the treatment opposite of that they were initially randomized, have many attractive features. The analysis of such trials is however complicated, and depending on the primary endpoint of the trial, may greatly confuse the overall study result.
Methods: This talk will present the statistical issues related to cross-over designs in both phase II and phase III trials. Attention will be paid to both trials with a continuous (such as a symptom measurement) and a time to event (such as time to tumour progression) endpoint.
Results: The decision as to whether to allow cross-over or not depends entirely on the primary trial endpoint.
Conclusion: When used appropriately, a cross-over clinical trial can be an effective tool for clinical trial conduct.

158 INVITED

Cross-over in Clinical Trials − the Clinician's Perspective

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The goal of any treatment is to improve duration and/or quality of survival, and hence important endpoints of phase III trials are overall survival (OS) and a measure of its quality. A trial to evaluate a new treatment, B, compared with the current standard, A, is easier to evaluate if crossover from A to B is not allowed. However, ethical questions arise when (often imperfect) evidence emerges that treatment B might be superior while many patients on the control arm remain alive. Such evidence might arise from other trials, or from improvement in surrogate endpoints (e.g. disease-free survival [DFS] or progression-free survival [PFS]) in the ongoing trial. Denying the new treatment to the control group might then be considered unethical. However, it may also be unethical to allow crossover that compromises the ability to detect a difference in OS (the comparison is no longer A vs. B, but for some patients A $\rightarrow$ B vs. B), with uncertainty about outcome then leading to inappropriate treatment of many subsequent patients.
Decisions about crossover must depend on the individual clinical trial and potential for it to occur should be considered during its design. Important considerations are: (i) The nature and strength of evidence to support superiority of treatment B. (ii) Evidence that DFS or PFS are valid surrogates for OS. (iii) Availability of other treatments if crossover is denied. These scenarios will be illustrated by three trials: (i) The BIG-1−98 trial of adjuvant letrozole versus tamoxifen for postmenopausal women with ER+ breast cancer (crossover allowed following improved DFS − the primary endpoint − for women receiving letrozole). (ii) Sunitinib vs. interferon-α for patients with metastatic clear cell Ca kidney (crossover allowed following improved PFS − the primary endpoint − for patients receiving suntinib. (iii) The COU AA-302 trial of abiraterone acetate/prednisone vs. prednisone for men with metastatic castrate resistant prostate cancer who had not received chemotherapy (with dual primary endpoints of OS and PFS), where crossover was denied to participants who progressed after subsequent chemotherapy, despite results from the COU AA-301 trial showing benefit in OS for patients receiving abiraterone acetate after chemotherapy.
The independent data monitoring committee (IDMC) should advise the sponsor about crossover decisions. They should not be made by the sponsor alone, or by registration agencies such as the FDA or EMA.

Special Session (Sun, 25 Sep, 13:15−14:15)
Stem Cells

159 INVITED

Stem Cells and Skin Cancer

Abstract not received

160 INVITED

Haematopoietic Stem Cells

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Recent findings support the concept that cells with the properties of stem cells (SC) are integral to the development and perpetuation of several forms of human cancer, and that eradication of cancer stem cells (CSC) may be essential to achieve cancer cure. However, direct proof of these concepts is still lacking, mainly due the scarcity of appropriate model systems. We are characterizing the biological differences between normal and transformed SCs. SCs are defined by their abilities to generate more SCs ('self-renewal') and to produce cells that differentiate. One mechanism by which SCs accomplish these two tasks is *asymmetric cell division*, whereby each SC divides to generate one daughter with SC fate and one that differentiates. SCs, however, possess the ability to expand in number, as it occurs during development and in adulthood after injury or disease. This increase is not accounted by asymmetric divisions, in which only one daughter cell maintains SC identity. Recent findings in *C.elegans* and *Drosophila* indicate that SCs can also generate daughter cells that are destined to acquire the same fate (*symmetric cell division*). On the other hand, SC quiescence is critical to maintain tissue homeostasis after injury. We will discuss our recent findings showing increased symmetric divisions of CSCs in breast tumours (due to inactivation of the p53 tumour suppressor) and dependency of leukemia development on quiescent leukemia SCs (due to transcriptional up-regulation of the cell cycle inhibitor p21 by leukemia-associated fusion proteins). Our findings suggest that that asymmetric divisions of stem cells function as a mechanism of tumour suppression, that SC quiescence is critical to the maintenance of the transformed clone and that symmetric divisions of SCs permits its geometric expansion. Finally, I will discuss downstreeam mechanisms of regulation of SC divisions by p53 and implications of these findings for the mechanisms regulating checkpoint activation in tissue stem cells.

161 INVITED

Stem Cells

S.P. Niclou[1], A. Golebiewska[1], D. Stiebe[1], R. Bjerkvig[1]. [1]*NorLux Neuro-Oncology Laboratory, Oncology Department, Centre de Recherche Public de la Santé (CRP-Santé), Luxembourg*

Stem cells are characterized by their self-renewal capacity and by their ability to produce cell progeny that differentiate into more specialized, organ-specific cells. During the last two decades numerous groups have identified cells within leukemias as well as within solid tumours that show stem cell-like characteristics. Such cancer stem cells (CSCs) have been proposed to be important for a hierarchical cell organization within cancers where they are defined by (1) their ability to generate tumours in experimental systems in vivo, (2) the ability to undergo self-renewal and (3) the developmental potential to recapitulate all the cell types found in a given tumour. A major problem in solid tumours has been to establish a clear phenotypic definition of CSCs. Many reports have been defining CSCs by one or several phenotypic markers. Yet, subsequent studies frequently show that also other tumour cells that are not defined by the identified markers can have tumour initiating capacities. In addition it was shown that tumour initiating potential is highly dependent on environmental factors. Such observations have led to several controversies within the research field. At present, what seems clear is that tumour cells exist in various solid tumours that share the unique adaptive capacities of normal stem cells. A major question is whether such cells represent a defined subpopulation of tumour cells or whether they represent a changing identity that every cancer cell can adopt depending on the environmental conditions they encounter. This is important not only for our understanding of tumour progression, but also for the successful design of novel therapeutic strategies. Importantly, specifically targeting CSCs only makes sense if it is a relatively stable population. If however genetic, epigenetic or cellular properties of CSCs demonstrate significant plasticity, then we are confronted with exactly the same problems for treating bulk tumour populations. Thus a re-evaluation of the CSC concept in solid tumours appears mandatory before major conclusions can be drawn. We will discuss our recent data obtained in gliomas biopsies and orthotopic xenograft tumours derived thereof, by analysing the adaptive capacities of tumour cells under different environmental conditions using multicolor flow cytometry. The results are correlated with high resolution genomics analysis to distinguish genetic versus phenotypic differences within the identified tumour populations. Our data demonstrate a large genetic heterogeneity in glioblastoma and provide evidence for high adaptability of gliomas cells to a changing environment. The data will be discussed with regard to the concept of clonal evolution of glioma versus the hierarchical cancer stem cell hypothesis.

Special Session (Sun, 25 Sep, 13:15−14:15)
Endpoints in Clinical Trials

162 INVITED

MR-response Criteria in Neurooncology

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Magnetic resonance imaging (MRI) is pivotal in the initial diagnosis and follow-up assessment of cerebral neoplasms. Conventional MR sequences include a) T2-w and b) contrast-enhanced T1-w sequences which reflect a) changes in the amount and state of protons and b) a disruption of the blood-brain-barrier. Recently, new criteria for response assessment

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