leaving behind adjacent peritumoral tissues and organs. Radical resection, or en bloc esophagectomy, removes all peritumoral tissues in addition to the esophagus. The extent of lymphadenectomy performed during esophagectomy is also highly variable, ranging from minimal to radical. A radical esophagectomy refers to a procedure by which the esophagus and its enveloping tissues are removed as a single specimen (en bloc), combined with either two-field (abdominal and mediastinal), or three-field (abdominal, mediastinal, cervical) lymphadenectomy. Nonrandomized comparative studies evaluating radical lymphadenectomy have reported mixed findings, with a number that have failed to identify a survival benefit, whereas some others have reported a benefit. An indirect evidence supports radical lymphadenectomy with an independent association found between the number of surgically removed lymph nodes and overall survival. Despite these data, the answer to this controversy should ideally come from prospective, randomized trials, since the phenomenon of stage migration may occur in comparison with non-randomized series of patients. In this regard, the only published phase III trial till this date compared non-radical transhiatal esophagectomy with transthoracic esophagectomy with two-field lymphadenectomy for patients with adenocarcinoma of the esophagus. The overall 5-year survival with the radical approach was 39%, compared with 29% for the patients undergoing the non-radical resection. Although not statistically significant due to underpowered study, many esophageal cancer specialists would consider less of an increase in survival to be clinically relevant. For squamous cancer there have been two small randomized controlled trials published. The first one compared 2-field lymphadenectomy to 3-field lymphadenectomy without significant 5-year survival difference (48% vs. 66%, respectively). The second one compared 2-field lymphadenectomy to lymph node sampling with a survival benefit favoring radical resection (36% vs. 25%). To conclude, radical transthoracic esophagectomy with two-field lymphadenectomy appears to offer an optimal balance between benefits and risks to a majority of EC patients, especially in the growing area of neoadjuvant treatments. Non-radical resection should be probably reserved for patients with a poor general status whereas 3-field lymphadenectomy may be reserved to selected patients with loco-regional disease in experienced hands, surely for patients with upper esophageal tumours.

154 INVITED

Neoadjuvant Treatment – Better Than Surgery Alone?

Abstract not received

155 INVITED

Will Centralization Improve Outcome?

R. Mason[1]. [1]*Guy's & St. Thomas Hospital NHS Trust, Gastro Intestinal Surgery, London, United Kingdom*

Oesophageal cancer particularly adenocarcinoma is increasing in incidence in the west. Resection of such tumours has been associated with significant morbidity and mortality and poor long term survival. In recent studies from the UK, Europe and USA improved outcomes for surgical resection have been achieved by centralisation of services to specialist centres. It appears that both surgeon and institution volume are equally important. This has achieved in hospital mortality figures of well under 5%. This may well be a combination of better staging and selection as well as improved technique and postoperative care.

Whether this improvement in short term outcome can be reflected in improvement in long term survival is not clear and there are conflicting results. Such an improvement will undoubtably be the result of better selection and staging, and the recruitment of patients into trials of multimodality treatment. It is suggested that radical surgery with extensive resection and lymphadenectomy will improve long term survival. There is little evidence to support this in oesophageal resection in contrast to radical gastrectomy.

The most important factors for improvement in outcome are a multidiciplinary approach with accurate staging, selection and multimodal therapy of a high standard.

Taking this approach over the last 20 years we have reduced inhospital mortality from 3.5% to 0.9% and 5 year survival from 28% to 48% with no significant change in stage of presentation but an increased use of preoperative chemotherapy from <10% to >90%.

Special Session (Sun, 25 Sep, 13:15–14:15)
Cross-Over in Trials

156 INVITED

Early Approval Versus Late Approval

F. Pignatti[1]. [1]*European Medicines Agency (EMA), Safety and Efficacy Sector, London, United Kingdom*

"Early approval" strategies include the "Conditional Marketing Authorisation" in the E.U. and "Accelerated Approval" in the U.S.A. Both mechanisms aim to license new drugs as early as possible in the development, while ensuring that confirmatory efficacy and safety data are duly submitted post-marketing. Regardless of the approval mechanism, sufficient data need to be available in terms of clinically relevant endpoints, to allow a benefit-risk assessment before an approval can be granted.

Acceptable primary endpoints for phase III studies for licensing include overall survival (OS) and progression-free survival (PFS) [1,2]. From the perspective of drug developers, the interest in PFS is because of the expectation that treatment effect will be numerically larger and quicker to observe compared to OS, making PFS an ideal candidate for "early approval" strategies. However, the general acceptance of PFS as a primary endpoint from a regulatory perspective is frequently debated. This is often due to difficulties in quantifying the clinical benefit of this radiological endpoint in the context of the benefit-risk balance assessment for regulatory decision. Furthermore, EMA guidelines recommend that when PFS is the chosen primary endpoint, sufficient data on OS have to be available at the time of assessment in order to at least rule out a negative effect. The analysis of OS can be done on the basis of planned secondary analyses or planned co-primary analyses.

Where one-way cross-over to the experimental arm after progression is considered appropriate (e.g. studies *v.* best supportive care with the possibility to switch to experimental treatment at time of progression), non-compliance with the randomized treatment is likely to hamper any subsequent comparisons in terms of OS. Currently, there is no general agreement on acceptable methods or modelling assumptions to correct for non-compliance for subjects who cross-over after progression. Thus, when PFS is the primary endpoint, there is a need to define situations and timing when cross-over is appropriate, to ensure adequately powered treatment comparisons, in accordance with the objectives of the study. The lack of well-powered OS analyses may be less of a concern when the treatment in terms of PFS is large or the expected OS after progression is short.

When the clinical relevance of PFS in its own right is questioned, this endpoint may still be used for "early approval" if it is considered to be a reasonably likely surrogate endpoint for OS. However, in these situations, conclusive results to confirm a benefit in terms of OS would be expected from relevant trials to be submitted post-approval. In this case, the timing of the post-marketing studies is critical, since "early approval" may again hamper the conduct of ongoing or subsequent randomized studies in the same indication.

Although at times relevant post-marketing studies can be conducted in related indications or combinations, there needs to be sufficient biological and pharmacological rationale to allow meaningful extrapolation of results across different settings.

In conclusion, when considering "early approval" strategies it is critical to consider the clinical relevance of the primary endpoint to allow a benefit-risk assessment at the time of approval, the appropriateness and timing of cross-over, and the feasibility of completing further studies post-marketing.

Publication disclaimer: The views presented here are personal and should not be understood or quoted as those of the European Medicines Agency.

References

[1] European Medicines Agency. Guideline On The Evaluation Of Anticancer Medicinal Products In Man. 2006; Available from: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500017748.

[2] Food and Drug Administration. Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. [Internet] 2007; Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.

157 INVITED

Cross-over in Oncology Clinical Trials – Statistical Issues

D. Sargent[1]. [1]*Mayo Clinic Cancer Center, Health Science Research, Rochester Minnesota, USA*

Background: Cross-over randomized clinical trials, where patients in one arm are allowed (or required) after some predefined time event to receive

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

I. Tannock[1]. [1]*Princess Margaret Hospital, Toronto, Canada*

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

P. Pelicci[1], P.G. Pelicci[1]. [1]*European Institute of Oncology-IEO, Experimental Oncology, Milano, Italy*

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

M. Bendszus[1]. [1]*University of Heidelberg, Heidelberg, Germany*

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