were differentially expressed, Fibronectin, basic breast conserved gene (BBC 1) and ubiquitin enzyme variant -1 (UEV-1/CROC1) which all Inocalise to regions of chromosomal aberration in prostate cancer (2q 3.4, 16q 24.3 and 20q 13.2 respectively). Further data on the expression of these genes in prostate cancer will be present.

We have also examined the relationship between androgen-regulated gene expression and all cycle regulation and apoptosis using an AR-cell line, doubly transfected with the AR gene and bcl-2 gene, (the latter being closely associated with the AI state). Bcl-2 overexpression confers and antiapoptotic effect against both androgen deprivation and cytotoxic chemotherapy.

An understanding of the mechanisms of AI prostate cancer will provide new therapeutic options to treat this presently incurable disease.

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Meta analysis of the randomised trials in prostate cancer

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The Prostate Cancer Trialists Collaborative Group (PCTCG) is performing an overview of randomised trials of the treatment of prostate cancer. The aim of the cycle 1997–2000, is to bring together mortality results from randomised trials that began before 1991. Two hundred randomised studies were identified that included 40,000 patients. Data from each individual patient in each study was requested. Three main questions were addressed by many of these studies and for these an overview was considered relevant:

MAB vs castration alone;

Immediate vs deferred hormone treatment;

Chemotherapy vs no (or delayed) chemotherapy;

In 1995, a first cycle an overview by the of the results of these trials organised by the PCTCG found no significant overall survival advantage by MAB as compared to androgen suppression alone. However, the confidence limits were rather large and, therefore, the possibility of a small improvement in survival was not excluded. This second cycle of the overview includes in excess of 40% more information (8,000 patients with almost 6,000 deaths).

For the question of immediate vs deferred hormonal treatment 15 trials were identified including more than 7,000 patients. Analyses of mortality and cause specific mortality were performed.

Concerning the question of (first line) immediate chemotherapy vs no (or delayed) chemotherapy 9 studies were identified including circa 2000 patients. Results of this cycle will be presented.

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Biology of lung tumours: Targeting bcl-xL and EGP-2

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We have previously demonstrated the anti-apoptotic protein Bcl-2 to be a promising target for antisense-based therapy of small cell lung cancer. In contrast to small cell lung cancer, in non-small cell lung cancer the Bcl-2 homologue and related cell death antagonist Bcl-xL is more commonly overexpressed. Using the secondary structure of the bcl-xL mRNA to predict the most promising target sites for antisense binding a series of dodecamer phosphorothioate antisense oligonucleotides were designed. Oligonucleotide 3011 was found to most effectively downregulate Bcl-xL protein levels and to induce apoptosis in non-small lung cancer cell lines. However, sequence control oligonucleotides also revealed a certain degree of unspecific cytotoxicity, making it difficult to discern the true antisense effect. To overcome this limitation, novel 2'-O-methoxyethly modified gapmer oligonucleotides with improved binding affinity and stability were designed. Three compounds were tested, including oligonucleotide 4259 (identical sequence as 3011), 4625 (with specificity for bcl-2 and 3 mismatches to bcl-xL) and 4627 (with one mismatch to bcl-2 and 2 mismatches to bcl-xL). Although oligonucleotide 4259 reduced bcl-xL message and protein levels in a dose dependent manner in non-small cell as well as small cell lung cancer cell lines, its effect on cell viability was more pronounced in non-small cell compared to small cell lung cancer cell lines. In contrast to the deoxy compounds the 2'-MOE modified sequence control oligonucleotides did not significantly reduce cell viability. Induction of apoptosis in non-small cell lung cancer cell lines was demonstrated by induction of caspase-3-like activity. The potentially bispecific antisense oligonucleotides 4625 and 4627 inhibited both bcl-2 and bcl-xL expression and reduced cell viability of non-small cell and small cell lung cancer cell lines. Our results imply the importance of the Bcl-xL protein in the tumorigenesis of non-small cell lung cancer and suggest the use of gene therapy approaches to counteract the expression of this cell death antagonist. Moreover, we show for the first time that it is possible to target the expression of Bcl-2 and Bcl-xL with a single antisense compound.

The epithelial glycoprotein-2 (EGP-2) is a surface antigen highly expressed in small cell and lung adenocarcinoma. Based on the monoclonal antibody MOC-31, we developed a single-chain antibody fragment (scFv) against EGP-2. To stabilize the unstable scFc we chose rational loop grafting of the binding residues on a stable antibody framework with favorable biophysical properties. The resulting molecule 4D5MOCB retained the high binding affinity of 10-9 M, while exhibiting a better expression behavior and serum stability, and demonstrated good tumor to blood ratios in a xenograft model. 4D5MOCB new serves as a basis to develop better targeting molecules directed against small cell and non-small cell lung cancer, as well as other solid tumors.

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Early non small cell lung cancer: The need for combined treatments

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As result of several randomized studies and the large meta-analysis published in 1995 on the BJC, locally advanced non-small cell lung cancer (NSCLC) is nowadays mainly treated by combined modality treatments. Chemotherapy including a platinum compound is generally part of the combined modality treatment. The local treatment varies depending on the staing of the disease, but also by country. In stage III technically resectable, the addition of neoadjuvant chemotherapy has been showed to improve survival in 3 small randomized trials. However, whether radical radiotherapy can achieve results similar to surgery is still a matter of debate. A large EORTC randomized trial is addressing this question in patients with histologically verified stage IIIaN2 disease who respond to platinum-based chemotherapy. The study has now accrued over 400 patients and randomized over 200 of them; the response rate to the newest combination chemotherapy (e.g. cisplatin-gemcitabine or carboplatin-paclitaxel) is well over 50% in this patient population. Other similar studies are running the the US. However, in the US chemotherapy is usually given concomitant to radiation. This leads to an improved response rate, with over 20% pathological complete response rates (it is less than 10% in chemotherapy only treatments), but also increased toxicity and morbidity of operation. For inoperable stage III (usually stage IIIb) radiation therapy has been standard treatment in several institutions. The combination of chemotherapy and radiation has now become standard in many centers. However, the optimal way of combining these modalities still needs further investigation. In particular the timing of the treatments, the radiation dose and volume, the type of chemotherapy are still under evaluation.

Recently combined modality treatment has been evaluated also in early stage (stage I, II, IIIa) resectable NSCLC, and promising results have been recently reported. Neoadjuvant chemotherapy seems feasible in this patient category with very few progressions before surgery. Response rates are very high and the only randomized study so far presented appears to be positive for some subgroups of patients. Tolerability of the chemotherapy, together with its effectiveness are major issues in this type of studies. It is however clear that the compliance to neoadjuvant chemotherapy is higher than that to post-operative chemotherapy.

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Post-operative treatments in resected NSCLC

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Five-year survival rate of patients (pts) with non-small cell lung cancer (NSCLC) who undergo complete surgical resection is only 40–69%, depending on the stage. It is well known that distant metastatic disease is the dominant site of recurrence in such patients and this observation served as the basis for trials of postoperative systemic therapy. The earliest trials of adjuvant chemotherapy, which consisted of single alkylating agents, could not achieve this goal or, even worse, showed a detrimental effect of chemotherapy on survival. The introduction of more active drags, such as cisplatin and vinca alkaloids, made it possible to obtain more promising results in terms of delayed recurrence of the disease. A recent meta-analysis including all randomized trials with accrual from January 1965 to December 1991 showed that the absolute risk of death was reduced by 3% at two years and by 5% at 5 years for pts who were treated with postoperative cisplatin-con-