Results: we have identified a panel of 53 sequences differentially expressed in EEC when compared to healthy endometrium. Among these, the transcription factors RUNX1/AML1 and ERM/ETV5 have been studied in detail and their expression significantly related with the early myometrial infiltration phase (stage IC). Moreover, increased ERM/ETV5 expression was associated with matrix-degrading metalloprotease-2 (MMP2) activity, and ERM/ETV5 up-regulation correlated to that of RUNX1/AML1.
Conclusions: We propose a cooperative role between RUNX1/AML1 and ERM/ETV5 during the early events of endometrial tumorigenesis, which may be associated with an initial switch to myometrial infiltration. The further characterization of the mechanism of action of both genes during endometrial tumorigenesis will contribute with the clues of the initial mechanisms of invasion and dissemination in EEC, their validation as early markers of myometrial invasion and metastasis in EEC, and to design and evaluate preclinical assays based on the characterization of potential therapeutic targets.

907 ORAL

A Phase II study of Temsirolimus (CCI-779) in patients with metastatic and/or recurrent endometrial cancer – NCIC CTG IND 160

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Background: PTEN is a tumor suppressor gene and mutations in PTEN leading to loss of protein expression/function appear to play a significant role in the pathogenesis of endometrial carcinoma based on laboratory and clinical studies. In various series, loss of PTEN protein expression, occurs in 26–80% of endometrial carcinomas in various series. Loss of PTEN function leads to deregulated PI3K/Akt/mTOR signalling, an event that is thought to provide neoplastic cells with a selective survival advantage by enhancing angiogenesis, protein translation and cell cycle progression. Inhibition of mTOR, a protein kinase downstream of the PI3K/Akt pathway and target of rapamycins, inhibits proliferation of endometrial carcinoma cell lines and formation of endometrial neoplasias including carcinomas in PTEN± heterozygous mice. Given the frequent loss of PTEN in human endometrial carcinomas, and the anti-tumour activity induced with mTOR inhibition, temsirolimus an ester derivative of rapamycin that inhibits mTOR was evaluated in this setting.
Methods: A 2 stage, phase II study is underway to evaluate single agent activity of temsirolimus in endometrial cancer. Women with recurrent or metastatic endometrial cancer, who are chemotherapy naïve and have received up to one prior line of hormonal therapy, are eligible. Treatment is given at a dose of 25 mg weekly. One cycle is defined as 4 weeks of therapy. Eighteen patients have been registered to date, and 15 are evaluable for toxicity and 14 for response. Eleven had received prior radiation and seven hormonal therapy. Sixteen patients had adenocarcinoma and 2 had adeno-squamous carcinoma; 14 patients had grade 2/3 disease.
Results: Hematologic toxicity has been mild with 6 episodes of grade 3 lymphopenia; 4 patients had grade 3 non-hematologic adverse events [hypotension, rash, GI, neuropathy, pain] and 1 patient had grade 5 renal failure [secondary to dehydration and CT contrast]. There have been no grade 3 or 4 biochemical toxicities. Three patients have had a confirmed partial response (21%) and 10 patients have stable disease (71%). One patient had progressive disease (7%). Results will be correlated with PTEN status. Using multinomial endpoints incorporating response and stable disease, the study has met the pre-defined requirements for expansion to the second stage.
Conclusions: The preliminary results suggest encouraging single agent activity for temsirolimus in recurrent and metastatic endometrial cancer.

Poster presentations (Tue, 1 Nov)
Gynaecological cancer

908 POSTER

A Randomised Phase II study of Phenoxodiol with platinum or taxane chemotherapy in chemoresistant epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer

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Background: Despite high rates of response to initial chemotherapy, most patients with ovarian cancer relapse with chemoresistant disease. The development of platinum- and taxane-resistance is associated with over-expression of anti-apoptotic factors. Phenoxodiol (PXD, 2H-1-benzopyran-7−0, 1, 3-[4-hydroxylphenyl]) a flavonoid derivative synergizes the cytotoxicity of platinums, taxanes and gemcitabine in chemosensitive ovarian cancer cells. *In vitro* PXD-induces apoptosis in chemoresistant ovarian cancer cells and restores chemo-sensitivity to platinum, taxanes and topotecan in chemo-resistant ovarian cancer cells. These data support the study of PXD in chemoresistant ovarian cancer.
Methods: Eligible patients (pts) had recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer with rising CA125 within 6 months of prior therapy. Pts had <4 prior chemotherapy regimens, measurable disease and Karnofsky performance status >60%. Pts were randomised to receive PXD (3 mg/kg) days 1 and 2 and either cisplatin (40 mg/m^2) or paclitaxel (80 mg/m^2) on day 2 until disease progression or prohibitive toxicity. Primary endpoints were response rate by RECIST (Therasse *et al.*, 2000) and GCIG criteria (Rustin *et al.*, 2004), progression free survival (PFS) and toxicity by NCI criteria.
Results: Forty patients have been randomised (20 to PXD+CDDP, 20 to PXD+Paclitaxel) and 36 are evaluable for response. Median age was 56 (45–72) and median number of prior chemotherapy regimens was 3 (1–4). Complete response (CR) was observed by RECIST in 4 pts (11%), partial response (PR) in 8 pts (22%) and stable disease (SD) in 15 pts (42%) for an overall clinical benefit in 75%. Nine patients had disease progression within 6 weeks of randomisation. Objective tumor responses (CR+PR) were observed in 43% of pts where prior platinum or taxane free interval was >12 months and 25% when PFI/TFI was <12 months.. Toxicity was related to chemotherapy with no additional toxicity observed. Toxicity and QOL data will be presented.
Conclusions: Preliminary results indicate that PXD administered with chemotherapy results in high response rates among women with chemoresistant epithelial ovarian cancer.

909 POSTER

Phase I/II dose-escalation trial of patupilone every 3 weeks in patients with resistant/refractory ovarian cancer

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Background: The current standard of care for patients with newly diagnosed advanced ovarian cancer is therapy with a platinum and taxane-based combination regimen. However, patients who are refractory or resistant to the regimen have a poor prognosis. Patupilone, a natural epothilone, is a microtubule-targeting agent that has demonstrated clinical activity in taxane-sensitive and -resistant tumors. We are investigating the safety and efficacy of patupilone in patients with advanced ovarian cancer who failed to respond to or relapsed within 6 months of first-line platinum therapy.
Material and methods: Patients received patupilone at a starting dose of 6.5 mg/m^2 via 10- to 20-minute IV infusion once every 3 weeks (q3w) with proactive diarrhea management.
Results: To date, 45 patients have been enrolled in 10 cohorts receiving 6.5 (n = 3), 7.0 (n = 3), 7.5 (n = 3), 8.0 (n = 6), 8.5 (n = 3), 9.0 (n = 6), 9.5 (n = 6), 10.0 (n = 6), 10.5 (n = 3), and 11.0 (n = 6) mg/m^2 patupilone. Currently, 32 patients are eligible for assessment; 94% had received prior taxane therapy. Dose-limiting toxicities were reported in the 8.0 and 8.5 mg/m^2 cohorts: 1 patient in each cohort had grade 3 fatigue. Grade 4 serum uric acid precipitated by an ileus, grade 3 hypomagnesemia, and grade 3 diarrhea were reported on day 21 of the first cycle by a patient enrolled in the 9.0 mg/m^2 cohort. Because these toxicities were deemed unrelated to study drug, the cohort was expanded and no further dose-limiting toxicities were reported. Dose escalation continued up to the 11.0 mg/m^2 cohort, wherein grade 3 diarrhea was reported by 1 patient. Overall, 19% of patients reported grade 3 diarrhea and 9% reported grade 3 fatigue. Eleven (34%) patients had grade 1/2 neuropathy/paresthesia and 1 heavily pretreated (19 platinum cycles) patient had grade 3 neuropathy/paresthesia. Alopecia was infrequent and mild in severity. Hematologic toxicity was rare. Dose escalation was halted at 11.0 mg/m^2 and, based on acute and chronic toxicities, the recommended phase II dose was determined to be 10.0 mg/m^2 patupilone. Thirty-two patients were evaluable for tumor response by Response Evaluation Criteria in Solid Tumors: 1 had a complete response, 7 had a partial response, and 8 had stable disease.

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.

910 POSTER

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.

911 POSTER

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.

912 POSTER

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,