Gynaecological cancer

Oral presentations (Thu, 24 Sep, 09:00−11:00)
Gynaecological cancer

8000 ORAL

Efficacy and safety of farletuzumab, a humanized monoclonal antibody to folate receptor alpha, in platinum-sensitive relapsed ovarian cancer subjects: preliminary data from a phase-2 study

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Background: Farletuzumab (MORAb-003) is a humanized monoclonal antibody to folate receptor alpha (FRα). FRα is over-expressed in most epithelial ovarian cancers (EOC), but largely absent on normal tissue. Farletuzumab is effective in preclinical xenograft models of ovarian cancer, active in ADCC assays, and inhibits phosphorylation of proteins by Lyn kinase. A Phase 1 study conducted with single agent farletuzumab in platinum resistant or refractory EOC subjects demonstrated signals of efficacy, and no dose-limiting toxicities or drug-related serious or severe AEs were observed.
Materials and Methods: The current study is an open-label, phase 2 study of farletuzumab in platinum-sensitive first relapsed subjects to determine the efficacy of farletuzumab as a single agent (SA), or in combination with platinum and taxane (P/T). A total of 54 subjects were eligible. Twenty eight (28) subjects who had asymptomatic CA-125 relapse received SA farletuzumab. A total of 46 subjects received P/T plus farletuzumab; 26 subjects experienced symptomatic relapse, 20 progressed on SA farletuzumab. Subjects who attained a complete or partial response (37) received SA farletuzumab maintenance therapy.
Results: Preliminary data show that of the 41 evaluable subjects receiving farletuzumab with P/T, 37 subjects (90.2%) normalized CA-125. In 10 (27%) of these 37 subjects who normalized, the second remission has been equal or as long as the first remission. Historically less than 5% patients achieve second remission longer than the first remission. By RECIST criteria (best response), 73.5% subjects achieved objective response (CR+PR), and the median PFS was 10.3 months. Subjects on SA farletuzumab had frequent SD or improvement, but no objective response or remissions were observed. No grade 3 or 4 farletuzumab-related AEs were observed and farletuzumab did not increase the toxicities of concomitant chemotherapy. The most common drug-related AEs were pyrexia, headache, and flushing.
Conclusions: Preliminary data for this study indicates that Farletuzumab with P/T significantly increases objective response rate compared to historic data for P/T alone in relapsed platinum-sensitive first-relapsed ovarian cancer subjects and increases the duration of second remission compared to first remission. A randomized global phase-3 study to test farletuzumab in combination with P/T in platinum-sensitive EOC, and a phase 2 in combination with weekly taxane in platinum-resistant EOC are currently ongoing.

8001 ORAL

Randomized multicenter phase II trial of cisplatin and ifosfamide with or without paclitaxel in recurrent or metastatic carcinoma of the uterine cervix: a Hellenic Co-operative Oncology Group (HeCOG) study

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Background: We undertook a randomized phase II trial to test whether the addition of paclitaxel to the cisplatin and ifosfamide (IP) combination could improve objective-response (OR) rate, progression-free (PFS) and overall survival (OS) in patients with recurrent or metastatic cancer of the uterine cervix.
Methods: Eligible patients were randomly allocated to receive either the IP regimen (ifosfamide 1.5 g/m^2, intravenously, daily, on days 1 through 3 with Mesna uroprotection and cisplatin 70 mg/m^2 on day 2) or the same drug combination with the addition of paclitaxel 175 mg/m^2, given on day 1 as a 3-hour infusion (ITP regimen). Cycles were administered every 4 weeks on an outpatient basis for a target of six cycles using G-CSF support. The primary endpoint of the study was objective response, while PFS, OS and toxicity were secondary endpoints.
Results: One-hundred fifty-three patients were randomly assigned to either IP (74 patients) or ITP (79 patients) regimen. Median follow-up was 57.3 months. Toxicity was similar in both arms with the exception of a modest increase in neurotoxicity in the ITP arm. OR rate was significantly higher in the ITP group (59% versus 33%, p = 0.002, Fisher's exact test). Median PFS was 7.9 months (95% CI, 6.1−9.8) for patients in the ITP arm and 6.3 months (95% CI, 4.3−8.2) in the IP arm (p = 0.023). Median OS was 15.4 months (95% CI, 8.6−22.3) for patients in the ITP arm and 13.2 months (95% CI, 10.9−15.5) in the IP arm, respectively (p = 0.048). In multivariate analysis, patients in the ITP arm had a Hazard Ratio (HR) of 0.70 (95% CI, 0.49−0.99; p = 0.046) for relapse or progression and a HR of 0.75 (95% CI, 0.53−1.08; p = 0.124) for death compared to patients in the IP arm. Only performance status (PS), age at diagnosis and treatment arm were predictive for relapse/progression and survival in the multivariate setting.
Conclusions: The addition of paclitaxel to the IP combination leads to a significant improvement in OR rate and PFS in women with recurrent or metastatic cancer of the uterine cervix at the cost of a modest increase in neurotoxicity. The ITP regimen merits further investigation in randomized phase III studies.

8002 ORAL

What is the best schedule of Topotecan? – weekly versus routine 5-day schedule in patients with platinum-resistant ovarian cancer – a randomized, multicenter trial of the North-Eastern German Society of Gynaecological Oncology (TOWER)

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Background: A 5-day regimen (Tc) of Topotecan is approved and effective in women with platinum-resistant recurrent ovarian cancer. Newer phase-two trials show a more favourable toxicity profile of weekly administration of Topotecan (Tw) without compromising its anti-tumor activity. Therefore we conducted the first randomized multicenter trial to validate this assumption.
Materials and Methods: The trial was pre-registered at clinicaltrials.gov (NCT00170677). Women with platinum-resistant ovarian and fallopian tube cancers or primary peritoneal carcinoma, and measurable or assessable disease (GCIG criteria) were randomized to receive either Tw (d1,8,15/q28d, 4 mg/m^2) or Tc (d1−5/q21d, 1.25 mg/m^2). The pre-defined stopping rule, based on the primary endpoint of best CA-125 or tumor response, was not reached (presented at ASCO 2007, Abstract 5526). This permitted the accrual of 194 patients, 154 of whom could be assessed for CA-125 or tumor response (SD + CR + PR). We also compared progression-free (PFS) and overall survival (OS), as well as toxicity between trial groups.
Results: Mean age was 61.8 (SD 9.8) years, and 59 women were on third-line treatment. Patients received a total of 809 cycles of chemotherapy. Demographic baseline characteristics, tumor stages and grades, and previous lines of chemotherapy were well balanced between treatment groups. There were 35 / 75 (47%) and 45 / 79 (57%) responses in the Tw and Tc groups, respectively (Risk Ratio [RR] 1.22, 95% CI 0.89−1.66). Median PFS and OS did not differ markedly between both regimens (3.2 versus 4.4 months, hazard ratio [HR] 1.30, 95% CI 0.96−1.77 and 9.8 versus 10.0 months, HR 1.08, 95% CI 0.77−1.52). The risk of grade III/IV hematological toxicity was significantly lower in the Tw group (anemia: RR 0.35, p = 0.007, neutropenia: RR 0.38, p = 0.0001, thrombopenia: RR 0.23, p = 0.0004). QoL data were similar in both arms.

Conclusions: Weekly administration of topotecan shows no substantial difference in endpoints of effectiveness compared to conventional dosing, but is associated with a significantly lower likelihood of severe hematological toxicity. Weekly topotecan should be considered as a possible treatment alternative in women with platinum-resistant ovarian cancer.

8003 ORAL

Bevacizumab in heavily pre-treated ovarian cancer patients and the predictive value of serum VEGF

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Background: Ovarian cancer remains the leading cause of death in gynecologic malignancy in the western world and therefore new treatment strategies are urgently needed. Bevacizumab, a recombinant humanized monoclonal antibody against VEGF (Vascular Endothelial Growth Factor), has shown antitumor activity in several cancer types including ovarian cancer with acceptable toxicity. The purpose of the present study was to evaluate treatment with single agent bevacizumab in heavily pre-treated advanced epithelial ovarian cancer patients, expressed by RR (response rate), PFS (progression free survival) and OS (overall survival).
Furthermore we aimed at defining the possible prognostic and predictive value of serum VEGF analyzed in blood samples by each cycle.
Material and Methods: Thirty-eight patients with advanced ovarian cancer were treated with bevacizumab every three weeks, 10 mg/kg. Serum VEGF concentration was analyzed before treatment and in every cycle by ELISA technique (Quantikine ELISA kit no: 1190951, R & D Systems, Minneapolis, USA).
Results: The median number of prior regimens was five and the median number of bevacizumab treatment cycles was four. Thirteen patients were still under treatment at the time of analysis. Nine out of 33 evaluable patients (27%) showed response by CA 125 according to the modified GCIG criteria's. Median PFS was 6.3 months (95% CI; 3.5−17.7) and median OS was 8.2 months (95% CI; 5.0−9.2).
Two patients suffered from gastrointestinal perforation during treatment, one from ileo-vaginal fistula and two were diagnosed with trombo-embolia and transient cerebral ischemia.
All patients decreased their serum VEGF concentration after the first cycle of treatment with a mean of 89%. There was a significant difference in VEGF level between responders and no responders ($p = 0.004$). The CA 125 response rate was 63% for VEGF <275 pg/ml whereas 14% for VEGF > 275 pg/ml ($p = 0.009$). This cut off was chosen as the 25% percentile for all serum VEGF analyses. No association with clinicopathological parameters was demonstrated and no significant difference in PFS or OS was shown according to low/high serum VEGF.
Conclusion: Single agent bevacizumab therapy demonstrated activity in heavily pre-treated ovarian cancer women with a CA 125 response rate of 27%. Gastrointestinal perforations were identified in 5% of patients. Baseline serum VEGF levels seem to have predictive importance for the effect of bevacizumab treatment.

8004 ORAL

Effectiveness of multiple lines of chemotherapy in platinum-resistant ovarian cancer: the Christie experience

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Background: Platinum-resistant ovarian cancer defined by a treatment-free interval of less than 6 months is characterised by chemoresistance with response rates in the range of 10−20% with non-platinum compounds. Higher response rates have been reported with combination chemotherapy from non-randomised studies although the effect on survival is uncertain. However the efficacy of multiple lines of chemotherapy in patients with platinum-resistant ovarian cancer remains to be determined. Crucially, is it appropriate to consider palliative chemotherapy in patients that have progressed through previous chemotherapy. Here we present data on over 150 patients treated sequentially with single-agent non-platinum compounds and combination chemotherapy.
Methods: Patients with platinum-resistant ovarian cancer treated with chemotherapy were extracted from the Christie ovarian cancer database. The regimens evaluated were Liposomal doxorubucin, Carboplatin/Liposomal doxorubicin, Cisplatin and oral Etoposide, weekly Paclitaxel, Gemcitabine/Platinum and Topotecan. Data were analysed for prognostic factors, response rates, toxicity, progression-free survival and overall survival.
Results: Majority of patients were stage III/IV at presentation and 80% had debulking surgery. Patients were evenly matched with respect to degree of tumour burden (> 2 sites of disease; tumour bulk> 5cms). Liposomal doxorubicin and the dose-dense weekly Cisplatin and oral Etoposide were used more commonly in 'early' platinum-resistant disease. The best response rates were seen with Carboplatin/Liposomal doxorubicin and the dose-dense cisplatin/oral etoposide regime. Progression-free survival and overall survival were significantly higher in the Carboplatin/Liposomal doxorubicin group perhaps indicative of its use early in platinum-resistant disease. On the other hand Topotecan was associated with negligible efficacy given its use in heavily pre-treated disease. The overall incidence of grade 3/4 toxicities was low. Mature data and full statistical analyses will be presented at the meeting.

	Liposomal doxorubicin	Carboplatin/ Liposomal doxorubicin	Cisplatin/ Etoposide	Paclitaxel weekly	Gemcitabine/ Platinum	Topotecan
Median age	64	65	65	71	65	60
Lines of chemo-median	2	2	2	2	3	3
Ca125 response GCIG criteria	30%	48%	43%	63%	33%	11%
Radiological Response	22%	37%	35%	24%	17%	0
Median PFS weeks (range)	21.5*	26.6*	17 (1−110)	18.5 (2−80)	15.5 (1−48)	13.5 (1−34)
Median OS weeks (range)	58*	58*	36 (1−147)	35 (3−88)	46 (2−130)	36 (4−116)

*Data (range) not mature, available by presentation

Conclusion: Multiple courses of chemotherapy are effective in platinum-resistant ovarian cancer.

8005 ORAL

Correlation of RNA expression of DNA repair genes with clinical outcomes of advanced ovarian cancer (OC) pts treated with pegylated liposomal doxorubicin (PLD) vs Trabectedin (T) + PLD in the ET743-OVA-301 clinical trial

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Background: Enhanced sensitivity to T has been observed in cells that, in addition to a proficient NER pathway, are deficient in homologous recombination repair (HRR). In a retrospective series, pts with soft-tissue sarcoma expressing high levels of ERCC1 and XPD [NER] and low levels of BRCA1 [HRR] experienced more favourable outcomes with T. These markers were prospectively investigated in available OC samples from the randomised Phase III study OVA-301.
Materials and Methods: Tumor tissue blocks from 183 consenting pts of the 672 OC pts enrolled in OVA-301 were analysed by qRT-PCR. 139 (76%) samples had at least one detectable expression level. High and low mRNA expressions were defined for levels above *vs* below the median, respectively. For progression-free survival [PFS] and overall survival [OS] association analyses to investigate outcomes by expression levels, and the relative benefit due to T depending on expression were carried out.
Results: Both in the overall study population (SP) and in the analyzed cohort, PFS and OS were significantly longer in the platinum (P)-sensitive *vs* P-resistant pts. In the SP, T+PLD induced a significantly longer PFS and a trend for longer OS than PLD. Pts with low BRCA1 mRNA levels had significantly longer OS ($p = 0.0297$) and PFS ($p = 0.0427$) than those with high BRCA1 levels, indicating the prognostic value of BRCA1 expression in the OC population studied. A trend ($p = 0.0765$) for longer OS (but not PFS) was found for pts with high ERCC1 expression levels. No significant differences in PFS or OS emerged for low or high XPD expression levels. PLD-treated pts with high ERCC1 mRNA levels tended to have longer PFS than those with low ERCC1 levels. No significant differences in PFS or OS were observed with the combined expression of BRCA1+ERCC1. Caveats of these analyses include low numbers of pts in each of the subgroups, prior P-based therapy in all pts (+ 80% prior taxanes) which might have modified the tumor RNA expression levels, immature OS data, and the effect of PLD added to T in the assessment of outcomes *vs* mRNA expression levels.