EC50 values of 4.3 μM and 2.6 μM, respectively, and time-course studies showed that WIN55,212−2 (6 μM) exhibited significant cytotoxicity 24 h after treatment and decreased cell numbers by 3% and 20% of control, respectively. Flow cytometry experiments demonstrated that WIN55,212−2 (6 μM) increased the proportion of apoptotic cells by 11 and 5.5 fold compared to control in MDA-MB-231 and MDA-MB-468 cells, respectively. WIN55,212−2 (6 μM) also significantly increased the proportion of MDA-MB-231 and MDA-MB-468 cells in G1 phase at 36 h by 114% and 115% of control. Western blotting showed the expression of CB1 and CB2 receptors in both the cell lines. *In vivo*, mice treated with WIN55,212−2 (25 μg/day i.p. for 10 weeks) showed a 74% reduction in tumour volume and 59% reduction in tumour weight compared to vehicle treament. This effect was reversed by CB2 antagonist AM630. Moreover, CB1 expression in tumours of WIN55,212−2 treated mice was higher than the vehicle group. In conclusion, the results demonstrated antiproliferative effects of WIN55,212−2 both *in vitro* and *in vivo* and suggested a relationship between these effects and G1-phase cell cycle arrest, apoptosis induction, and CB1 and CB2 receptor expression.

1238   POSTER
Phase 1 Clinical Trial of Oral PPAR − Agonist Efatutazone (CS-7017) in Japanese Patients With Metastatic Solid Tumours

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Background: Peroxisome proliferator-activated receptor gamma (PPARg) agonists are potent anticancer agents in preclinical models. Efatutazone is a novel, third-generation thiazolidinedione (TZD) showing higher potency over second-generation TZDs, such as pioglitazone. Now, phase 2 clinical trials of efatutazone in patients with metastatic non-small cell lung cancer and colorectal cancer at doses of 0.50 mg twice-daily (BID) are ongoing in the USA and Europe.
Material and Methods: This phase 1 dose-escalation study using a 3+3 design was initiated in Japanese patients with metastatic solid tumours. Patients with preexisting severe fluid retention were excluded. Efatutazone was administered orally BID starting at a dose of 0.25 mg. Pharmacodynamic (PD) and pharmacokinetic (PK) samples were collected on Day 1 and Day 22. Archived tumour specimens were used for immunohistochemistry. Primary objectives of this study were to assess safety profile and PK. All subjects provided written informed consent.
Results: A total of 13 patients were enrolled (8 male and 5 female; age range 45−73 years), and received treatment at doses 0.25 mg BID (n = 4), 0.50 mg BID (n = 6) and 0.75 mg BID (n = 3). Efatutazone was tolerated. Dose-limiting toxicity (DLT) was not observed, but one grade 3 edema, unresponsive to therapy, occurred after DLT evaluation period (Day 27). The maximum tolerated dose (MTD) was not reached. Observed common adverse events were edema, weight increase, hemoglobin decrease, creatinine increase, and malaise. Particularly, creatinine increase was shown in patients previously treated with cisplatin. All patients were evaluable for response. No objective response was observed, and 5 out of 13 patients showed stable disease. Two of them (thymic cancer and pleural mesothelioma) showed tumour decrease. Efatutazone increased plasma adiponectin levels. Plasma concentration of efatutazone and adiponectin had a tendency to be saturated in the 0.50 mg cohort.
Conclusions: Efatutazone is a novel anticancer therapy, which is tolerated and demonstrates evidence of antitumour activity and disease stabilization. Although the MTD was not reached, 0.50 mg BID, corresponding to the global recommended dose, was selected as the recommended phase 2 dose. Full safety data and clinical activity data will be presented.
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1239   POSTER
Novel Glycan Based Antibodies Highly Selective for Cancer Cells

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Background: Aberrant glycosylation occurs in essentially all types of human cancers, as has been reported in the last decades. Many glycosyl epitopes constitute tumour-associated antigens. Recent studies indicate that some aberrant glycosylation is a result of initial oncogenic transformation, as well as a key event in the induction of metastasis. Therefore, it is expected that cancer cells will express different glycan epitopes on their surface, compared to non-cancerous cells. Lectins are plant-derived proteins, which recognize and bind structures or carbohydrate

sequence features of glycans. The current research utilized lectins to isolate antibodies that bind specifically to cancer cells.
Materials and Methods: Lectins that bind specifically to cancer cells were selected by staining of Non Small Cell Lung Cancer (NSCLC) cell line (A549) and cancer vs. normal tissue specimens.
The most selective lectins were used to isolate human antibodies from phage display library of single chains fragments (scFv) with the same binding properties as the lectins. The proprietary screening method led to isolation of five human scFvs out of 1x10^9 different fragments, expressed on a phage display library. The specificity and selectivity of these scFvs were tested in two types of Adenocarcinomas: NSCLC and Colon cancer. The binding of each scFv was tested on cancerous and normal (dermal fibroblasts) cell lines and on 30 & 25 lung and colon cancer paraffin-embedded tissue specimens, respectively and their normal adjacent tissues by immunohistochemisry.
Results: The selectivity and specificity were demonstrated in both cell lines and paraffin-embedded tissues. In the cell line model, all scFvs showed binding to the cancer cells and none bound to the control cell line. In the paraffin-embedded tissue cohort, each scFvs was able to bind 53−92% of the tested cancer tissues and with lower intensity to 20−25% of the normal adjacent tissues. Furthermore, the combination of all scFvs resulted in 94% binding of the lung tumour tissues.
Conclusions: These results indicate that the selected scFv molecules, directed to glycan epitopes, have an impressive selectivity and specificity in binding to NSCLC and Colon cancer cells. Preliminary experiments using these scFvs in mice models of colon cancer demonstrated their capability to detect tumours in-vivo. Therefore, these molecules have huge potential in cancer therapy and diagnostics and are expected to evolve to breakthrough in cancer management.

1240   POSTER
Proprotein Convertases as Novel Targets for Treatment of Rhabdomyosarcoma

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Many who survive childhood cancer experience treatment complications as adults. One of the biggest challenges of treating children with cancer is achieving complete remission, while ensuring that they will be able to lead normal, productive life in adulthood.
To improve therapies for embryonal pediatric tumours such as rhabdomyosarcoma (RMS), the most common soft tissue sarcoma in children, we have selected peptides that bind to RMS with high specificity and are able to increase drug delivery to the tumour site. We have identified proprotein convertases (PC), a family of ten serine proteases which convert inactive proprotein into their active form, as targets RMS binding peptides (Hajdin et al. PLoS ONE 2010). In particular we have shown that coupling of Doxorubicin to the RMS targeting peptide RMS-P3 considerably increases its therapeutic impact in a mouse model for RMS.
Now we aim at elucidating the function of the proprotein convertases which we found highly expressed in RMS tumours: furin and PC7. In particular, our study should determine if these PCs might offer an additional therapeutic option based on their inhibition, which might be combined with targeted drug delivery.
To assess the functional role of furin and PC7 in RMS we have generated cell lines overexpressing furin, overexpressing a specific intrinsic PC inhibitor called α1 PDX, as well as cell lines were expression of furin or PC7 has been stably blocked by shRNA. These cells have been tested for their growth, migration and invasion potential in vitro as well as for their growth in vivo as subcutaneous xenografts. Histological analysis of tumour sections, in particular of microvessel density and angiogenesis has been performed to reveal if PC activity correlates with RMS progression.
Our results confirm a strong correlation between PCs activity and RMS growth in vivo and suggest furin and/or PC7 as viable target for therapeutic intervention and warrant further studies in the development of novel specific inhibitors of PCs protease activity. Moreover, the knowledge that furin/PC7 are valuable targets for RMS therapy reinforce the notion that furin targeting peptides must be considered for the development of novel targeted therapies and imaging approaches.