not significantly different across response types (complete, partial, or no response – p=0.80) and was not predictive for time to symptomatic progression. Response rate was dependent on site of metastases (p=0.002) with bone having the greatest likelihood of response (96% CR or PR). Patients with bone metastases received less total dose (p=0.001), less biological effective dose (p=0.001), and had a significantly longer time to progression than other sites (hazard ratio 0.4 – 95% CI 0.2-0.7; p=0.004). Primary interferon treatment (i.e. treatment of the primary tumour with interferon only, without surgery or radiotherapy) was also associated with a shorter time to progression (hazard ratio 4.6 – 95% CI 1.5-14.1, p=0.007). On removal of these criteria, brain metastases became a significant predictor of progression time with a hazard ratio of 2.5 (95% CI 1.0 – 5.9; p=0.05) showing a increased risk of progression with brain metastases compared to metastases at other sites. Patients presenting with spinal cord compression had a particularly poor response rate (50%). Similar results were found from the sensitivity analysis.

CONCLUSION: Despite the widespread assumption that renal cell carcinoma is radioresistant, response rates to palliative radiotherapy are high. Higher BED does not appear from our data to be a predictor of symptomatic improvement or duration of response. Palliation of bone pain seems to be particularly durable compared to the palliation of symptoms at other sites of metastases. A trend for shorter duration of the palliative effect of whole brain radiotherapy is noted. Wherever possible, patients presenting with spinal cord compression are more appropriately treated with surgery in the first instance.

3.8

OPTIMAL RADIOTHERAPY DOSE FOR METASTATIC SPINAL CANAL COMPRESSION.

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Optimal radiotherapy dose fractionation for spinal cord compression has not been defined. This retrospective study has compared patients treated in a single centre receiving either 1 or 2 fractions of radiotherapy or a fractionated course of more prolonged treatment for spinal cord compression.

A total of 102 consecutive patients have been analysed, treated between January 1999 and June 2001. Sixty patients were male with a median age of 68 (range 32 to 90 years). The most common primary sites were breast (28%), prostate (28%) and lung (20%). The median duration of symptoms prior to diagnosis was 3 weeks (range 0 to 40); diagnosis within 24 hours of symptoms was achieved in only 13% and within one week in 29%. The diagnosis was confirmed on MRI in 93 patients (95%); the site of compression was dorsal spine (58%), lumbosacral (33%) and cervical cord (9%). Multiple levels of compression were present in 34 patients (33%). In 93 patients (91%) there were other sites of metastatic disease the most common of these being other bone metastasis.

51% were fully ambulant at diagnosis and 8% had complete paraplegia, the remainder having paraparesis with impaired mobility. At two months after RT the number of patients fully ambulant without significant neurological signs increased from 51% to 71% but the number of patients with complete paraplegia remained unchanged at 8%. A reduction in the incidence of impaired bladder function from 31% at presentation to 14% over the same time period was seen. Pain scores were derived for all patients on a simple retrospective 4 point scale. At presentation 59% recorded severe pain (grade III) and 30% moderate pain (grade II). Only 4% had no pain (grade 0). At two weeks there was a substantial improvement in pain control with only 8% recording severe pain.

Patients received a range of radiotherapy dose fractionation schedules the most common of which were 8Gy in a single fraction (22%) or 20Gy in 5 fractions (64%). In total 24 patients (23.5%) received a single or only 2 fractions (total dose 8 to 12Gy), the remainder receiving 20Gy in 5 fractions or in one case each 13Gy in 3 fractions, 13Gy in 4 fractions and 40Gy in 20 fractions. Patients receiving 1 or 2 fractions (1/2#) have been compared with the remainder (multi#). No difference in demographic parameters including primary tumour type and sites of cord compression was seen. A higher proportion of patients were paraplegic at presentation in the 1/2# (19%) than multi# (3%); when comparing outcome at two months from treatment the number of patients retaining mobility was statistically no different (80%,1/2# *vs* 68% multi#) and the proportion remaining paraplegic was unchanged (20%,1/2# *vs* 4% multi#). Pain control was also the same in both groups.

In conclusion this series has confirmed that spinal cord compression should be diagnosed and treated urgently whilst the patient is mobile. Recovery after established paraplegia is rare. No advantage for protracted courses of radiotherapy over 1 or 2 fractions has been observed in this retrospective analysis. This data provides a strong basis for a prospective randomised trial evaluating dose fractionation in this condition.

4.1

HYPERMETHYLATION OF AN INTRAGENIC CPG ISLAND OF THE MCJ GENE CORRELATES WITH LOSS OF EXPRESSION AND DRUG RESISTANCE IN OVARIAN CANCER CELLS

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Alterations in DNA methylation probably play a major role in the development and progression of most, or all, tumour types. Many recent studies have identified increased methylation within the promoter regions of genes known to play important roles in cancer and demonstrated that such promoter hypermethylation was associated with loss of gene expression. Alteration in DNA methylation outside of promoter regions are also frequently observed, although the significance of such changes is less clear. We have previously demonstrated that aberrant promoter hypermethylation is common in ovarian cancer, targeting numerous genes, including many with known roles in tumour development (e.g. *BRCA1*) and resistance to chemotherapeutic agents (e.g. *MLH1*).

Recently, the *MCJ* gene has been identified as a target for aberrant methylation in ovarian cancer and shown to play a role in sensitivity to several important anti-cancer drugs, such as cisplatin (Shridhar et al 2001, Cancer Res. 61:4258). Analysis of MCJ expression in our cell line models demonstrated that expression of the gene was lost in 8/10 cisplatin-resistant derivatives of the ovarian carcinoma cell line A2780. Furthermore, treatment of two of the resistant cell lines with 5-azacytidine, which inhibits DNA methyltransferase activity, resulted in re-expression of MCJ, suggesting that loss of expression may be due to increased methylation. Although the MCJ gene does not contain a classic CpG island within its promoter a previous report suggested that methylation of one particular CpG site within the promoter correlated with loss of expression. However, bisulfite sequencing analysis of this region, in the A2780 derivatives, identified no correlation between methylation of this, or other proximal CpG sites and gene expression. However, a CpG island was identified beginning within the first exon of MCJ, 164bp downstream of the transcriptional start site. Bisulfite sequencing of this region in DNA extracted from normal ovarian tissue determined that about 50% of clones were densely methylated and about 50% clones largely unmethylated. Sequencing of expressing cell lines revealed a pattern of methylation similar to normal DNA, whereas the cisplatin-resistant, non-expressing, cell lines exhibited dense methylation of all clones. 5-azacytidine treatment of one of the non-expressing cell lines, which resulted in re-expression of MCJ, gave a methylation pattern similar to the MCJ expressing cell lines. These results suggest that methylation of the intragenic CpG island of MCJ may be responsible for loss of gene expression. Furthermore, sequencing of this region in ovarian tumour samples identified a subset of tumour (30%) which, similar to the non-expressing ovarian cell lines, exhibited high levels of methylation of all clones. This raises the possibility that increased methylation of MCJ could play a role in controlling MCJ expression, and consequently in determining drug sensitivity, in ovarian cancer.

4.2

EXPRESSION OF SMAC/DIABLO IN OVARIAN CARCINOMA CELLS INDUCES APOPTOSIS PREDOMINANTLY VIA A CASPASE-9-MEDIATED PATHWAY AND ENHANCES SENSITIVITY TO CISPLATIN AND PACLITAXEL

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A key step in the execution of apoptosis is the activation of caspases, one pathway of which involves the release of cytochrome c from mitochondria, which then binds to Apaf-1 leading to the activation of caspase-9. This, in turn, activates downstream execution caspases. Recently, a second mitochondrial activator of caspases, known as Smac or DIABLO, was described, which is proposed to function by inhibiting the anti-apoptotic

protein XIAP (X-linked Inhibitor of Apoptosis Protein). The suggested mechanism is an interaction between the N-terminal region of Smac and the BIR3 domain of XIAP, although there is also evidence that a Smac mutant that lacks the N-terminal amino acids still remains capable of potentiating apoptosis. Recently, it was shown that release of Smac from mitochondria is involved in dexamethasone-induced apoptosis in multiple myeloma cells and may a key link between the two pathways of caspase activation.
We have constructed Ad CMV-Smac, a recombinant adenovirus encoding Smac/DIABLO. We demonstrate for the first time that delivery of the Smac gene to malignant cells can induce apoptosis: transfection of ovarian carcinoma cells with Ad CMV-Smac at multiplicities of infection of 3 – 30 pfu/cell leads to increasing apoptosis in a dose-dependent manner. Western blot analysis confirms that Smac-induced apoptosis proceeds via a caspase-9 dependent pathway, which can be partially inhibited by the caspase-9 inhibitor zLEHD-fmk and by over-expression of XIAP. At later time points, however, there is also caspase-8 activation, which suggests that Smac may be able to activate multiple apoptotic pathways. We also show that Ad CMV-Smac can combine with other pro-apoptotic factors, such as cisplatin, paclitaxel and pro-caspase-3, to produce greater levels of apoptosis in transfected cells.
Abnormalities in the cytochrome c/Apaf-1 pathway of caspase activation have been found in ovarian carcinoma cells. Furthermore, there is evidence that XIAP may be intimately linked to chemotherapy resistance in ovarian cancer and that down-regulation of XIAP can induce apoptosis in chemoresistant ovarian cancer cells. In light of this, we suggest that up-regulation of Smac activity may have genuine potential in the treatment of ovarian cancer.

4.3

β-GALACTOSIDE BINDING PROTEIN (βGBP) SELECTIVELY REDUCES THE PROLIFERATIVE CAPACITY OF PRIMARY CML CELLS AND EVADES P210$^{BCR-ABL}$ MEDIATED RESISTANCE TO APOPTOSIS; A ROLE FOR A NATURAL CYTOKINE IN TUMOUR REGULATION.

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Chronic myelogenous leukaemia (CML) is characterised at the molecular level by a (9;22) translocation which places the *abl* oncogene under the control of the *bcr* promoter generating a fusion protein (p210) with enhanced tyrosine kinase activity. CML cells are inherently resistant to apoptosis. The negative regulatory cytokine β-galactoside binding protein (β-GBP) induces cell cycle arrest at the late S/G2 threshold. Negation of this block via anti-βGBP antibodies allows normal cells to resume growth but neoplastic cells undergo apoptosis. Preliminary results indicate that lymphomas, mammary cell cancers and certain leukaemic cells undergo apoptosis following treatment with β-GBP at nanomolar concentrations, suggesting that βGBP may offer a novel and selective means of controlling neoplastic growth. We have examined the effect of βGBP on CML cell lines (K562, BV173, LAMA84, KYO-1) and have demonstrated apoptosis in 30-50% of the cells via TUNEL assays and Annexin V staining at 48 hours. Dual staining with propidium iodide, indicating cell cycle distribution, showed that at 24 hours cells exposed to βGBP had been arrested in S phase. Thus βGBP blocks the cell cycle in CML prior to activating cell death. These results prompted analysis of the effect of β-GBP on primary hemopoeitic progenitor cells (HPC's) from bone marrow donors and CML patients using *in vitro* colony forming assays. Treatment of HPC's from normal BM donors (n=22) with 400ng/ml βGBP did not significantly reduce CFU-GM number (median inhibition 0 -17%). By contrast treatment of HPC's from CML patients at diagnosis (n=13) resulted in a significant decrease in colony number (median inhibition 49-63%, $p < 0.005$). Thus βGBP has a significant effect on the proliferative ability of leukemic progenitors while sparing normal hemopoeitic progenitor cells. Treatment of CML cells with βGBP also resulted in a significant decrease in the levels of the p210$^{BCR-ABL}$ protein after 40-44 hours incubation and this downregulation preceded the appearance of significant numbers of apoptotic cells. Quantitation of bcr-abl mRNA levels by real time PCR using TaqMan technology indicated that mRNA levels are unchanged following treatment with βGBP indicating that P210 downregulation occurs at the post transcriptional level. p210 downregulation by βGBP is caspase-3 and proteasome independent. Thus two critical events, the prior introduction of a cell cycle block, allied to the subsequent down-regulation of p210$^{BCR-ABL}$ may both be required for apoptosis induction by βGBP in CML. The selective anti-proliferative and pro-apoptotic effect of βGBP on leukemic HPC's and its ability to downregulate p210$^{BCR-ABL}$ may offer a new method to selectively induce apoptosis in CML cells while sparing normal hemopoietic progenitors. This may be useful in purging marrow in the context of autografting for CML or as an *in vivo* treatment, either alone or in combination with other chemotherapeutic agents.

4.4

IDENTIFICATION OF 5-FU INDUCIBLE GENES IN TUMOUR CELL LINES BY cDNA MIRCROARRAY

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Thymidylate synthase (TS) is a critical chemotherapeutic target for fluoropyrimidines such as 5-fluorouracil (5-FU) and antifolates such as tomudex (TDX). The major limitations to TS-directed therapies are acquired or inherent resistance of tumour cells to these agents. Previous studies have demonstrated that TS expression levels are a key determinant of sensitivity of tumour cells to 5-FU and TDX. In order to identify more potential markers of response to TS-directed therapy, we have used DNA microarray technology to identify genes that are induced by 5-FU treatment in the MCF-7 breast cancer cell line. Of 2,400 genes analysed 30 were up-regulated by >8-fold. Of 10 highly up-regulated genes identified by the DNA microarray, only 6 were consistently found to be up-regulated in a dose and time dependent manner by Northern blot analysis. Consistently up-regulated genes included spermine/spermidine acetyl transferase (SSAT), annexin II, MAT8 and thymosin β-10. Analysis of other cell lines treated with 5-FU revealed that the induction of SSAT, annexin II, MAT8 and thymosin β-10 by 5-FU was not cell line specific. Furthermore, analysis of MCF-7 cells treated with TDX and oxaliplatin indicated that the expression of SSAT, annexin II, MAT8 and thymosin β-10 could be induced by both TS-specific and non-specific therapies. In addition, our results have shown that the expression of MAT-8 and thymosin β-10 were reduced significantly in a TDX resistant MCF-7 cell line compared to the parental line.
Our results suggest that SSAT, annexin II MAT8 and thymosin β-10 may be involved in mediating the response of tumour cells to chemotherapy. Furthermore, our analysis demonstrates the potential of DNA microarrays to identify novel predictive markers and/or therapeutic targets.

4.5

CYCLO-OXYGENASE INHIBITORS REDUCE METASTASIS, AND SERUM VEGF FOLLOWING EXCISION OF A PRIMARY TUMOUR.

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Cyclo-oxygenase-2 (COX-2) expression is increased in breast cancer and surgery has been shown to increase the growth of metastatic tumours. The aim of our experiment was to investigate the effect of selective COX-2 inhibition on tumour metastases in an experimental excision model of breast cancer.50000 4T1 mammary carcinoma cells were injected into the mammary fat pad of 9 week old female BALB/c mice .On day 14 post injection (mean tumour size= 8.0+/-0.4 mm) the primary tumours were excised and the mice were randomised into 2 groups (n=7/group). One group received daily intra peritoneal (IP) injections of the selective COX-2 inhibitor, SC-236, the second group only received drug vehicle. Animals were sacrificed 14 days post excision of primary. At harvest there was a significant reduction in the number of lung metastases and serum VEGF levels between the SC-236 and control group. We also found a reduction in microvessel density and an increase in the apoptotic index.

At Harvest	Control	SC-236
No of Pulmonary Metastases	22.5+/-5.2	5+/- 5.8*
Serum VEGF / pg ml^{-1}	83.5+/-20.9	30.5+/-6*
Apoptosis (apoptotic index %)	0.67	2.3*
Micro Vessel density (vessels/hpf)	16±2.2	27±4 *

*ANOVA; non parametric analysed with Kruskal Wallis; *=p< 0.05*

This data demonstrates that selective COX-2 inhibition significantly reduces the number of spontaneous metastases in an experimental model of breast cancer excision. We have also shown that this may occur secondary to a reduction in the potent pro-angiogenic and anti-apoptotic factor VEGF.

4.6
A MECHANISM OF DRUG RESISTANCE IN BREAST CANCER IMPLICATING COX-2. WILL NSAIDs BE THE ANSWER?

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Introduction. The iso-enzyme cyclooxygenase-2 (Cox-2) is associated with inflammation, cellular proliferation and apoptotic resistance and is implicated in tumour invasion, neo-angiogenesis and multi-drug resistance. The aims of this study were to establish a role for Cox-2 in the modulation of apoptosis in breast cancer cells.

Methods. The oestrogen receptor positive MCF-7 and negative MDA-MB-231 (MDA) breast cancer cell lines were grown to confluence. Cells were pre-treated with or without phorbol-12-myristate-13-acetate (PMA) in serum free media to induce Cox-2, or NS-398 (NS, 100μM) a selective Cox-2 inhibitor. Apoptotic susceptibility was assessed in response to Etoposide (Etop, 62.5μM) and Adriamycin (ADR, 5μM), and quantified using propidium iodide DNA staining and flow cytometry. Western Blotting measured Cox-2 expression.

Results. The MCF-7 cells did not express basal or inducible Cox-2 and were sensitive to Etoposide induced apoptosis. Western blotting demonstrated the constitutive expression of Cox-2 in the MDA cells, which was stimulated in a dose and time dependent manner by PMA.

MDA	Con	NS	PMA	PMA NS	Etop	Etop NS	Etop PMA	Etop PMA NS	ADR	ADR NS	ADR PMA	ADR PMA NS
Cox-2 Expression	+	+	+++	+++								
PGE_2 (pg/ml)	2275.7 ± 245.8	1900.4 ± 198.6	49057.9 ± 250.3[§]	1688.6 ± 324.4								
% Apoptosis	2.99 ± 1.04	4.67 ± 1.42	3.75 ± 1.28	4.77 ± 1.87*	18.42 ± 1.87	10.7 ± 2.98	11.04 ± 2.16*[#]	12.15 ± 4.37*[#]	9.53 ± 0.95*	5.87 ± 1.2	3.32 ± 0.25*[Ω]	3.7 ± 0.6

Data = Mean ± S.D. *p<0.05 v control. [#]p<0.05 v control + etoposide. [§]p<0.05 v control PGE_2. [Ω] p<0.05 v adriamycin. Student t test

PMA stimulated Cox-2 expression and PGE_2 release, increased MDA-MB-231 cell resistance to Etoposide and Adriamycin induced apoptosis. NS-398 which blocks Cox-2 activity i.e. PGE_2 did not increase, spontaneous, Etoposide or Adriamycin induced apoptosis.

Increased Cox-2 expression significantly increases apoptotic resistance. Despite previous studies showing that NS-398 increases apoptotic susceptibility in certain gastrointestinal and lung cancers we did not demonstrate this effect in breast cancer cells.

Conclusion. This study demonstrates that it is Cox-2 expression and not activity that is central to apoptotic resistance in breast cancer epithelial cells. This has obvious implications for therapy.

4.7
CHANGES IN EXPRESSION OF ESTROGEN RECEPTOR AND COREGULATORY PROTEINS IN THE ACQUISITION OF ENDOCRINE-RESISTANT BREAST CANCER, AS DEMONSTRATED USING AN *IN VITRO* CELL MODEL.

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Breast cancer patients designated estrogen receptor (ER)-α positive by immunohistochemistry receive Tamoxifen (TAM) as adjuvant endocrine therapy. Despite an initial response many patients often relapse and become resistant to the drug. Factors contributing to the resistant phenotype are poorly understood. The aim of this study was to determine the expression of wild-type ER-α, -β, the ER-β variant, ER-βcx and their associated coregulatory proteins during the acquisition of TAM resistance, using an *in vitro* model. The TAM-sensitive breast cancer cell line MCF-7, was continuously cultured in 4-OH TAM (10^{-7}M) over an 18-month period. Cell growth in response to TAM was monitored regularly using the MTT assay to determine stage of resistance. RNA was extracted monthly, over the first six months of development. Real-Time PCR was used to quantify gene expression of ER-α, -β, and -βcx as well as the ER coactivators SRC-1, AIB-1, SRA and the corepressors NCoR, SMRT and REA. An overall down-regulation of all three ER subtypes was observed. ER-α was more highly expressed than –β and –βcx (1000-fold and 100 fold respectively). Loss of ER-α was gradual with a steady decline in expression resulting in an overall loss of one third of the initial expression from month 1 to month 6. For both ER-β subtypes, approximately two thirds of expression was lost after month 1, following which, steady-state levels were observed. For the coregulator proteins, expression of AIB-1 was 10-fold greater than the others. AIB-1, SRC-1 and SRA all displayed an increase in expression, (approximately one quarter of the initial expression level), as did the corepressor REA. In contrast the corepressors NCoR and SMRT retained steady-state levels showing minimal variation over this period. Alterations in the ratio of coactivators: corepressors and changes in ER subtype expression may influence the mechanism and/or rate by which TAM-sensitive cells give rise to a resistant phenotype.

4.8
ASSESSMENT OF MODULATOR ACTION ON DRUG- RESISTANT AND SENSITIVE CANCER CELLS USING DIELECTROPHORETIC METHODS

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Several mechanisms may contribute to the multidrug resistant (MDR) phenotype seen in tumour cells, giving rise to broad spectrum cross-resistance to many anticancer agents. A common feature of MDR positive tumour cells is the over-expression of a 170kDa plasma membrane protein (P- glycoprotein). In addition to a drug pumping activity, Pgp has been shown to give rise to physical changes in MDR cells, relative to wild-type counterparts, such altered membrane fluidity. Dielectrophoresis (DEP) is the name given to the motion of polarised particles in non- uniform electric fields. When applied to suspensions of cells it can provide biophysical data, which correspond to physiological parameters such as cytoplasmic ionic strength and membrane morphology and surface area. DEP has been used in separating breast cancer cells from whole blood *(1)* and to measure membrane changes accompanying differentiation of erythroleukaemic cells *(2)*. Previous studies using flow cytometry and a membrane potential sensitive dye indicated that MDR leukaemic cells showed a lower membrane potential than parental cells *(3)*.

We have examined human drug sensitive and MDR cancer cell lines: myelogenous leukaemia (K562, K562AR) and breast cancer (MCF-7, MCF-7mdr, *MDR1* transfected). MTT cytotoxicity testing and Western blotting for presence of Pgp was used to confirm the drug resistant phenotypes. For DEP analysis, cells were re-suspended in iso-osmotic sucrose/ glucose solution adjusted to 2.5mS/ m by the addition of PBS. Dielectrophoretic response was

determined by the collection-rate method *(2)*. Results show that the parent K562 and MCF cells exhibit significantly lower cytoplasmic conductivities of $0.026Sm^{-1}$ and $0.025Sm^{-1}$, respectively than their drug resistant cells:- 0.3 Sm^{-1} and $0.45Sm^{-1}$, K562AR and MCF-7mdr, respectively. Furthermore, treatment of resistant cells with the Pgp specific MDR inhibitor XR 9576 showed a significant lowering of the internal conductivity to a value similar to that of the parental cells. A decrease in membrane permittivity was observed after treating K562AR with the modulator (from 10 to 6.9).
In conclusion, We propose that this method offers great potential for the rapid assessment of the mechanisms of cancer drug action *in vitro*.as these data indicate that the electrical character of the cell is altered in MDR, but following modulation therapy, MDR cells achieve a similar profile to drug sensitive cells.
(1) Gascoyne, P.R.C. Wang, X. Huang, Y. Becker, F. 1997, IEEE Transactions on industry applications, Vol. 33(3): 670. *(2)* Gascoyne, P.R.C. Pethig, R. Burt, J., Becker, F. 1993, Biochemica et Biophysica Acta, Vol. 1149:119. *(3)* Vyuvegula, B. et al, 1988, Cancer Chemotherapy and Pharmacology, Vol. 22:163.

5.1

UPDATED RESULTS OF A RANDOMISED CONTROLLED TRIAL OF NEOADJUVANT CISPLATIN (C), METHOTREXATE (M) AND VINBLASTINE (V) CHEMOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER.

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An international multi-centre randomised controlled trial was conducted comparing whether the addition of neoadjuvant CMV to radical surgery or radiotherapy for patients with muscle-invasive transitional cell carcinoma of the bladder would improve survival. Eligible patients had histologically confirmed T2(G3), T3, T4a, N0/NX, M0 transitional cell carcinoma of the bladder and were judged suitable for curative treatment. CMV was given as 3 cycles consisting of $30mg/m^2$ M & $4mg/m^2$ V on days 1,8 and $100mg/m^2$ C on day 2 of each cycle. From November 1989 to July 1995 a total of 976 patients were entered by 106 centres in 20 countries, 491 randomised to CMV and 485 to no CMV. 36% of patients were <60 years, 88% male, 69% WHO PS 0, 58% T3, 65% N0 and 88% G3. First results with a median follow-up of 4 years have been reported[1] in 1999 which showed a statistically non-significant 15% decrease in the risk of death after CMV (Hazard ratio 0.85 [95% CI 0.71-1.02] p=0.075). Currently a total of 559 patients have died and a final analysis is planned early 2002. At this time the median follow-up will be approximately 7 years. This is the largest trial making this comparison and the mature data will enable us to examine whether there is any evidence of CMV having a long-term effect on the main outcome of overall survival and other endpoints.
[1] International collaboration of trialists. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle invasive bladder cancer: a randomised controlled trial. The Lancet 1999, 354, p533-40.

5.2

THE EMI STUDY: A REGIONAL FEASIBILITY STUDY FOR A RANDOMISED TRIAL OF ADJUVANT CHEMOTHERAPY FOLLOWING DEFINITIVE TREATMENT FOR TRANSITIONAL CELL CANCER (TCC) OF THE BLADDER.

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Introduction: Cancer networks have the potential to make a powerful contribution to cancer research through collaborative studies. We conducted a feasibility study in the Northern and Yorkshire Region that attempted to recruit all eligible patients (pts.) into a randomised trial of adjuvant chemotherapy following radical local treatment for muscle invasive TCC of the bladder.
Patients and Methods: The protocol was approved by Northern and Yorkshire Multicentre Research Ethics Committee. The target was to randomise 60 pts. within 2 years. Consenting pts. were registered at diagnosis. Following primary therapy (cystectectomy [CYST] or radical radiotherapy [RRT]), pts. were assessed for fitness to start 3 cycles of MVAC chemotherapy within 12 weeks. If suitable, they were given further information and randomised if they consented.
Result: The trial was activated in 20 hospitals with enthusiastic support. 354 pts. were registered. 21% were not suitable for radical primary therapy due to metastatic disease or co-morbidity. Of the remainder, 50% had CYST and 50% had RRT. After CYST/RRT, 67% / 81% were medically unfit for chemotherapy. Of the 15% eligible for randomisation, 75% declined. The final number of patients randomised was 6.
Conclusion: This study demonstrates that population-based cancer research within the NHS is feasible. In the patient group studied there was a higher incidence of co-morbidity than expected and many pts. declined randomisation. This experience is relevant to the development of the new National Cancer Research Network. The difficulty in recruitment in this area supports the recent decision by co-operative groups to collaborate in a international intergroup study to address the issue of adjuvant chemotherapy for bladder cancer.

5.3

MICROARRAY GENERATED ONCOGENE COPY NUMBER PROFILING IN HUMAN BLADDER CANCER.

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Using the Vysis GenoSensor Micro array System and the AmpliconI oncogene specific chip, we have screened 59 oncogenes for altered copy number in a cohort of 30 bladder patient samples consisting of 14 paired and 2 unpaired transitional cell carcinomas (TCC's). Following DNA extraction, nick translation and hybridisation, amplification profiles for each of the 59 arrayed oncogenes were generated. Using a stringent cut off value of 1.75, seven tumour samples showed normal copy number at all loci, while 9 tumours showed increased copy number of 1 (n=7) or multiple loci (n=2) involving 12 out of the 59 arrayed oncogenes when compared to paired normal samples. The genes identified were MDM2 (12q14.3), c-*erb*B-2 (17q), FGR (1p36), PIK3CA (3q26.3), ZNF127 (20q), AR (Xq) and JUNB (19p13.2). The c-MET (7q21) locus was the most commonly altered gene, with 3/16 (19%) tumours displaying increased copy number. The findings with c-MET are novel and significant for a number of reasons. Firstly, it functions as the receptor for the hepatocyte growth factor/ scatter factor (HGF/SF); a growth factor known to be a marker of disease stage and poor outcome in bladder cancer (Gohji, K., *et al.,* 2000). Secondly, stimulation of c-met by its ligand HGF/SF leads to a whole range of biological downstream affects including scattering, angiogenesis, proliferation enhanced cell motility and invasion (Reviewed Maulik, G., *et al.,* 2002). Finally, due to data already indicating the efficacy of receptor specific inhibitors to the c-*kit* and PDGFR receptor tyrosine kinases in gastrointestinal stromal tumours and NCLC tumours respectively, the possibility that c-MET may also be a suitable target for such antineoplastic therapy is clinically significant.
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5.4

INFLUENCE OF CYTOKINE POLYMORPHISMS ON SUSCEPTIBILITY TO AND/OR PROGNOSIS IN PROSTATE CANCER

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Prostate cancer (PC) is one of the leading causes of male deaths in the western hemisphere with approximately 134,000 new cases and 56,000 deaths occurring annually in the EU. Polymorphisms in immune response genes may influence susceptibility to and/or prognosis in sporadic cases of PC, resulting from inter-individual differences in the anti-tumour immune response.

In this study, 250 PC patients and 256 cancer-free controls were genotypes by ARMS-PCR for 5 polymorphisms: Interleukin (IL) -1□(-511, A/G), IL-8 (-251, A/T), IL-10 (-1082, A/G), Tumour Necrosis Factor-□(-308, A/G) and Vascular Endothelial Growth Factor (VEGF), (-1154, A/G). Patient control genotype comparisons revealed that IL-8 AA (high producer) and VEGF AA (low producer) genotypes were significantly decreased in the patients when compared to the controls, (23.9% v 32.3%; OR=0.66; p=0.04) and (6.3% v 12.9%; OR=0.45; p=0.01) respectively. IL-10 AA (low producer) genotype was significantly increased in the patients when compared to the controls, (31.6% v 17.1%; OR=2.24; p=0.001). Within the PC group, IL-8 genotype was associated with prostate specific antigen (PSA) level at diagnosis, at a borderline level of significance (p=0.05).

These results suggest that genotypes associated with differential production of IL-8, IL-10 and VEGF are risk factors for PC. Genotypes associated with high IL-10 and low VEGF production may act via their influence on angiogenesis, necessary for metastasis. Therefore polymorphisms in cytokine genes may influence susceptibility to and prognosis in PC, indicating that a definitive investigation is required in a larger study group.

5.5

OBCAM, AN IGLON CELL ADHESION MOLECULE FROM 11Q25, IS FREQUENTLY INACTIVATED IN SPORADIC EPITHELIAL OVARIAN CANCER

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We present evidence that OBCAM (Opioid Binding Cell Adhesion Molecule) is a strong candidate tumor suppressor gene (TSG) inactivation of which is a fundamental event in the development of EOC.

A frequent LOH rate of 51% was observed at the 11q25 marker D11S4085 in a series of 100 fresh and archive derived EOC normal/tumor pairs in an analysis using all polymorphic microsatellite markers from the region. In many cases, LOH demonstrated complete loss of an allele rather than allelic imbalance, suggesting lack of tumor heterogeneity. This indicated that LOH at D11S4085 is an early event in epithelial ovarian carcinogenesis.

Bioinformatic analysis mapped D11S4085 within an intron of the OBCAM gene, a member of the IgLON family of GPI-anchored cell adhesion molecules. OBCAM may also be involved in signal transduction, and we have preliminary evidence that this is mediated through the raf/erk pathway. By quantitative RT-PCR, OBCAM expression is strong in normal human ovarian surface epithelium, but is extremely weak or undetectable in almost all primary ovarian tumours and cancer cell lines tested.

Using Methylation Specific PCR, the OBCAM 5' CpG island is methylated in 81% (13/16) of ovarian cancer cell lines, and somatically methylated in 76% (32/42) of primary EOCs. In contrast, the OBCAM CpG island in normal ovary is unmethylated. In patients with LOH at D11S4085, i.e. within OBCAM, the second allele was somatically methylated in 81% of cases. Demethylation studies using 5'-aza 2'-deoxycytidine have demonstrated re-expression of OBCAM in a CpG island methylated, non-expressing clonal derivative of the ovarian cancer cell line, SKOV3.

OBCAM transfection into this methylated SKOV3 clonal derivative resulted in functional phenotypes in keeping with TSG function. OBCAM re-expression resulted in suppressed growth and enhanced aggregation of cells *in vitro*, markedly suppressed sub-cutaneous tumor growth *in vivo* and almost completely abolished intra-peritoneal tumorigenicity.

OBCAM mutation analysis by SSCPE across approximately 200 ovarian primary tumors and cell lines has identified a single somatic mis-sense (Proline to Arginine) mutation within the first Ig domain in an ovarian tumor. As somatic mutation is an infrequent event, this supports abrogation of expression by LOH and by epigenetic mechanisms as the favoured means of OBCAM inactivation in epithelial ovarian cancer.

The data presented is the first description of involvement of the IgLON family in cancer.

5.6

REAL TIME QUANTITATIVE POLYMERASE CHAIN REACTION ANALYSIS OF HPV 16 IN ADENOCARCINOMA OF CERVIX

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There has been a relative and absolute increase in the incidence of adenocarcinoma of the cervix (ACC), particularly in the younger women. ACC represents 15-20% of all cervical cancer and will become more prominent as the incidence of squamous cell carcinoma of the cervix (SCC) continues to fall with organised cervical screening. Both HPV 16 and 18 are associated with ACC. In some in-situ polymerase chain reaction (PCR), HPV 16 was noted to be present in the adjacent uninvolved cervical epithelium. In this study, we have coupled two powerful techniques, laser capture microdissection and real-time quantitative PCR to determine the HPV16 prevalence in the women with ACC and to accurately assess the HPV16 DNA copy number in the cells. The association between HPV16 positivity and the age of the women, grade and stage of the cancer was analysed.A cohort of women diagnosed with ACC between 1991-2000 inclusive was identified. The histology was reviewed to confirm the diagnosis and adenosquamous carcinomas were excluded. The ACC cells were isolated from archival paraffin-fixed 5μm sections using a PixCell II laser microdissection system (Arcturus Engineering). Tumour tissue was identified and removed by the laser onto a transfer film. Approximately 200 laser pulses were taken per tumour specimen. DNA extraction was carried out by incubating the dissected cells in a 3mg/ml proteinase K at 55°C for 4 hours and then heat inactivated. DNA was assessed by Taqman PCR using the ABI7700 (PE Applied Biosystems). Real time quantitative PCR was used to amplify the internal control gene, *Beta-globin* and the HPV 16 gene. The Caski cell line is known to have 600 copies HPV16 DNA per cell. DNA was extracted from a known number of Caski cells and serially diluted to 10^{-9} concentration. Real-time quantitative PCR was used to determine the C_t count for *Beta-globin* and HPV 16 at the different concentrations in order to generate a standard curve. For each case, the HPV16 and *Beta-globin* gene copy number was calculated using the mean values of C_t (each case was assayed in triplicate) and plotted against the standard curve to determine the gene copy number.55 women were identified to have ACC cervix from 1991-2000 inclusive. The age distribution of this cohort showed a bimodal pattern, with peaks in the 36-45 and >55 years age groups. In 3 cases, the DNA extraction was unsuccessful and these cases were excluded. Of the remaining 52 women, 25% were HPV 16 positive. HPV positivity was more common in the well and moderately differentiated tumours and in women less than 45 years old. There is no difference in the HPV copy number in the grade and stage of the cancer. The HPV 16 gene copy number is significantly higher in women more than 45 years old (p=0.03).

Acknowledgements: This research was funded by Grampian University Hospitals NHS Trust Endowments, Gynaecology Oncology Research Fund and University of Aberdeen development trust.

5.7
CHEMORADIOTHERAPY: A SIGNIFICANT ADVANCE IN THE TREATMENT OF CERVICAL CANCER

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Summary

Background Our aim was to review the effects of chemoradiotherapy on overall and progression-free survival, local and distant control, and acute and late toxicity in patients with cervical cancer.

Methods With the methodology of the Cochrane Collaboration, we did a systematic review of all known randomised controlled trials done between 1981 and 2000 (17 published, two unpublished) of chemoradiation for cervical cancer.

Findings The trials included 4580 randomised patients, and 2865-3611 patients (62-78%) were available for analysis. Cisplatin was the most common agent used. The findings suggest that chemoradiation improves overall survival (hazard ratio 0.71, p<0.0001), whether platinum was used (0.70, p<0.0001) or not (0.81, p=0.20). A greater beneficial effect was seen in trials that included a high proportion of stage I and II patients (p=0.009). An improvement in progression-free survival was also seen with chemoradiation (0.61, p<0.0001). Thus, the absolute benefit in progression-free and overall survival was 16% (95% CI 13-19) and 12% (8-16), respectively. A significant benefit of chemoradiation on both local (odds ratio 0.61, p< 0.0001) and distant recurrence (0.57, p<0.0001) was also recorded. Grade 3 or 4 haematological (odds ratio 1.49-8.60) and gastrointestinal (2.22) toxicities were significantly greater in the concomitant chemoradiation group than the control group. There was insufficient data to establish whether late toxicity was increased in the concomitant chemoradiation group.

Interpretation Concomitant chemotherapy and radiotherapy improves overall and progression-free survival and reduces local and distant recurrence in selected patients with cervical cancer, which may give a cytotoxic and sensitisation effect.

5.8
NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADIOTHERAPY FOR LOCALLY ADVANCED CERVIX CANCER: A META-ANALYSIS USING INDIVIDUAL PATIENT DATA FROM RANDOMISED CONTROLLED TRIALS (RCTS).

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The NACCMA Collaboration initiated a systematic review and meta-analysis to assess the role of neoadjuvant chemotherapy followed by radiotherapy for locally advanced cervix cancer. These preliminary results are based on updated individual patient data from 15 RCTs, conducted world-wide, that compared neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone. 1605 patients and 911 deaths were included.

Trial Group	HR (95%CI)	Absolute Effect at 5 years (95% CIs)	Effect P-value	Interaction P-value
Dose Intensity				
<25mg/m^2 trials	1.10 (0.90-1.33)	-3% (from -10 to 4%)	0.36	
≥25mg/m^2 trials	0.88 (0.73-1.05)	4% (from -2 to 10%)	0.16	0.06
Chemotherapy cycle length				
>2 week cycle length trials	1.15 (0.96-1.38)	-5% (from -12 to 1%)	0.13	
≤ 2 week cycle length trials	0.80 (0.66-0.97)	8% (from -1 to 14%)	0.02	0.008

The overall results showed no significant benefit of neoadjuvant chemotherapy (HR=1.01, 95%CI=0.88-1.15, p=0.913). A high level of statistical heterogeneity (p=0.001) makes it questionable whether all trials should be pooled in this way. This heterogeneity across trials can be explained largely by differences in cisplatin dose intensity and to a greater degree by differences in chemotherapy cycle length across trials (but not by the cisplatin total dose or use of adjuvant chemotherapy). Trials using a higher dose intensity and shorter cycle length appeared to increase survival, while a lower dose intensity and a longer cycle length, appeared to reduce survival. This was also true for local, distant and overall progression-free survival. There was no good evidence that patient subgroups defined by age, stage, histology, grade or performance status, benefited more or less from neaodjuvant chemotherapy. These **preliminary results** suggest that neoadjuvant chemotherapy may induce both benefit and harm depending on how it is administered. Extra data has now been obtained and an **updated analysis** will be presented. This will include additional analyses relating to duration of treatment.

6.1
THE ULKG LY09 ADVANCED HODGKIN'S DISEASE TRIAL: INITIAL DATA ON TREATMENT INTENSITY AND TOXICITY (ISRCTN 97144519).

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Background: Between 04/1997 and 09/2001, 807 patients (pts) with advanced (stage II_{AX}-IV) Hodgkin's disease were randomised in the LY09 trial. **Treatment:** The trial compared standard ABVD against one of 2 regimens: Alternating ChlVPP/PABlOE or Hybrid ChlVPP/EVA. 6 cycles of chemotherapy were given (+2 extra &/or involved-field radiotherapy, if indicated). Intended dose intensities of the drugs per 2 cycles are given below:

Drug	ABVD (8wks)	Alternating (7wks)	Hybrid (8wks)
Doxorubicin	100 mg/m^2	40 mg/m^2	100 mg/m^2
Vinblastine	24 mg/m^2	-	12 mg/m^2
Bleomycin	40,000 iu/m^2	20,000 iu/m^2	-
Dacarbazine	1,500 mg/m^2	-	-
Etoposide po	-	600 mg/m^2	750 mg/m^2
Vincristine	-	2.8 mg/m^2	2.8 mg/m^2
Chlorambucil po	-	84 mg/m^2	84 mg/m^2
Procarbazine po	-	400 mg/m^2	1,260 mg/m^2
Prednisolone po	-	9,600 mg/m^2	700 mg/m^2

Results: Presented are total dose (TD) & dose intensity (DI) in the first 6 cycles (n=757 completed 6 cycles by 12/2001) & toxicity for all pts with the post-chemotherapy assessment form completed & returned (n=687). Dose intensity & total dose: Chemotherapy was administered as per protocol with the majority of patients receiving at least 80% of the intended TD (73%) & DI (71%) for all drugs. The patterns were similar across the treatment arms. Vinblastine & vincristine were most commonly reduced drugs. For doxorubicin, DI was ≥80% planned for 82% of patients in ABVD, 90% in Alternating, 86% in Hybrid. Half of patients allocated to Hybrid (55%) or ABVD (44%) received G-CSF ≥1 cycles, versus 28% of Alternating patients. Toxicity: Grade III/IV haematologic toxicity showed variation between arms: for Alternating 68%, Hybrid 50%; ABVD was 61% when randomised vs Alternating, 38% vs Hybrid, suggesting a centre effect. When ABVD was analysed by size of centre, overall DI was ≥80% for all drugs for 64% of patients treated at small (n<10pts), 70% medium (10-19pts) & 60% large (20+ pts) centres; doxorubicin DI was ≥80% for 83%, 84% & 80% respectively. Grd III/IV haematological toxicity was 52%, 62% & 50% by centre size. Other toxicities were comparable, but Grd III/IV infection & mucositis were more frequent with Hybrid. **Conclusions:** This trial shows that intensive chemotherapy with curative intent can be tested in a large multicentre trial with a high degree of compliance to protocol. There was no evidence of significant differences in compliance according to centre size, but the use of growth factors and haematologic toxicity were heterogeneous across the treatment arms.

6.2
BEXXAR™: OVER FIVE YEARS EXPERIENCE IN TWO UNITED KINGDOM CENTRES

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Between March 1996 and March 2001, 96 patients (pts.), aged 27-90 (median 53 years) with recurrent or refractory follicular lymphoma (FL) 64 pts., mantle cell lymphoma 5 pts., lymphoplasmacytic lymphoma (LPC) 4 pts., small lymphocytic lymphoma 3 pts. and a further 20 pts. who had undergone transformation (Tx) to large B cell lymphoma (LBCL, 19 pts. previous FL, 1 pt. LPC) were enrolled to be treated either in an open phase II trial (61 pts.) or on a compassionate basis (35 pts.) with Bexxar™(tositumomab and I^{131} tositumomab). Forty patients had bone marrow infiltration (all <25%). The median number of previous therapies was 2 (range 1-9). Eleven pts. had progressed following previous high-dose therapy (HDT), Rituximab (RXB) 13pts., or Bexxar™ 3 pts. Administration, after dosimetry, was as previously described, delivering a whole body dose of 75cGy if the platelet (plt.) count was >$150x10^9$/l, 65 cGy for pts. with a plt. count of 100-$149x10^9$/l and 45cGy following HDT. Seven pts. did not receive therapy; 3 because of human anti-mouse antibodies, 1 pt. withdrew and 3 progressed after dosimetry. Response was first evaluated 7 weeks post therapy and repeated 3 monthly. Further disease regressions were observed for upto 1 year, although progressions occurred in other pts. during this time. Toxicity was principally haematological. Median neutrophil and plt. nadirs occured at 7 and 6 weeks respectively. Grade 3 or 4 toxicity: neutropenia in 38% of pts. and thrombocytopenia in 31%. With a median follow up of $2^1/_4$ years, the median duration of response was $2^1/_4$ years (95% CI:1.1 to not reached) for those in CR/CR(u) and 7 months (3 mo. to not reached) for those in PR. Overall response rate at first evaluation declined with successive number of previous therapies: 73%, 66% and 46% respectively for 1, 2 or 3 or more treatments. The efficacy of Bexxar™ has been demonstrated in a range of clinical settings with the longest remission duration in those who achieve CR/CR(u). Supported by the ICRF, CRC, Corixa Corp and the NHS.

	At 7 weeks ORR	At 7 weeks CR/CR PR	At 7 Weeks TotalReaching CR/CR(u)	
All patients	59% (55/93)	10% (9/93)	49% (46/93)	25%(23/93)
FL	70% (44/63)	13% (8/63)	57% (36/63)	30% (19/63)
Tx to LBCL	32% (6/19)	5% (1/19)	26% (5/19)	16% (3/19)
Other Histology	36% (4/11)	0% (0/11)	36% (4/11)	0% (0/11)
Previous RXB	62% (8/13)	0%(0/13)	62% (8/13)	
Previous HDT	36% (4/11)	9% (1/11)	27% (3/11)	

(Responses based upon total no. of pts. that received dosimetry. 2 additional pts. are non evaluable.

6.3
A PHASE I/II DENDRITIC CELL (DC) IMMUNOTHERAPY TRIAL FOR HEPATOCELLULAR CARCINOMA (HC)

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Background and Purpose: Cytotoxic tumour infiltrating lymphocytes (TILs) are observed in HC, a tumour with poor prognosis and no established treatment. This phase I/II trial was designed to assess the safety and efficacy of dendritic cell vaccination, administered in an attempt to convert latent anti-tumour immunological responses into effective tumour rejection.
Patients and Methods: 21 patients (16M, 5F) with surgically non-curative HC (2 post-optimal debulking; 5 post-chemotherapy) have been recruited. DCs are prepared from peripheral blood by culture of plastic-adherent peripheral blood mononuclear cells (PBMCs) in GM-CSF and IL4 (phenotype confirmed by FACS analysis). TNF-α-matured DCs ($3-5x10^6$) are pulsed with hepatoma (hepG2)-lysate, washed and re-injected intravenously. Patients undergo vaccination every 3 weeks and, if achieving stable or responding disease (bi-dimensional measurement on CT or US), after 3 cycles, a further 3 vaccinations are offered. Immunological assays (T-cell proliferation, γ-IFN ELIspot) of patient non-adherent cell populations (T-cell enriched) are performed with each cycle.
Results: 65 DC vaccinations have been administered with 12 patients assessable for response and toxicity, 5 assessable for toxicity alone, 1 non-assessable, and 3 have not yet reached the review point. Of 12 assessable for response – 1 partial response (confirmed), 3 disease stabilisations, and 8 progressive disease. Toxicity was mild with G2 nausea/vomiting (n=2), G1 flu-like illness (n=3), G1 fever (n=2).
Conclusion: This DC vaccination study demonstrates low toxicity and some clinical activity that warrants further patient recruitment. Parallel immunological assays will be presented. Comparison of intravenous and sub-cutaneous administration is now underway.
All work was governed by standards for Good Clinical Practice and reviewed regularly by the Local Research Ethics Committee.

6.4
THALIDOMIDE ANALOGUE CDC-501 IS SAFE AND WELL TOLERATED BY PATIENTS WITH END STAGE CANCER AND SHOWS EVIDENCE OF CLINICAL RESPONSES AND EXTENSIVE IMMUNE ACTIVATION

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PURPOSE: To assess the safety, tolerability, efficacy, immune stimulatory and anti-angiogenic effects of a novel thalidomide analogue, CDC-501 (REVIMID™), in the treatment of patients with advanced cancer. PATIENTS AND METHODS: Twenty patients with heavily pre-treated advanced stage IV malignant melanoma (n=13), pancreatic (n=2) and other cancers (n=5) were treated with a dose escalating regimen of CDC-501 starting at 5mg and rising to 50mg after 4 weeks. Clinical efficacy, tolerance and adverse effects were evaluated. *In vitro* analysis of peripheral T cell surface markers and serum for cytokines and pro-angiogenic factors were performed. RESULTS: CDC-501 was generally well tolerated and no serious adverse events were attributed to its use. Fourteen patients completed the study, 3 withdrew due to disease progression and 3 due to withdrawal of consent. CDC-501 treatment led to clinical responses in a number of patients. All patients showed evidence of activation of both CD4+ and CD8+ T cells as measured by increased CD45RO+ expression. Furthermore, activation of memory cells (CD45RA+/L-$selectin_{low}$) in some patients may indicate activation of tumour-specific cells. This was associated with increased serum levels of GM-CSF, sIL-2Rα, IL-12 and TNF-α. However, levels of pro-angiogenic factors were unchanged. CONCLUSION: This study demonstrates the safety and significant clinical efficacy of CDC-501 in the treatment of recalcitrant advanced cancer. The induction of immune activation suggests a more beneficial role for this class of compound in less advanced patients as an immunostimulatory adjuvant perhaps combined with tumour cell vaccination regimens.

6.5
PHASE 1 TRIAL OF HERPES SIMPLEX VIRUS, HSV1716 FOLLOWING INJECTION INTO BRAIN ADJACENT TO TUMOUR IN PATIENTS WITH PRIMARY MALIGNANT GLIOMA.

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The most common primary brain tumours are glial tumours, including the highly malignant glioblastoma. With current treatments of surgery, radiotherapy and chemotherapy outcome remains poor with a median survival of one year. A novel strategy to combat this disease is the utilisation of the oncolytic herpes simplex virus, HSV1716. HSV1716 selectively replicates in actively dividing cells.
Two phase I clinical trials using HSV1716 have been completed. In the first, patients with recurrent glioma received direct intratumoural injection of escalating virus dose. In the second, patients with recurrent as well as newly diagnosed high grade glioma were injected with HSV1716 into the tumour prior to resection at 5-8 days. No toxicity was seen in any patients and