estradiol (FES), [F-18]-fluorodihydrotestosterone (FDHT), and [Ga-68]-labeled F(ab′)2 fragments of trastuzumab.
PET can measure tumor hypoxia using probes such as [F-18]-fluoromisonidazole. Hypoxia is a well-established resistance factor for radiotherapy, increasingly also recognized as a factor that mediate resistance to systemic therapy through the activation of pathways, such as the VEGF pathway, that mediate tumor growth and metastasis. PET can also measure drug resistance arising from barriers to drug delivery to the tumor, for example, by using [C-11]-verapamil to measure regional P-glycoprotein transport.
Finally, PET can detect early changes in response to therapy, for example by measuring tumor proliferation, using tracers such as [F-18]-fluorothymidine and/or cell death, using [F-18]-fluoroannexin. This approach can identify at an early stage which drugs have had a pharmacokinetic effect on the tumor and likely response, and importantly, which drugs are not likely to be effective.
Conclusions: These new radiopharmaceuticals, combined with conventional imaging and established PET procedures using FDG, hold great promise for directing effective, targeted cancer therapy. Further development of the new PET imaging probes will require development of rigorous and robust methods of image quantification, and careful study design to validate the information provided by PET imaging compared to both in vitro assay and to well-defined patient outcomes [5].
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S10
DCE-MRI as a biomarker of tumor angiogenesis

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Introduction: Several randomized trials have demonstrated in a range of tumours the clinical benefit associated with augmenting conventional chemotherapy with inhibitors of Vascular Endothelial Growth Factor (VEGF). This class of drug has been extensively evaluated with Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI), largely during trials conducted in the phase I/II setting.
Main Message: DCE-MRI is an attractive biomarker for drugs that inhibit VEGF because the cytokine is the major mediator of vascular permeability. Thus agents that inhibit VEGF should reduce vascular permeability, a feature of the malignant vasculature, and this impacts on the rate of egress of contrast from the vasculature into the interstitial space. This transfer of contrast has been measured in several studies as the Ktrans, the endothelial surface area $\times$ permeability constant. By far the majority of studies have demonstrated that broad spectrum VEGF inhibitors impact on Ktrans and that the degree of change of this parameter correlates with the dose of the drug and with clinical benefit. However, in a recent phase I study of a pure VEGFR2 inhibitor we have seen evidence of an active drug that does not impact on Ktrans, suggesting that the latter parameter is regulated by a more widespread effect on the VEGF system. We have therefore carried out a detailed time course study of patients receiving the monoclonal anti-VEGF antibody, bevacizumab and the data will be presented.
Conclusions: One of the difficulties with DCE-MRI and imaging in general is heterogeneity. We have demonstrated that the vascular enhancing fraction of ovarian cancer and the histographical distribution of other MRI parameters have clinical significance, highlighting the importance of detailed and comprehensive image analysis. This is of continued relevance as the new targets of anti-angiogenic drugs are likely to have effects that are detected through DCE-MRI, confirming the importance of this biomarker in early clinical trial evaluation of new drugs.

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S11
The functional diffusion map (fDM): an early predictive biomarker of tumor response

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Introduction: Diffusion MRI measurements can be used to quantify water diffusion values within tumors. Diffusion of water molecules are sensitive to celluar density/structures and as such, therapeutic-induced changes in tumor architecture can be detected through alterations in tumor diffusion values thus the diffusion imaging approach can be used as a sensitive surrogate for early detection of treatment response. Applications of this technology in grade III/IV gliomas, head and neck tumors, breast and metastatic prostate cancer to the bone will be shown.
Main Message: Diffusion MRI (D-MRI), which measures changes in cellular water mobility, has been proposed as an early surrogate for treatment response. Previously we reported that using a functional diffusion map (fDM) at 3 weeks D-MRI was closely associated with RR, time to progression, and OS. Data on fDM in 60 patients with MG are now reported. Sixty patients were recruited for this study. There were no differences in pre-treatment variables between groups (age, KPS, pathologic grade, or surgical resection (all $p > 0.05$, Fisher's Exact Test)). Mean change in ADC, as well as the percentage of

tumor with increasing ADC (VI), decreasing ADC (VD), or the total percentage of tumor unchanged (VU) were assessed by ROC Analysis to predict the probability of being alive one year from diagnosis. VI and VU were significant predictors (p=0.0001 and 0.0025, respectively). Overall survival of patients stratified by the median VI of the total population at 3 weeks was found to be significant (Kaplan Meier p=0.0046, log rank; hazard ratio 2.4 (95% C.I., 1.3 –4.8)). Similar results were observed by McDonald Criteria at 10 weeks (Kaplan Meier 0.0006; log-rank test; hazard ratio 2.9 (95% C.I., 1.7– 7.2)). Significant results were not observed for fDM at 1 and 10 weeks. These data support fDM as a validated early marker for treatment response in MG and reveal that fDM adds further prognostic value to conventional radiographic assessment. Preliminary examples will also be shown in non-CNS tumor types as well revealing the general extrapolation of this approach to a wide variety of clinical oncological applications.

Conclusions: The capability of acquiring fDM data in a wide variety of tumor types in the clinical setting provides the opportunity to pursue the validation of this approach as an early imaging surrogate of treatment response. The successful outcome of these studies would allow for individualization of patient care based upon this early, quantifiable imaging biomarker.

S12
MR spectroscopy for patient stratification and tumor monitoring

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Introduction: Magnetic Resonance Spectroscopy (MRS) is the only non-invasive modality that can monitor body chemistry in the living patient, so it can generate a unique class of biomarkers. MRS can be performed as part of a routine imaging examination on most hospital MRI instruments after minor modifications, and specialised laboratory instruments can be used for animal studies. I shall briefly describe two on-going multi-national studies on patients that are developing biomarkers for (i) diagnosing and grading brain tumours and (ii) predicting response to chemotherapy.

Main Message: Brain tumours are currently diagnosed by stereotactic biopsy – unpleasant and risky for the patient. Two EU programmes, INTERPRET (FP5) and eTumour (FP6, ongoing) [1], have developed a computer-based Decision Support System (DSS) that recognises the characteristic MR spectra of brain tumours, giving a non-invasive diagnosis and also the grade of malignancy. A database of >600 quality-controlled spectra, along with their associated images and clinical data, is available. A spectrum from a new case is compared with those in the database by a pattern recognition algorithm, and plotted in a data-space showing its relationship to spectra of tumours in the various classes [2]. The prototype DSS is surprisingly robust and has "learned" to ignore characteristics of different pulse sequences or instruments. In a prospective study it significantly improved the diagnostic accuracy of radiologists, even though many rarer tumour types are as yet insufficiently represented in the database.

A biomarker for predicting response to chemotherapy in individual patients would enable physicians to choose the most appropriate drug and avoid expensive administration of ineffective (but still toxic) agents. CoGMAC, an on-going, NCI-funded project, is developing a ^{31}P MRS biomarker for predicting response to chemotherapy. After studying several tumour types the project focussed on non-Hodgkin's lymphomas (NHLs) [3]. Initially, CoGMAC tested the hypothesis that the ^{31}P spectrum would change after a single round of chemotherapy to which the tumour responded, and this was, indeed, observed. However, it was shown that an even better prediction of response to chemotherapy could be obtained from the initial, pre-chemotherapy spectrum, by measurement of the ratio of the area of the PME peak to that of the NTP peak. This PME/NTP ratio was a better predictor of NHL response than the International Prognostic Index (IPI) which is currently used to predict response of NHLs to chemotherapy. When PME/NTP is combined with the IPI prediction is still better. This biomarker, too, has proved to be robust: it seems to work for all types of NHL and several chemotherapy regimes.

Conclusions: MRS-based biomarkers, which can already improve the diagnosis and treatment of cancer, could also be used to provide pharmacodynamic information in trials of novel anticancer drugs.

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S13
Meta-analysis of gene-expression profiles: towards a unified understanding of breast cancer sub-typing and prognosis

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Introduction: It is evident that even though several breast cancer studies have generated a large number of arrays with complex genomic data, numerous questions remain unanswered. What is the relationship between the molecular classification and several prognosis signatures? What is the role of individual genes in a signature and what is their biological meaning? How are different prognostic signatures related with respect to prognostication and should clinical, pathological and currently used biomarkers be integrated in this process?

Main Message: To address these issues, our group, in collaboration with a team at the Swiss Institute of Bioinformatics, undertook a comprehensive meta-analysis of publicly available gene-expression and clinical data totaling 2833 breast tumors. In this meta-analysis we