vs 46%. There were not differences between both groups in % of patients who received consolidation therapy or in the best response to salvage regimens.

Results: (NOTAX-P vs TAX-P): Clinical response rates were complete (CCR): 38.2% vs 50%, partial (CPR): 17.1% vs 26% and overall (OCR): 55.3% vs 76%. The 95% CI values for the difference in response were for CCR: -4 to 27% and for OCR: 6 - 35% in favour of TAX-P. In 68 p with CCR or CPR who underwent 2nd look laparotomy, pathologic complete response rates (PCR) were 48.8% vs 48.1% (p ns). With a median follow-up of 81 and 31 months, median survival are 26 vs 29 months respectively, and 3-y survival rates (95% CI) are 42.8% (32 - 53%) vs 41.3% (25.9 - 56.7%).

Conclusion: We have obtained a better OCR rate with TAX-P compared to NOTAX-P regimens, but, contrary to the results of some randomized clinical trials, PCR rates, median survival and 3-y overall survival remain basically unchanged in our series.

964 POSTER DISCUSSION

Clinical development of Ovarex MAb-B43.13 monoclonal antibody for treatment of ovarian cancer: impact of immune responses and circulating CA125 levels on clinical efficacy

H. Fingert, C. Nicodemus, M. Siemens, B.C. Schultes. *AltaRex Corporation, Waltham, USA*

OvaRex Mab-B43.13 is a murine monoclonal antibody (MAb) targeting the tumor-associated antigen CA125. Intravenous administration was associated with prolonged survival in patients (pts) with relapsed ovarian cancer, correlated with nonspecific (HAMA) and specific (Ab2) immune responses (Bolle, Proc. ASCO 19:476a, 2000). Paradoxically, prolonged survivals were seen in poor-risk pts, assessed by elevated circulating CA125 levels relative to pts with lower levels of CA125 (Noujaim A.A., Cancer Biother Radiopharm, in press). A prospective, randomized, placebo-controlled, double blind study of 345 pts with stage III-IV ovarian cancer was designed to determine clinical efficacy, safety, and biologic activity of OvaRex MAb administered after attainment of CR from primary chemotherapy. Preserving integrity of the blind, independent review was conducted from an initial cohort of 252 pts. Clinically meaningful immune responses were observed in >50% of the MAb-treated pts, measured by serum HAMA >5000 ng/mL and Ab2 >100 ng/mL associated with improved time to relapse (TTR). Pts with specific immune response (Ab2 serum level >100 ng/mL) demonstrated two-fold improved TTR to 18.9 mos vs. 7.4 mos in pts with Ab2 < 100 ng/mL. Irrespective of immune response, baseline CA125 prior to protocol treatment was a strong predictor of TTR, similar to previous reports (Makar, Gyn Oncol 49:73, 1993) and was confirmed to be a valid covariate for analysis of efficacy outcomes. In a poor prognosis subgroup (CA125 >20 U/mL), the proportion of pts surviving 6 months without disease relapse improved two-fold with OvaRex MAb therapy (relapse-free survival 79% vs. 39% in placebo-treated controls, p <0.05). Taken together, the favorable clinical outcomes in the high-risk pts with elevated CA125 levels support the proposed mechanism to induce immune responses to MAb + CA125 immune complexes, generated after intravenous MAb administration. Results from prospective, controlled trials confirm that OvaRex Mab-B43.13 frequently induces immune responses relevant to clinical efficacy, and provide rational approaches to development as an adjunct to treatment of ovarian cancer and possibly to treatment of other types of cancer associated with circulating serum CA125 levels.

965 POSTER DISCUSSION

Phase II clinical study of BBR 3464, a novel, bifunctional platinum analogue, in patients with advanced ovarian cancer

A.H. Calvert[1], H. Thomas[2], N. Colombo[3], M. Gore[4], H. Earl[5], L. Sena[6], G. Camboni[7], P. Liati[8], C. Sessa[9]. *[1] Newcastle General Hospital, Newcastle upon Tyne, UK; [2] The Royal Surrey County Hospital, Guildford, UK; [3] Istituto Europeo di Oncologia, Milan, Italy; [4] The Royal Marsden Hospital, London, UK; [5] Addenbrooke's Hospital, Cambridge, UK; [6] Drug Development Office, The Cancer Research Campaign, London, UK; [7] NovusPharma SpA, Milan, Italy; [8] South Europe New Drug Organisation, Milan, Italy, [9] Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*

BBR 3464 is a trinucleate platinum compound, differing from cisplatin in its structure, nature of the adducts formed, and pre-clinical spectrum of anti-tumour activity. The Phase I study of a 1 hour infusion every 28 days identified diarrhoea and myelosuppression as the dose limiting toxicities and initially 1.1mg/m2 as the recommended Phase II dose. Activity was observed in three patients, with respectively melanoma, pancreatic and lung cancer.

Purpose: The objectives of this Phase II study are to determine the efficacy of BBR 3464 in patients with ovarian cancer failing platinum-taxane regimens and to further characterise the toxicity and pharmacokinetic profile of this compound.

Methods: This is a multi-centre, open label, Gehan design study. Patients are stratified into two categories: those who relapsed following a response after 6 months from the discontinuation of chemotherapy and those who have not responded or have relapsed within 6 months.

Results: 28 relapsed and 18 refractory patients have been recruited to date and have received in total 164 infusions of BBR 3464. Five partial responses, confirmed by independent peer review, have been reported and in three of them a repeat scan for confirmation was obtained. In responding patients, the average interval between previous treatment and the first BBR 3464 treatment was 18 months. Toxicity data is available on 44 patients. The main toxicity seen so far is neutropenia (G3 n=7 (16%), G4 n=5 (11%)) which led to a dose reduction to 0.9mg/m2 in 6 patients. In addition, anaemia (G2 n=8, G3 n=1), thrombocytopenia (G2 n=1), nausea (G2 n=11, G3 n=8) and vomiting (G2 n=11, G3 n=5) were reported. Diarrhoea was observed (G2 n=14, G3 n=3) but was kept manageable by a policy of active intervention with loperamide. No clear signs of drug-related neurotoxicity were seen. One patient with pre-existing hypomagnesaemia and paraesthesiae experienced grade 2 paraesthesiae associated with course 3 of treatment. Since the haematological toxicities were reversible within 3 weeks and there was no evidence of cumulative renal or lung toxicity, a schedule of 0.9mg/m2 every 21 days, which in the ongoing Phase I trial was shown to be better tolerated and of a similar dose intensity, has now been introduced. Recruitment into the refractory category continues using this amended schedule. Efficacy and toxicity analysis is ongoing.

Conclusion: BBR 3464 is showing provisional evidence of activity in relapsed ovarian cancer.

966 POSTER DISCUSSION

Weekly paclitaxel and carboplatin followed by topotecan (TC-TP), as first-line therapy for patients with advanced epithelial ovarian cancer (AOC) suboptimally debulked. Updated preliminary results

J.A. Arranz Arija[1], R. Gonzalez-Beca[1], A. Velasco[2], M.M. Perez[2], P. Borrega[3], M. Bolaoos[3], A. Bernal[4], J.J. Cruz[4], V. Alija[5], P. Martinez-Prado[5]. *[1] H. Gregorio Marañon, Medical Oncology, Madrid, Spain; [2] H. Princesa, Medical Oncology, Madrid, Spain; [3] H. San Pedro, Medical Oncology, Caceres, Spain; [4] H. Clinico, Medical Oncology, Salamanca, Spain; [5] H. Basurto, Medical Oncology, Bilbao, Spain*

Objective: To evaluate clinical response (overall, complete and partial: cOR, cCR and cPR respectively), pathological CR rate (pCR), and toxicity, of the schedule TC-Tp, administered as first-line therapy in patients (pt) with AOC suboptimally debulked, defined as FIGO III-IV with residual disease (RD)> 1 cm.

Patients and Methods: Phase II design. TC-Tp consisted of 2 courses of TC (weekly Paclitaxel 60 mg/m2 + Carboplatin AUC 2, x 6 doses each course) separated by a 14-day rest period, and followed by 4 courses of Tp (Topotecan 1.5 mg/m2/d x 5d every 3 weeks). All pt received Tp after TC even if they had no response to TC. Prophylactic filgrastim was allowed after an episode of neutropenia grade 3-4, and Tp doses were reduced after other G3-4 toxicities. Second-look laparotomy was planned at least for pt with cCR after TC-Tp. In those pt with pCR or microscopic residual disease, consolidation with TCx1 + Tp x2 was recommended.

Results: Since March '99, 65 pt have been included and 50 pt have already completed TC-Tp. Preliminary results from the first 37 pt were presented in ASCO'01. Results from the first 50 pt are presented here. Mean age was 58 y (34-77). There were 78% stages III and 22% IV. Debulking surgery was performed in 86% of pt, but 88% had RD >2 cm.

Grade 3-4 toxicities with TC were anemia 2%, neutropenia 23%, thrombocytopenia 4%, alopecia 37% and nephrotoxicity 2%. Toxicity after Tp was anemia 13%, neutropenia 40%, thrombocytopenia 11% and alopecia 70%. Astenia was present in some pt but it was not properly registered. There were no toxic deaths. Other toxicities were G1-2 or absent.

Response rate after TC (and 95% CI) were: cOR: 82% (69 - 91%), cCR: 36% (23 - 50%) and cPR: 46%. After TCTp we found cOR: 78% (64 - 88%), cCR: 48% (34 - 63%) and 30% cPR.

The difference in cCR between TCTp and TC is 12% (95% CI: -0.85 to 16%). Five pt have achieved pCR until now (11.6%, 95% CI: 4 - 25%), but results of 2nd look are pending for another 5 pt with cCR. Fourteen pt received consolidation therapy and 19 pt other 2nd line therapies. With a

median follow-up of 15 months for this 50 pt, 15 pt have died due to AOC. Median survival has not been reached, and 2-year overall survival is 76%.

Conclusion: In this population of pt with AOC suboptimally debulked, TC-Tp seems to be a very active and safe regimen. Final results of cCR, pCR and toxicity will be available next year.

967 POSTER DISCUSSION

ZD0473 phase II monotherapy trial in second-line ovarian cancer

M. Gore[1], R.J. Atkinson[2], L. Dirix[3], D. Rischin[4], P. Beale[5], P. Harnet[6], D. Hacking[7], H. Cure[8], J. Cosaert[9]. [1] *Medical Oncology, Royal Marsden Hospital NHS Trust, London;* [2] *Department of Oncology, Belfast City Hospital, Belfast;* [9] *AstraZeneca, Alderley Park, UK;* [3] *Oncologisch Centrum, Oosterveldann, Wilrijk, Belgium;* [4] *Peter McCallum Cancer Institute, St. Andrews Place, East Melbourne;* [5] *Royal Prince Alfred Hospital, Camperdown, New South Wales;* [6] *Nepean Hospital Penrith, Kingswood, New South Wales, Australia;* [7] *Durban Ontology Centre, Mayville, South Africa;* [8] *CAC Jean Perrin, Clermont Ferrand, Cedex, France*

Aims: ZD0473 (cis-amminedichloro[2-methylpyridine]platinum [II]) is a new generation platinum drug designed to deliver an extended spectrum of antitumour activity and overcome platinum resistance mechanisms. In this ongoing Phase II open-label, multicentre trial, the efficacy and tolerability of ZD0473 was evaluated in patients (pts) with ovarian cancer who have failed one prior platinum-based therapy.

Methods: Pts were to receive ZD0473 120 mg/m^2 1-h iv infusion on day 1, every 3 weeks. Later the dose was increased to 150 mg/m^2, every 3 weeks. Pts were considered resistant (cohorts 1–3) or sensitive (cohort 4) if they relapsed/progressed ≤26 weeks or >26 weeks, respectively, following completion of prior platinum-based chemotherapy.

Results: To date, 58 pts have been recruited to this study (32 resistant, 26 sensitive; median age 58 years [range 35–75 years]; 57 with performance status 0/1; 45 with distant metastases). Twenty pts received a starting dose of 120 mg/m^2 without escalation, 16 pts received a starting dose of 120 mg/m^2 escalated to 150 mg/m^2, and 22 pts received a starting dose of 150 mg/m^2. Dose reductions and delays occurred primarily in the pts receiving the higher dose of 150 mg/m^2 (58%). Grade 3/4 anaemia, neutropenia or thrombocytopenia was observed in 5, 8, and 7 pts at a dose of 120 mg/m^2; 7, 6 and 9 pts at 120/150 mg/m^2; and 5, 18 and 17 pts at 150 mg/m^2, respectively. The extent of prior exposure to carboplatin appears to be an important factor for haematological toxicity. Three pts were withdrawn from the trial due to drug-related toxicity and no drug-related deaths occurred. No clinically relevant nephro- or neurotoxicity were reported. Grade 3/4 nausea or vomiting was reported in 5 and 6 pts, respectively. Preliminary data have shown that an objective response was observed in 3/21 evaluable resistant pts (2 CR, 1 PR) and 7/22 evaluable sensitive pts (2 CR, 5 PR*). Five of the responses were observed at a dose of 120 mg/m^2, the other 5 responses were observed in pts who started on 120 mg/m^2 and were escalated to 150 mg/m^2. A further 6 resistant pts and 10 sensitive pts had stable disease (2 and 5 pts with some evidence of tumour shrinkage, respectively).

Conclusion: ZD0473 shows encouraging activity in second-line ovarian cancer including resistant disease. ZD0473 has an acceptable safety profile at 120 mg/m^2 and this is the preferred dose in this patient population who have received a high number of prior cycles of carboplatin.

*3/5 PR are currently unconfirmed.

Breast cancer biology

968 POSTER DISCUSSION

Mutation analysis of the CHK2 gene in breast carcinoma and other cancers

S. Ingvarsson[1,2], B.I. Sigbjornsdottir[2], S.H. Hafsteinsdottir[2], V. Egilsson[2], J.T. Bergthorsson[2]. [1] *University of Iceland, Institute of Experimental Pathology, Reykjavik, Iceland;* [2] *University Hospital of Iceland, Department of Pathology, Reykjavik, Iceland*

Mutations in the CHK2 gene at chromosome 22q12.1 have been reported in families with Li-Fraumeni syndrome. The Chk2 is an effector kinase that is activated in response to DNA damage and is involved in cell cycle and p53 pathways. We have screened 139 sporadic breast tumours for LOH at chromosome 22q, using 7 microsatellite markers. Seventy four breast tumours (53%) show LOH with at least one marker. These samples and 45 tumours from individuals carrying the BRCA2 999del5 mutation were screened with SSCP and DNA sequencing for mutations in the CHK2 gene. In addition to putative polymorphic regions in short mononucleotide repeats in a noncoding exon and intron 2, a germ line variant (T59K) in the first coding exon was detected. By screening additional 1137 cancer patients for the T59K sequence variant, it was detected in totally 4 breast-, 3 colon-, 1 stomach- and 1 ovary cancer patients, but not in 178 healthy individuals, suggesting that this is a low penetrance allele. A tumour specific 5' splice site mutation at site +3 in intron 8 (TTgt(a->c)atg) was detected in a tumour with extensive LOH in the genome. We conclude that somatic CHK2 mutations are rare in breast cancer, but our results suggest a tumour suppressor function for CHK2 in a minority of breast tumours.

969 POSTER DISCUSSION

The EGFR-selective tyrosine kinase inhibitor ZD1839 ('Iressa') is an effective inhibitor of tamoxifen-resistant breast cancer growth

J. Gee[1], I. Hutcheson[1], J. Knowlden[1], D. Barrow[1], M. Harper[1], H. Jones[1], A. Wakeling[2], R. Nicholson[1]. [1] *Tenovus Centre for Cancer Research, Cardiff, UK;* [2] *AstraZeneca, Macclesfield, UK*

Purpose: Many ER+ breast cancer (BC) patients initially respond to antihormone agents, eg tamoxifen ('Nolvadex'); however, acquisition of resistance is often seen. Overexpression of EGFR and/or EGFR ligands (EGF or TGFalpha;) is associated with the antihormone-resistant phase of clinical disease.

Methods: This study investigated the potential of the EGFR-selective tyrosine kinase inhibitor ZD1839 ('Iressa') to treat antihormone-resistant BC using tamoxifen-resistant (R) and tamoxifen-sensitive (wild type [WT]) MCF-7 BC cell lines.

Results: As with tumours from patients with resistance to tamoxifen, R-MCF-7 cells exhibit markedly elevated mRNA and expression of EGFR and c-erbB2 compared with WT-MCF-7 cells. Western blotting and immunocytochemical analysis showed that in R-MCF-7 cells these receptors immunoprecipitated as heterodimers, had increased activity, and were associated with increased levels of the phosphorylated mitogen-activated protein kinases, ERK 1/2. In R-MCF-7 cells treated with EGF and TGFalpha further increases in activation of EGFR-signalling elements and substantial growth responses were observed. Under ligand-stimulated conditions, ERK 1/2 activation was increased in a sustained manner, but ERK 1/2 exhibited only transient activation in WT-MCF-7 cells. ZD1839 blocked activation of EGFR signalling in R-MCF-7 cells under basal and ligand-stimulated conditions, and resulted in profound, long-lasting growth inhibition. WT-MCF-7 cells were much less sensitive to growth inhibition by ZD1839 (15% decrease in WT-MCF-7 cells vs up to 90% for R-MCF-7). These studies show that in BC cells with acquired resistance to tamoxifen, autocrine activation of the EGFR signalling pathway is of critical importance to growth and that these cells are substantially more sensitive to ZD1839 than WT-MCF-7 cells. Finally, co-treating WT-MCF-7 cells with tamoxifen and ZD1839, in anticipation of the switch to EGFR signalling on acquisition of antihormonal resistance, results in synergistic growth inhibition, marked decreases in proliferation, increased apoptosis, and failure to develop resistant growth.

Conclusion: Since the biochemical characteristics of tumours from patients with antihormone-resistant disease parallel those of R-MCF-7 cells, these studies predict that ZD1839 may provide an effective treatment for tamoxifen-resistant BC and prevent the development of this condition.

'Iressa'and 'Nolvadex' are trademarks of the AstraZeneca group of companies

970 POSTER DISCUSSION

Fluorescence in situ hybridization (FISH) may accurately identify patients who obtain survival benefit from herceptin plus chemotherapy

R. Mass[1], M. Press[2], S. Anderson[1], M. Murphy[1], D. Slamon[3]. [1] *Genentech Inc., South San Francisco, CA, USA;* [2] *University of Southern California, School of Medicine, Los Angeles, CA, USA;* [3] *UCLA School of Medicine, Los Angeles, CA, USA*

Background: Women eligible for the pivotal phase III trial of chemotherapy (C) (doxorubicin/epirubicin and cyclophosphamide [AC] or paclitaxel [T]) with or without Herceptin (H) had metastatic breast cancer overexpressing HER2 at the 2+ or 3+ level measured using a standardized, semi-quantitative, immunohistochemistry (IHC) assay. This trial demonstrated that the addition of H to C improved response rate (RR) (50% vs 38%, p=0.003) and survival (25.1 vs 20.3 months, odds ratio, 0.80, p=0.046). These benefits were