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.

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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

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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