Conclusions: Patupilone administered once q3w is safe and well tolerated. The preliminary antitumor response is promising in this previously treated, platinum- and taxane-resistant population.

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Randomized phase III trial of gemcitabine (GEM) versus pegylated liposomal doxorubicin (PLDOX) for patients (pts.) with platinum-resistant (pt-r) ovarian cancer (oc) undergoing second or third-line chemotherapy (ct)

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Background: OC pts with progression (prog) during or within 6 months (m) from primary therapy (tx) are considered Pt-R. Inclusion of paclitaxel in 1st-line tx requires agents lacking cross-resistance to both paclitaxel and platinum compounds for pts with refractory disease. Given the promising phase II results with Gem, comparison to PLDox, an approved therapy, was warranted.
Material and methods: Pt eligibility for this multicenter, open-label, randomized phase III study included: age $\geqslant$18 years, recurrent Pt-R epithelial ovarian, fallopian tube or primary peritoneal carcinoma, Pt-based 1st line CT ($\leqslant$ 2 prior regimens), measurable disease or CA-125$\geqslant$100 U/l, adequate organ function, and ECOG PS 0–2. Pts were randomized to receive Gem 1000 mg/m^2/d (30' infusion) on days 1 and 8 every 21 days or PLDox 50 mg/m^2 day 1 every 28 days. Treatment continued until prog or undue toxicity (tox). Pts had the option to cross (X–) over to the alternative regimen at disease prog, tox (after reversal to <grade 2), or a cumulative dose of PLDox of 500 mg/m^2. The primary end point was progression-free survival (PFS).
Results: Between July 2002 and May 2004, 195 pts were enrolled. Baseline characteristics (age, PS, type/response to prior tx, measurable disease) were balanced between arms. 65%/35% received 1/2 prior regimens.

Parameter	Gem (n = 99)	PLDox (n = 96)	*P*-value
Median of Cycles (range)	4 (1–21)	3 (1–13)	
ORR (CR+PR) (95%-CI)	7.1% (3.1–14.5%)	7.3% (3.2–14.9%)	
ORR in pts (n = 65/60) with measurable disease	10.7%	10.0%	
SD	50.5%	40.6%	
PD	36.3%	45.8%	
Clinical Benefit (CR+PR+SD) (95%-CI)	57.6% (47.2–67.3%)	47.9% (37.7–58.3%)	0.198[a]
PFS, median (weeks) (95%-CI)	15.6 (10.6–9.7)	13.3 (8.6–17.4)	0.869[b]

[a]Fisher's exact test;[b]Log-Rank test

Toxicity was generally mild on both arms. Grade 3/4 Neutropenia was more common on Gem (36% vs 18%) while grade 2/3 hand–foot syndrome (0% vs 19%) and mucositis (3% vs 18%) were more common on PLDox. Febrile neutropenia (2% vs 2%), grade 3 Thrombocytopenia (6% vs 4%), grade 2/4 fatigue (24% vs 19%), emesis (17% vs 15%), rash (6% vs 6%) rates were similar. Only one pt died from tx-related tox. ~ 60% of pts went on to receive X-over tx. Only pts initially on PLDox X-over due to tox (14 pts. vs 0).
Conclusions: GEM and PLDox have comparable efficacy in Pt-R OC. Tox patterns differ between arms (laboratory vs symptomatic), however they are manageable. Follow-up continues to assess X-over outcomes and survival.

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Expression of FLICE-like inhibitory protein (c-FLIPL) is associated with ovarian cancer patient's chemoresistance

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Background: Ovarian carcinoma is a highly lethal malignancy that often becomes resistant to chemotherapy. Alterations in apoptotic signals and p53 status contribute to drug resistance. We recently showed that the apoptosis inhibitory protein c-FLIP$_L$ is involved in resistance to CD95-mediated apoptosis in ovarian carcinoma cells with wild-type p53 and that there is a significant (P = 0.034) inverse relationship between c-FLIP$_L$ expression in ovarian cancer specimens and p53 accumulation or mutation.
Material and methods: Archival material from 74 stage III-IV ovarian cancer patients with known clinical history was analyzed for c-FLIP$_L$ expression and p53 nuclear accumulation by immunohistochemistry and for p53 mutational status by automated DNA sequencing. P53 mutations were classified as missense or non-missense according to the functional state of the molecule. Statistical analyses were performed to discover possible significant correlation between c-FLIP$_L$ expression and different clinical parameters including: patient's age, tumor histotype and grading, p53 mutational status, p53 nuclear accumulation and response to front-line treatment.
Results: The inverse relationship between c-FLIP$_L$ expression and p53 mutation (P = 0.0094) as well as p53 nuclear accumulation (P = 0.037) that we observed in our preliminary study, was confirmed in this larger clinical case material. No correlation was observed with tumor histotype or grading, although in a tissue micro array including normal, borderline and stage I-IV tumors, c-FLIP$_L$ was mainly expressed in borderline and stage I tumors. This discrepancy might be due to the fact that the new case material only includes stages III and IV tumors. Although the overall survival curves of patients expressing or not the molecule are not statistically significant (P = 0.08), the median survival of patients expressing c-FLIP$_L$ is much shorter than that of patients not expressing the molecule (40 versus 53 months). This difference further increased if only patient carrying a functional active p53 were considered (median survival 40 versus 58 months). Among 34 patients not responding to platinum-based chemotherapy, 22 expressed c-FLIP$_L$.
Conclusion: These data support the significant role of c-FLIP$_L$ in the regulation of apoptosis in ovarian cancer and, as a cell survival factor, in resistance to platinum-based chemotherapy. Data validation is ongoing on an independent case material including more than 100 tumors from patients at all stages of the disease and with known clinical history.

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The prediction of the response to chemotherapy and survival of patients with ovarian clear cell carcinoma by ABCF2 expression

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Background: Ovarian clear cell adenocarcinoma (CC) generally shows little response to combination chemotherapy and the overall prognosis is poor. We previously reported that ABCF2 might be a new biomarker for CC using cDNA microarray analysis. In this study, we raised a polyclonal antibody directed against ABCF2 and evaluated the relationship between ABCF2 expression and the response to chemotherapy or overall survival (OS) in CC patients.
Materials and methods:

1. 307 epithelial ovarian cancer (Serous: 93; Mucinous: 46; Endometrioid: 56; CC: 80; Undifferentiated: 32) were included in this study. ABCF2 expression was investigated by immunohistochemistry in each histologic type.
2. For 61 CC (stage I: 28; II: 10; III: 22; IV: 1), we investigated the relationship between ABCF2 expression and the response to chemotherapy or OS. The percentage of positive cytoplasmic staining (Labeling index (LI)) for ABCF2 was calculated. In 28 CC patients,