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

A.M. Oza[1], L. Elit[1], J. Biagi[1], L. Panasci[1], K. Tonkin[1], M. Tsao[1], N. Dore[1], J. Dancey[2], E. Eisenhauer[1], L. Seymour[1]. *[1]National Cancer Institute of Canada, Clinical Trials Group, Kingston, Canada; [2]National Cancer Institute, Bethesda, USA*

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

G. Goss, M. Quinn, T. Rutherford, M. Kelly. *[1]Dept Gynaecologic Oncology, Royal Women's Hospital, Melbourne, VIC Australia; [2]Dept Obstetrics and Gynecology Yale University School of Medicine, New Haven, CT, USA; [3]Marshall Edwards Pty Ltd, North Ryde, NSW, Australia*

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

W.M. Smit[1], J. Sufliarsky[2], S. Spanik[3], M. Wagnerová[4], S. Kaye[5], A.M. Oza[6], M. Gore[5], K.J. Williams[7], A. Johri[8], W.W. ten Bokkel Huinink[9]. *[1]Medisch Spectrum Twente, Enschede, The Netherlands; [2]National Cancer Institute, Bratislava, Slovak Republic; [3]St. Elisabeth Cancer Institute, Bratislava, Slovak Republic; [4]Oncology Institute, Kosice, Slovak Republic; [5]The Royal Marsden Hospital, Sutton, Surrey, England; [6]Princess Margaret Hospital, Toronto, Ontario, Canada; [7]Novartis Pharma AG, Basel, Switzerland; [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [9]Netherlands Cancer Institute, Amsterdam, The Netherlands*

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.