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

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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 Three pts were withdrawn from the trial due to drug-related toxicity and no drug-related deaths occurred.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

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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

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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

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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