive disease is defined as the first date of the CA-125 elevation to ≥ 2x UNL or > 2x nadir value. • Normal organ functions:

	■ Adequate bone marrow function as indicated by: – Platelets ≥ 100,000/mm^3 – Hemoglobin ≥ 10 g/dL – Neutrophils ≥ 1.5 x 10^3/mm^3 ■ Adequate renal function as indicated by: – Serum Creatinine <1.5 x the upper limit of normal ■ Adequate liver function, as indicated by: – Bilirubin < 1,5 x upper limit of normal (if no liver metastases are present) – Bilirubin < 2,5 x upper limit of normal (if liver metastases are present) – AST/ALT < 2.5 x upper limit of normal unless caused by parenchymal liver metastases • Left ventricular ejection fraction of ≥50% in an echocardiography or MUGA Scan within 28 days of study start. • Written informed consent.
Exclusion criteria	• Patients with childbearing capacity. • Ovarian carcinosarcoma (malignant mixed Müllerian tumor) or pure sarcoma. • Any known hypersensitivity to study drugs. • Previous chemotherapy with liposomal doxorubicin, other anthracyclines or gemcitabine. • Significant comorbidity as e.g., uncontrolled infection, clinical signs of cardiac insufficiency, history of myocardial infarction or cardiac rhythmic disorders according to the NYHA classification LOWN ≥ 2. • Any condition (medical, social, psychological), which would prevent adequate follow-up. • **Active secondary malignant tumor** diagnosed < 5 years (e.g. metastases from primary breast cancer).
Statistical analysis	**Stratification:** *platinum-refractory disease* (disease progression during the first 6 cycles of platinum-based first line therapy) *platinum-resistant disease* (disease progression within 6 months after the last platinum-based chemotherapy cycle = day 21 or day 28 of the last chemotherapy cycle)
Endpoints	**Primary objectives:**

	Remission rates (CR, PR) **<u>Secondary objectives:</u>** quality of life (EORTC-QLQ30 + QLQ-OV28) Progression-free survival Toxicity Overall survival
Quality of life	QLQ-questionnaire (QLQ 28, QLQ 30) planned prior to each cycle of chemotherapy and every three months during follow-up
Duration of study	48 months inclusion period and 1-year follow-up
References	1. Haider K, Kornek G, Kwasny W et al. Multicenter phase II trial of gemcitabine plus liposomal doxorubicin in chemotherapeutically pretreated patients with advanced breast cancer. Proc ASCO 23: 50a, 2004 2. Markman M, Webster K, Zanotti K, Peterson G, Kulp B, Belinson J. Survival following the documentation of platinum and taxane resistance in ovarian cancer: a single institution experience involving multiple phade 2 clinical trials. Gynecol Oncol 93: 699-701, 2004 3. Doyle C, Crump M, Pintilie M, Oza A. Does palliative chemotherapy palliate ? Evaluation of expectations, outcomes, and costs in women receiving chemotherapy for advanced ovarian cancer. J Clin Oncol 19: 1266-1274, 2001 4. Tobias D, Runowicz C, Mandeli J et al. A phase I trial of gemcitabine and doxil for recurrent epithelial ovarian cancer. Proc ASCO 19: 329a, 2000 5. Petru E, Angleitner-Boubenizek L, Reinthaller A, Deibl M, Zeimet A, Volgger B, Stempfl A, Marth C. Combined PEG liposomal doxorubicin and gemcitabine are active and have acceptable toxicity in patients with platinum-refractory and –resistant ovarian cancer after previous platinum-taxane therapy: A phase II Austrian AGO study. Gynecol Oncol 102: 226-229, 2006 6. Gordon A, Tonda M, Sun S et al. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol 95: 1-8, 2004 7. Angioli R, Palaia J, Calcagno M et al.: Liposome-encapsulated doxorubicin citrate in previously treated recurrent/metastastic gynaecological malignancies. Int. J. Gynecol Cancer 17: 88-93; 2007