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Phase II study of Sorafenib (BAY 43–9006) in combination with Gemcitabine in recurrent epithelial ovarian cancer –a study of the PMH phase II consortium

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Background: Sorafenib is a novel multi-targeted tyrosine kinase inhibitor that targets RAF/MEK/ERK signaling pathway, vascular endothelial and platelet derived growth factors receptors and flt-3. Phase I studies have demonstrated safety and tolerability of sorafenib in combination with gemcitabine, with preliminary activity seen in recurrent ovarian cancer. VEGF is over expressed in human ovarian tumors and is associated with poor prognosis and development of ascites. Therefore sorafenib and gemcitbine would make a rational therapeutic strategy for combination in recurrent ovarian cancer.
Methods: A Phase II, two stage clinical trial in women with recurrent ovarian cancer who have received upto 2 prior lines of chemotherapy following recurrence is underway, assessing the activity of sorafenib 400 mg bid continuously in combination with weekly Gemcitabine 100 mg/m^2. Cycle 1 is an extended cycle of 7 weeks of G followed by a break for a week. Subsequent cycles are 4 weekly with G being administered for the first 3 weeks of each cycle. Twenty one patients have been enrolled to date; 14 are evaluable for toxicity having received 18 cycles of treatment and 9 are evaluable for response.
Results: Of patients evaluable for response, one patient has had a confirmed response and 8 patients had stable disease. Grade 3 toxicites that have been seen in more than one patient to date are pain (3), lymphopenia (5), thrombocytopenia (3), leucopenia/neutopenia (2) hand foot (2) and biochemical transaminitis (2).
Conclusions: This trial continues to accrue. Updated results will be presented.

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Hormone replacement therapy in cervix cancer survivors: is it safe?

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Introduction: The young patients with cancer of cervix will go into early menopuause due to surgery and adjuvant/or radiacal radiotherapy. In moste cases the oncologists would advised these women against the use of HRT. The purpose of this study was to evaluate the influence of HRT on the well being and the reccurence of squamous cell cevix carinoma in women treated with surgery and adjuvant or radical radiotherapy.
Materials and Methods: From 1992 to 2003, HRT was prescribed for 136 premenopause pts with cervix carcinoma St Ib1 to St IIIb. Each pts from HRT group was compared with pts from the group with same diagnosis who did not received HRT. The meching crieteria were: ageand, stadium of disease and DF interval until applying HRT. All patients had squamous cell cervix carcinoma Mean age was 32 years (rang 23–39years). Baseline mammography and/or brest ultrasound were performed in 136pts before starting HRTand control group. In HRT group 67/136pts underwent radical hysterectomy and adjuvant radiation due to carcinom of the cervix ST Ib1(>2 cm)and ST IIa. 69/136pts had radical radiation therapy for St IIb-IIIb cervix cancer. To relieve climacteric symptoms and to prevent osteoporosis mono-estogenes therapy (transdermal-67/136pts) and continuos combined HRT (E2/NETA-(45/69pts) and tibolone (24/69pts) were prescribed. The mean duration of treatment was 4.7 (rang 1.4–12.3 years).
Results: HRT is extremely effective in amelioratiomg the vasomotor symptoms associated with early menopause (136/136pts vs 91/136, $p < 0.001$). Vaginal dryness, dyspareunia and recurrent urinary tract infections are effectively treated with HTR (116/136pts vs 100/136, $p < 0.001$ (32/45pts receiving E2/NETA had an apparent increase in brest density, whereas no changes was recorded in patients on E2 and tibolone or without HRT. No other clinically significant abnormalities were observed. Brest pain was often reported as an adverse event in the E2/NETA(39/45pts) and tibolone group (19/24 pts) vs 48/136 pts no HRT, retrospecively. Normal baseline bone-mineral density had 127/136 pts. vs 119/136pts. Bone-osteodensitometry showed osteopeny in 6 pts before HRT (these patients were menopause 6.7 years; (Bone–mineral density increased in 5/6pts who received E2/NETA and tibolone. BMD after 5 years of treatment: osteoporosis 2/136 vs 36/136, $p < 0.001$. DFS was 86% in the group on E2 vs 82% no HRT ($p > 0.001$) and 65% in the group on E2/NETA or tibolone vs 61% ($p > 0.001$)
Conclusion: there is no evidence that HRT influence on development of the local or distant recurrences in the patients with the cervix carcinom in contrast to well-being.

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Efficacy of pegylated liposomal doxorubicin (PLD) plus carboplatin in patients with intermediate sensitive relapsing advanced ovarian cancer

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Background: The goal of first line chemotherapy in advanced ovarian cancer is to induce complete response in order to induce durable response and long progression free interval and even a cure. However, in relapsing disease, palliation and quality of life become very important goals as the chance for a cure becomes less probable. While single agent PLD (Caelyx®) is the treatment in some patients in early relapse <6 months and paclitaxel+carboplatin combination is well established in late relapse >12 months; The optimal therapy for the 6 and 12 months population still remains to be defined. The GINECO group showed that PLD+carboplatin can induce a high response rate with less alopecia, neuropathy and myelosuppression than the paclitaxel+carboplatin combination.
Methods: A multi-center single arm phase II trial to assess the safety and efficacy of PLD 30 mg/m^2 in combination with carboplatin AUC 5 mg/ml/min every 4 weeks was undertaken. Eligibility criteria included: Measurable disease, prior taxane and platinum regimen with a progression free interval >6 months and <12 months. The study is planned of 63 patients and the primary objective is response according to the RECIST criteria. Secondary objectives are duration of response, time to progression, safety and overall survival.
Results: Thirty-four patients have been enrolled and are the subjects of this early report, median age 61 years (44–80). Median progression free interval before entering the study is 37 weeks (26–52) with a median of 8 prior cycles (4–9) of paclitaxel carboplatin. No major toxicity has been reported; Only 3 grade 3–4 toxicities were reported: Anemia, abdominal pain and allergic reaction. The incidence of hand foot syndrome (HFS) is relatively low with no grade 3–4. Other toxicities were uncommon and usually did not lead to discontinuation of therapy. An early efficacy analysis revealed a 40% objective response rate with 36% of patients having stable disease. Median time to progression is 30.5 weeks with more then 40% still progression free.
Conclusion: The combination of PLD with carboplatin given every 4 weeks in the intermediate sensitive patients is active and well tolerated. This combination gives an interesting efficacy while minimizing toxicity in this difficult to treat patient population.

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Protective role of the polymorphism CCR2–64I in the progression from squamous intraepithelial lesions to invasive cervical carcinoma

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Background: Invasive cervical cancer (ICC) is one of the most common malignant diseases among women, representing almost 10% of all the cancers in the female population. The aim of this study was to explore the association of the *CCR2–64I* polymorphism with the risk of developing Invasive Cervical Cancer (ICC).
Methods: DNA samples were extracted from peripheral blood cells of 109 patients with squamous intraepithelial lesions (SIL) and 217 patients with ICC. The *CCR2–64I* polymorphism was analyzed through PCR-RFLP (BseJI). Analysis of data was performed using the computer software SPSS for windows. The odds ratio (OR) and its 95% confidence interval (CI) were calculated as a measure of the association between *CCR2–64I* genotypes and cervical cancer risk.
Results. The frequency of the G/A genotype was significantly higher in SIL patients (n = 109) than in ICC patients (n = 217) ($p = 0.005$; OR = 0.42; 95%IC: 0.22–0.83).