increases in BAP (p<0.001) and BSI scores (p=0.08) were suppressed when compared to placebo treatment.

Bone Alkaline Phosphatase*			Bone Scan Index*		
Baseline	N	median TTP (days)	Baseline	N	median TTP (days)
< 1.25 X ULN	165	199	< 1.4%	118	202
1.25 - 5 X ULN	66	102	1.4 - 5.1%	66	169
>5 X ULN	34	78	> 5.1%	53	83

*p < 0.001, log-rank test

Conclusions: In HRPCa patients, 10 mg atrasentan delays progression as measured by clinical, biochemical, and imaging criteria. The extent of skeletal tumor burden, assessed by biochemical and bone scan measures can provide prognostic information about patients clinical disease course.

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Preliminary results of carbon-11 acetate pet imaging in prostate cancer patients with rising PSA after radical therapy: clinical impact to choose appropriate further treatment strategies

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Purpose: Patients after radical therapy for prostate cancer (radical prostatectomy, radiation therapy) with rising PSA continue to be a diagnostic and therapeutic challenge. Recent studies reported promising data of C-11 acetate in visualization of recurrent tumor site as well as metatastatic spread of prostate cancer. In particular, this PET tracer does not undergo urinary tract excretion and seems therefore to be suitable for evaluation of locoregional disease. This study aims to evaluate the potential role of C-11 acetate PET imaging in patients with rising PSA after radical therapy in choosing the most appropriate treatment option (local and/or systemic therapy).

Methods: 13 clinically asymptomatic patients with rising PSA and evidence of recurrent/metastatic disease by standard imaging procedures (SIP) including bone scan, CT, MRI have been evaluated. C-11 acetate dynamic imaging of the prostate region has been performed after i.v administration of 400 MBq of C-11 acetate followed by whole body scans with a PET ring scanner. In case of abnormal C-11 acetate uptake in previously unknown localizations, additional radiological work-up has been done. C-11 acetate images were analyzed by visual interpretation followed by 3D image fusion of PET with CT and/or MRI for a better anatomical localization of suspected tumor sites.

Results: In 11 out of 13 patients (85%) increased C-11 acetate uptake was found. Seven of C-11 acetate positive patients (64%) demonstrated local and/or systemic manifestations which could be confirmed by SIP. In addition, previously unknown lesions could be detected by C-11 acetate imaging in 5 of 7 patients leading to modification of the treatment strategy. The remaining 4 patients demonstrated increased C-11 acetate uptake only locally and were therefore selected as candidates for local radiotherapy with potentially curative intention. In 2 patients (PSA level 0.6 and 1.4) no tumor sites were detected in accordance to SIP.

Conclusion: Our preliminary data demonstrate the feasibility of C-11 acetate whole body PET as a promising new imaging modality to localize the tumor sites in patients with rising PSA after radical therapy. These data indicate that C-11 acetate PET scan may be helpful to select patients with local disease from those having distant metastases to choose the most appropriate therapeutic option.

Immunobiology and biological therapies

579 ORAL

Pharmacodynamic studies of the specific oral EGFR tyrosine kinase inhibitor (EGFR-TKI) zd1839 ('Iressa') in skin from cancer patients participating in phase I trials: histopathological and molecular consequences of receptor inhibition

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Aim: The specific oral EGFR-tyrosine kinase inhibitor (EGFR-TKI) ZD1839 'Iressa' is under clinical development as an anticancer agent. Since receptor inhibition by ZD1839 is required for optimal antitumour activity, we have studied in vivo the pharmacodynamic (PD) effects of ZD1839 on EGFR activation and receptor-dependent events in the skin, an EGFR-dependent tissue, in cancer patients participating in ZD1839 Phase I clinical trials.

Methods: We studied the histopathological and molecular consequences of escalating doses of daily oral ZD1839 in 104 pre- and/or on-therapy (at approximately day 28 of therapy) skin biopsies from 65 cancer patients. We measured ZD1839 effects on EGFR activation by immunohistochemistry, using an antibody specific for the activated-phosphorylated-EGFR; effects on receptor signalling (activated MAPK), proliferation, p27KIP1 and maturation were also assessed. All statistical tests were two-sided.

Results: Histopathologically, the stratum corneum of the epidermis was thinner during therapy (p<0.001). In hair follicles, prominent keratin plugs and microorganisms were found in dilated infundibula. On the molecular level, ZD1839 suppressed EGFR phosphorylation in all EGFR-expressing cells (p<0.001). In addition, ZD1839 inhibited MAPK activation (p<0.001) and reduced the keratinocyte proliferation index (p<0.001). Concomitantly, ZD1839 increased the expression of the cyclin dependent kinase inhibitor p27KIP1 (p<0.001) and of maturation markers (keratin 1 and phospho-STAT3) (p<0.001) and increased apoptosis (p<0.001). These effects on the target and EGFR-dependent molecular endpoints were observed at all dose levels, before reaching dose-limiting toxicities.

Conclusions: Oral daily ZD1839 inhibits EGFR activation and affects downstream receptor dependent processes in vivo. The observed effects may be responsible for the acneiform rashes and desquamation that are seen in some patients. Effects of receptor inhibition were profound at doses well below the one producing unacceptable toxicity, a finding that strongly supports the use of PD assessments to select optimal doses, instead of a maximum tolerated dose, for definitive efficacy and safety trials. In addition, our studies show an important role for the EGFR in normal adult skin biology and provide a rationale for the investigation of ZD1839 in EGFR-dependent skin disorders, such as psoriasis or epithelial tumours.

'Iressa' is a trade mark of the AstraZeneca group of companies.

580 ORAL

Double suicide gene therapy for locally recurrent prostate cancer

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Purpose: We have demonstrated the potential of the HSV-1 TK/GCV and E.coli CD/5-FC enzyme/prodrugs systems as cancer therapies extensively in animal model systems. The present clinical study was carried out to determine whether the intraprostatic injection of E1B-attenuated adenoviral vector containing a double suicide gene together with two prodrugs administration would be safe and exhibit any therapeutic activity in patients with locally recurrent prostate cancer following radiation therapy.

Methods: A total of twelve patients with locally recurrent prostate cancer (biopsy proven and rising serum PSA on three consecutive measurements) were entered into the trial. Three cohorts of patients were used to escalate the viral dose administration ranging from 10 to the 10vp to 10 to the 12vp. The vector used was a E1B-attenuated adenoviral vector containing HSV-1 thymidine kinase/E.coli cytosine deaminase fusion gene. Two days after the TRUS guided viral injection into the prostate, patients received a 7 day course of two prodrugs, ganciclovir and 5-fluorocytosine. Regular follow-up tests including serum PSA, prostate biopsy to determine the transgene