

**Material and methods:** Prostate cancer cells (PC-3) were treated with either 2–20 Gy of  $^{60}\text{Co}$  gamma-IR or 0.5–50  $\mu\text{M}$  8-Cl-cAMP alone or as an adjuvant immediately after 10 Gy IR. The antiproliferative and cytotoxic effect of these treatments was followed by trypan-blue exclusion assay, MTT assay and BrdU incorporation, while cell cycle distribution and death were analyzed by flow-cytometry of PI stained cells. The combination index value (CI) was calculated by the Calcu syn software.

**Results:** Both 8-Cl-cAMP and IR showed significant inhibition of PC-3 cell proliferation with  $\text{IC}_{50}$  of 12.5  $\mu\text{M}$  and 11.9 Gy, respectively, according to BrdU test. The TBE assay showed that the number of viable cells in treated vs. control cells (*i.e.* Viability index) decreased, with  $\text{IC}_{50}$  values of 15  $\mu\text{M}$  and 10.4 Gy, respectively. The Viability index was further decreased when combined treatment was applied, demonstrating synergism (CI 0.5–0.7). Also, CI value for the same combination in BrdU assay demonstrated synergism (CI 0.4–0.9), suggesting that combined treatment significantly enhance either of single treatments of PC-3 cells. Cell cycle analysis showed S and G2/M arrest after all three applied treatments. However, combined treatment also demonstrated significant increase in hypodiploid cell population (18% in treated vs. 4% in control cells), suggesting possible induction of apoptosis.

**Conclusions:** This *in vitro* study indicates that, when used in combination with IR, 8-Cl-cAMP may be effective at concentrations that are lower than those required for efficiency as a single agent. Further preclinical tests should be introduced to confirm if 8-Cl-cAMP in combination with IR could successfully control growth of hormone-refractory prostate-cancer *in vivo*.

## 901

## PUBLICATION

### The preferred treatment for stage I seminoma: a survey of Canadian radiation oncologists

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**Purpose:** To evaluate the preferences for managing stage I seminoma patients post orchiectomy among Canadian radiation oncologists.

**Methods:** In February 2005 an electronic survey with questions related to the management of stage I seminoma post orchiectomy patients was sent, via email, to Canadian radiation oncologists who treat genitourinary malignancies. The preferences of the respondents with regards to treatment were analyzed and are presented.

**Results:** Of 119 oncologists surveyed, 93 responded (78% response rate). Fourteen responders did not manage seminoma patients, and one declined to complete the survey. Therefore, the survey completion rate was 74% of the 105 eligible responders. Among the respondents, 89% were male, 11%, female with the median age being 43 years. The median number of years in practice was 13, and 80% worked in academic centres. Responses to questions on the most appropriate and preferred treatment options are presented in table.

Question	Surveillance	Adjuvant radiation	Adjuvant chemotherapy	Unsure
The most appropriate treatment for most stage I seminoma patients	56%	31%	1%	12%
If I had Stage I seminoma, I would prefer ...	52%	27%	8%	13%

There was a strong association between what respondents thought was the best treatment for their patients and what they would choose for themselves ( $p < 0.001$ ). Older oncologists are more likely to choose radiotherapy for themselves ( $p = 0.05$ ) and there is a trend (non-significant) for older oncologist to choose radiotherapy for their patient ( $p = 0.07$ ). Years in practice, type of practice (academic vs. community) and provincial location did not appear to influence management choices.

**Conclusions:** There remains considerable variation in the opinions of Canadian radiation oncologists regarding the optimal treatment approach for stage I seminoma patients although currently the majority seem to favour surveillance post orchiectomy.

## Gynaecological Cancer

Oral presentations (Tue, 1 Nov, 9.15–11.15)

### Gynaecological cancer

## 902

## ORAL

### Paclitaxel-carboplatin-gemcitabine (TCG) versus paclitaxel-carboplatin (TC) as first line treatment in women with ovarian cancer: A randomized phase III GCG Intergroup study (AGO-OVAR 9, GINECO-TCG, NSGO-OC-0102)

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**Background:** Despite major progress achieved in the last decades, epithelial ovarian cancer is still not curable in the majority of patients. Addition of non cross-resistant drugs to standard TC is a potential option for improvement of efficacy. In phase II trials the addition of gemcitabine to TC resulted in high compliance and manageable toxicity. Therefore, a prospectively randomized phase III Intergroup study comparing TCG to standard TC was initiated within the GCG network.

**Patients and methods:** This protocol started in 8/02 and recruitment was completed in 04/04. Patients were 18 years or older, had epithelial ovarian cancer FIGO stages IC-IV, and were randomized within 6 weeks after primary surgery. Two-fold stratification was based on centre and disease characteristics: stratum I = FIGO stages IC-IIA, stratum II = FIGO stages IIB-IIC and residual tumor 0–1 cm, and stratum III = FIGO stage IV or residual tumor >1 cm. Patients were randomized to either TC (T 175 mg/m<sup>2</sup> 3h iv d1+C AUC 5 iv d1) or TCG (TC as above+G 800 mg/m<sup>2</sup> iv d1+8) for at least 6 cycles every 21 days.

**Results:** This first interim analysis was based on data from 1,724 patients receiving at least one cycle of study medication, 5,257 cycles of TC and 5,111 cycles of TCG. The strata distribution showed 175, 891, and 676 patients in strata I, II, and III respectively. Most patients received 6+ cycles (87.5% TC, 87.1% TCG). Dose reductions on d1 occurred in <10% in both arms and G d8 was omitted in 37% of cycles. Hematologic toxicity and need for support with G-CSF, blood products and antibiotics occurred significantly more frequent in the TCG arm, but neutropenic fever was rare with 2.1% and 6.5% ( $p < 0.0001$ ). Fatigue was the only non-hematological toxicity showing a significant difference favouring TC (Grade 3/4: 6.6% versus 10.4%,  $p = 0.005$ ). Until 04/05 166 deaths were observed of whom 142 were related to ovarian cancer. The other 24 deaths were equally distributed among patients in both arms and included 5 events possible related to study medication.

**Conclusion:** TCG was feasible but induced more haematological toxicity. Further follow-up will show if addition of G to TC will provide a meaningful benefit in women with ovarian cancer. (This study was supported by Eli Lilly & Co).

## 903

## ORAL

### Clinical activity of single agent pertuzumab (rhuMab 2C4), a HER dimerization inhibitor, in advanced ovarian cancer (OC): a HER predictive relationship with tumor HER2 activation status

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**Background:** Ovarian cancers (OC) frequently have activation of HER2 even in the absence of HER2 overexpression. Pertuzumab (P), a humanized HER2 antibody, represents a new class of targeted agents called HER dimerization inhibitors (HDIs) that inhibit dimerization of HER2 with EGFR, HER3 and HER4, and inhibit signaling through MAP and PI3 kinases. A phase I trial has demonstrated activity in OC.

**Methods:** 123 pts. with relapsed OC were treated with P, administered intravenously with a loading of 840 mg followed by 420 mg every 3 weeks to 61 pts. in cohort 1, while 62 pts. in cohort 2 received 1050 mg of P intravenously every 3 weeks. Response rate (RR) by RECIST was the primary endpoint, assessed after cycles 2, 4, 6, 8, 12 and 16. Fresh tumor biopsies were mandatory for cohort 1 in order to assay for HER2 phosphorylation (pHER2) status.

**Results:** Median age was 59 years (range 35–78) for cohort 1 and 57 years (range 35–83) for cohort 2. Median ECOG PS was 1 (range 0–3) for cohort 1 and 0 (range 0–1) for cohort 2. The median number of prior chemotherapy regimens was 5 for both cohorts. 60 pts. in cohort 1 and 62 pts. in an interim analysis of cohort 2 were evaluable for response. There were a total of 5 objective partial responses (PRs) (RR = 4%), 2 in cohort 1 and 3 in cohort 2. 7 pts. (6%) had SD with CA-125 reduction of  $\geq 50\%$  (4 in cohort 1, 3 in cohort 2). An additional 3 pts (2%) had SD for  $\geq 6$  months (all in cohort 1, cohort 2 data still premature). Overall rate of activity = 12%. Overall median time to progression (TTP) was 6.6 weeks (7.0 weeks in cohort 1, 6.6 weeks in cohort 2). Of the 65 tumor biopsies from cohort 1, 31 were evaluable and 8 (26%) were positive for pHER2 by ELISA. TTP for pHER2+ pts. was 20.9 weeks (n = 8), compared to 6.0 weeks for pHER2 – (n = 23), and 9.1 weeks for unknown pHER2 status (n = 29). P was well tolerated with diarrhea in 61% of pts (grade 1–3) (57% in cohort 1, 65% in cohort 2). 5 pts. had a drop in ejection fraction to  $<50\%$  with 1 confirmed by a central facility.

**Conclusions:** As a single agent P is well tolerated. Clinical activity was observed in 12% of pts with heavily pretreated OC as demonstrated by PRs, SD  $\geq 6$  months, and SD with CA-125 reductions of  $\geq 50\%$ . This study suggests P may be active in OC. Preliminary analysis suggests pHER2 status may be important for P activity.

904

ORAL

#### Adjuvant treatment of early stage cervix cancer: a systematic quantitative review

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**Background:** Patients with early stages cervix cancer (IA<sub>2</sub>-IIA) with postoperative findings of lymph node metastasis, lymphovascular space invasion, depth of invasion more than 10 mm, parametrial invasion, non-squamous histology, or positive surgical margins are at increased risk for subclinical dissemination of the disease. Postoperative radiotherapy has been found to decrease the incidence of local recurrence with little or no effect on overall survival. This review has been undertaken to assess the available evidence for adding chemotherapy to radiotherapy in the adjuvant treatment of those patients.

**Material and methods:** We have searched the Cochrane Library, CENTRAL, MEDLINE, EMBASE, LILACS, Biological Abstracts, CINAHL, SciSearch and Cancerlit. We have handsearched the congress proceedings of cancer societies. All randomised controlled trials comparing postoperative chemotherapy and radiotherapy (intervention group) with postoperative radiotherapy alone (control group) in the treatment of stages IA<sub>2</sub>-IIA cervix cancer were included. Outcome measures were overall survival, progression-free survival, local recurrence, distant recurrence, major treatment toxicities (grades 3 and 4) and quality of life.

**Results:** We found 10 randomised controlled trials, but only two met the selection criteria, including a total of 314 patients. Overall survival: Patients in the intervention group had a significantly reduced hazard of death at 48 months (HR 0.43, 95% CI 0.25 to 0.76). Progression-free survival: At 48 months the hazard ratio was estimated to be 0.45 (95% CI 0.28 to 0.74). Local recurrence: At 48 months, there was less local recurrence in the intervention group (HR 0.50; 95% CI 0.26 to 0.98). Distant recurrence: There was no difference between the intervention and the control groups in the hazard of distant recurrence at 48 months (HR 0.74; 95% CI 0.36 to 1.52). Major toxicities: The odds for grade 3 and 4 major toxicities was significantly higher in the intervention group (Peto OR 5.19 [95% CI 2.90 to 9.29] and 4.62 [95% CI 1.96 to 10.86], respectively). We were unable to obtain data about quality of life.

**Conclusions:** In this systematic review, the overall evidence suggests that the addition of chemotherapy in the adjuvant treatment of early stage cervix cancer with risk factors for recurrence provides clinical benefit. However, the evidence is limited because the selected studies were quantitatively and qualitatively limited, with small number of patients and limited time of follow-up. There is a need for further randomised controlled trials to compare adjuvant chemotherapy and radiotherapy with adjuvant radiotherapy alone in the treatment of early stage cervix cancer with risk factors for recurrence. This review is registered in the Cochrane Gynaecological Cancer Group (H011).

905

ORAL

#### A randomized phase III trial of concurrent chemoradiation in locally advanced cervical cancer: preliminary results

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**Background:** Concurrent chemoradiation by platinum based is the standard treatment for locally advanced cervical cancer. Carboplatin is platinum analogue which has comparable activity with cisplatin. 5FU is the drug that has synergistic effect with radiation. The therapeutic index of 5FU is improved when given as a continuous intravenous infusion. Tegafur-Uracil (UFT<sup>®</sup>) is an oral chemotherapy which is recommended to replace the continuous intravenous infusion of 5FU as a radiosensitizer. This study was a preliminary result of a randomized two arms, prospective, open-label phase III trial comparing the activity and safety of the concurrent chemoradiation of UFT & carboplatin or carboplatin alone in locally advanced cervical cancer.

**Materials and Methods:** The stage IIB-IIIB cervical cancer patients were randomized to have UFT 225 mg/m<sup>2</sup>/day orally and carboplatin 100 mg/m<sup>2</sup> IV over 30–60 minutes, weekly on day 1 concurrent with standard radiotherapy (UFT group) or carboplatin alone concurrent with standard radiotherapy (control group). In UFT group, UFT was taken in 3 divided doses daily at the same day of radiotherapy, 5 days a week and stopped on weekend. The tumor response and toxicity were evaluated weekly during treatment, 1 month interval for 3 months and 3–6 months for 5 years.

**Results:** From July 2001 to December 2003, 469 patients were randomized to UFT group (n = 234) or control group (n = 235). There was no significant imbalance in patient characteristics. The treatment interruption and the dose modification were nearly the same in both groups. The tumor response at 3 months follow up time was no significant difference. The only prognostic factor to improve the complete response rate was the hemoglobin (Hb) level. The patients in UFT group who had Hb  $< 10$  gm/dl had the relative risk to complete response 1.48 compared to that in control group (P = 0.025, 95% CI 1.07, 2.04). The severe toxicity or adverse event had not been reported. The median follow up time for UFT group and control group were 12.6 and 11.8 months, respectively. There was no statistical difference in PFS and OS.

**Conclusion:** Concurrent chemoradiation by UFT and carboplatin was not difference in tumor response rate or treatment toxicity compared to carboplatin alone. The combination drugs might have benefit in poor prognostic patients such as the baseline Hb  $< 10$  gm/dl.

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ORAL

#### A differential gene expression profile reveals RUNX1/AML1 and ERM/ETV5 up-regulation correlating to infiltration stages in endometrioid endometrial carcinoma

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**Background:** endometrial cancer (EC) is the most common gynaecological cancer in industrialized countries. Among the different subtypes, type I or endometrioid EC (EEC) represents the 80% of its incidence. It is associated with oestrogen exposition and affects mainly peri- and post-menopause young women. Good prognosis is related with early diagnosis and uterus localization. In this context, myometrial affectionation as the initial event of tumour invasion and distant dissemination, determines an increase in recurrences after a first surgical treatment, and a decrease in the five years survival. Studies focused on the molecular basis of EC have demonstrated correlations among molecular alterations (PTEN gene silencing, microsatellite instability associated with defects in DNA mismatch repair genes, or mutations in the K-ras gene) and tumour progression, its molecular pathology remaining essentially unknown.

**Material and methods:** identification of molecular factors responsible of endometrial tumorigenesis by cDNA microarrays. Validation of the candidate genes by Real-Time quantitative PCR and tissue arrays.