in neurooncology (RANO) have been introduced which are based on these MR-sequences, clinical findings and the steroid medication. These criteria include newly recognized phenonema as pseudoprogression (i.e. spontaneous stabilization or regression of new contrast enhancement within 3 months after completion of radio-chemotherapy) and pseudoregression (i.e. regression of contrast enhancing tumour with concomitant progression of non-enhancing tumour on T2-w sequences). To overcome the limitation of the pathophysiologically unspecific finding on conventional MR-sequences new functional and metabolic MR-techniques have been introduced in clinical practice. This talk will briefly summarize classical MR-response criteria and will give an overview on the opportunities and current limitations of new MR-techniques.

163 INVITED

Endpoints for Phase II Trials

S. Chang[1]. [1]*University of California San Francisco, Neurosurgery Division of Neuro-oncology, San Francisco, USA*

Phase II trials are screening studies with a primary goal of efficiently and accurately identifying a signal of antitumour activity of promising agents that justify subsequent phase III testing. One of the major barriers in achieving this goal is the lack of good surrogates of true patient benefit, classically defined in oncology as improvement in overall survival. Overall survival can have limited utility in phase II studies because of the time required to reach this endpoint, the confounding effects of cross over or effective second line therapies.
Endpoints in phase II studies that accurately predict phase III success are needed. Historically for cytotoxic agents, tumour shrinkage and objective response rates (RR) have been used, however, novel cytostatic agents that may result in prolongation of progression free survival and overall survival with very modest RR challenge the use of objective response as an indicator of patient benefit for this class of drug. The utility of RR is further complicated in the field of neuro-oncology, where imaging changes on standard anatomic magnetic resonance imaging can be confounded by treatment. This is evident in the case of pseudoprogression (increased enhancement related to treatment effect and not tumour progression) and pseudoresponse (decreased enhancement related to reconstitution of the blood brain barrier by anti vascular endothelial growth factor receptor inhibitors and not antitumour effect).
In this presentation we will review the advantages and limitations of commonly used endpoints in efficacy evaluation of agents in phase II testing and discuss alternate endpoints. The selection of the appropriate endpoint depends on the patient population, the nature of the agent being tested and the phase II trial design. Continued research to validate alternate phase II endpoints is critical.

164 INVITED

Endpoints for Phase III Trials

M. van den Bent[1]. [1]*Erasmus University Medical Center, Neuro-Oncology, Rotterdam, The Netherlands*

Clinical trials on novel treatments are aiming to establish the potential benefit of the new treatment. The trial must be designed to demonstrate the clinical benefit of the novel treatment, and the trial endpoints chosen should reflect that clinical benefit in a reliable way. The requirement 'reliable' implies that the endpoint can be unequivocally assessed, and can be safely assumed to reflect therapeutic efficacy of the investigational treatment. Overall Survival (OS) is generally agreed upon to reflect a clinically meaningful benefit for the patient and is easy to assess. There are however several drawbacks of this endpoint. First, cross over treatments (once the investigational compound is readily available) and effective cross in salvage treatments given at the time of progression after initial study treatment may dilute or even eradicate OS benefits. Then, OS will require a trial of longer duration and thus with higher costs. Numerous trials have used Progression Free Survival (PFS) as the primary endpoint, which endpoint is not confounded by subsequent salvage treatments. However, assessment of this endpoint is confounded by the way it is assessed and potentially by the knowledge of the given treatment. And, if the PFS endpoint is a mere radiological endpoint without clinical correlates, it becomes a pure radiological phenomenon without clinical consequences. Although it is often assumed that clinical deterioration occurs at the time of progression that deterioration has to be demonstrated in the trial to show the clinical impact of progression. Also, if an increase in PFS comes at the price of reduced quality of life because of toxicities, such increase becomes a questionable benefit. In some diseases a good correlation exists between PFS and OS, but that is not necessarily the case. Lastly, PFS depends on the ability to assess progression in a standardized fashion. In the field of neuro-oncology, pseudo-progression and pseudo-response may interfere with the reliability of the progression assessment. Because these pseudo-phenomena are treatment related (radiotherapy, VEGF inhibitors), this implies that endpoints must also be tailored to the investigational treatment. In particular if radiological PFS endpoints are used, blinded review is required to evaluate the local diagnosis − which will not save a trial in case of systematic local biases. Clinical functioning scales are necessary to support the benefit observed in PFS or OS. Domains chosen for these co-endpoints musts reflect clinically accepted area's of relevant morbidity for the disease under consideration (e.g., cognition, seizure activity). As a consequence of all this, there is no one size fits all solution for neuro-oncological phase III trials, but only tailor made solutions.

Special Session (Sun, 25 Sep, 13:15−14:15) **Calories and Cancer**

165 INVITED

Body Mass Index and Cancer Incidence

A.G. Renehan[1]. [1]*University of Manchester, Department of Surgery, Manchester, United Kingdom*

By 2008, we [1] and others had established that excess body mass index (BMI), as an approximation of general body adiposity and excess calorie intake, is associated with increased risk of several cancer types. These associations exist for both common (for example, colon, endometrial, post-menopausal breast, oesophageal adenocarcinoma) and less common malignancies (for example, thyroid carcinoma, non-Hodgkin lymphoma). Given the plausibility of the biological explanations, the consistency of associations, the sufficiently long latency times between BMI measurement and cancer occurrence, and the recent demonstrations of risk reversibility in morbidly obese cohorts undergoing bariatric surgery, many of these associations are probably causal. Approximately 124,000 new cancer cases may be attributable to excess BMI in Europe (2008). Since 2008, it has become clear that associations between BMI and cancer risk may be modified in the presence of other risk factors. For example, in users of hormonal replacement therapy, the associations between BMI and endometrial and post-menopausal breast cancers are attenuated. In turn, these observations point to a strong influence of oestrogen as an intermediary between obesity and cancer development in these cancer groups. Additionally, it is increasingly clear that approximations of central adiposity, for instance, waist circumference (WC), may better describe associations between adiposity and increased cancer risk, for example, in colon and rectal cancer, thus suggesting a key role for insulin resistance in these cancer types. Better understanding of these associations will facilitate refinements of approaches to prevent obesity-related cancers.

References

[1] Renehan et al. *Lancet* 2008;371(9612):569−78

166 INVITED

Starvation and DIfferential Stress Resistance in Cancer Treatment

V. Longo[1], C. Lee[1], L. Raffaghello[1], F. Safdie[1], G. Bianchi[1]. [1]*University of California, Davis School of Gerontology, Los Angeles, USA*

Short-term starvation (STS or fasting) provides protection to normal cells, mice, and possibly patients from a variety of chemotherapy drugs, but the possibility that it may also protect tumour cells renders its translational potential uncertain. Here we investigate the effect of fasting cycles on tumour progression independently of and in combination with toxic chemotherapy drugs, with focus on melanoma, glioma, breast cancer, and neuroblastoma *in vivo* models. We also present data on the effect of starvation on a wide variety of cancer cell lines and investigate its effect on a breast cancer cell line at the molecular level. Our studies suggest that multiple fasting cycles have the potential to protect the host against toxic chemotherapy drugs while enhancing the efficacy of the treatment.

167 INVITED

Energy Balance Including Physical Activity Influence Breast and Colon Carcinogenesis − Results From Recent Studies

I. Thune[1]. [1]*Ullevål University Hospital, Oslo, Norway*

There is a growing concern among scientists and recently also oncologists around the observation that the epidemic increase in unfavorable energy balance: excess body weight and physical inactivity are associated with biological mechanisms that may favor certain types of cancer development. Determine the biological mechanisms by which these lifestyle patterns