shorter tumour immunoediting process, and (iii) some tumours in infants can spontaneously regress arguing for a role of immune control.
This review will focus on the immune therapies that have been developed in paediatric solid tumours. Basically, immunotherapies could be classified into 3 categories: 1) Humoral therapy 2) Cellular therapy and 3) immunomodulatory agents. Monoclonal antibodies have been developed dramatically in the last decade and form one of the biggest classes of the new immune therapies with promising activities with IGF-1 receptor antibodies in sarcomas and anti-GD2 in neuroblastomas. Cellular therapies consist on T- or NK- or DC-based therapies and have been developed especially in high-risk neuroblastomas. Numerous immunomodulatory agents have been identified to date and some are of particular interest in paediatric solid tumours: immunomodulatory chemotherapies, Toll-like receptor agonists, mTOR inhibitors, epigenetic modulators (e.g., histone deacetylase inhibitors), and other immune modulators (e.g. muramyl tripeptide phosphatidylethanolamine in osteosarcomas). Although the impact of immunotherapy on the clinical management of most paediatric cancers is still negligible, it will certainly improve dramatically within the next years.

354 INVITED

Apoptosis Research in Paediatric Malignancies – New Targets for Therapy

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Resistance to apoptosis (programmed cell death) is a characteristic feature of human cancers including childhood malignancies. Further, evasion of apoptosis is a frequent cause of treatment resistance, since most anti-cancer therapies, for example chemo- or radiotherapy, act primarily by inducing cell death in cancer cells. Over the last two decades, the dissection of apoptosis pathways in pediatric tumours has resulted in the identification of many key molecules that may serve as molecular targets for drug discovery. Currently, components of the apoptotic cascade are exploited for the development of rationally designed molecular targeted therapies. For example, small molecule Smac mimetics that antagonize "Inhibitor of Apoptosis" (IAP) proteins prime childhood acute leukemia cells for TRAIL- or chemotherapy-induced apoptosis, bypass Bcl-2-imposed resistance and exert anti-leukemic activity in a NOD/SCID mouse model of pediatric acute leukemia. Besides overexpression of anti-apoptotic proteins, loss of expression or function of key pro-apoptotic proteins can confer apoptosis resistance. Caspase-8 is frequently epigenetically silenced in pediatric cancers. Re-expression of caspase-8 by e.g. histone deacetylase inhibitors restores sensitivity to death receptor-stimulated apoptosis. Furthermore, apoptosis signaling pathways can be impaired by aberrant activation of survival pathways. We identified increased PI3K/Akt signaling as a new negative prognostic factor in neuroblastoma. Importantly, small molecule dual PI3K/mTOR inhibitors sensitize neuroblastoma cells for death receptor- as well as for chemotherapy-induced apoptosis by shifting the balance between pro- and anti-apoptotic proteins and cooperate with TRAIL or chemotherapy to suppress neuroblastoma growth in vivo. Thus, this approach to target apoptosis signaling pathways is expected to generate new and more effective strategies for the treatment of childhood cancers.

Special Session (Mon, 26 Sep, 17:00–18:00)
Co-Development of Investigational Agents: Industry Experience and Perspective

355 INVITED

Scientific Rationale for the Development of Targeted Agent Combinations

Abstract not received

356 INVITED

Big Pharma: Competitors or Collaborators?

V. Zazulina[1], J. Ryan[1], K. Shannon[2], L. Yan[2]. [1]*AstraZeneca, Oncology Clinical Development, Macclesfield Cheshire, United Kingdom;* [2]*Merck Sharp and Dohme Corp, Oncology Clinical Research, Whitehouse Station NJ, USA*

Successful treatment strategies in the challenging and at times frustrating field of cancer research are often reliant on development of fine-tuned novel combinations. However, agents for these scientifically promising combinations may belong to early phase portfolios of rival Pharmaceutical companies. Whilst true science knows no borders, the competitive nature of Pharmaceutical business will predictably pose questions as to how cross-company development is possible, if at all. In 2009, AstraZeneca and Merck embarked on such collaboration (NCT01021748), joining forces and paving the way to a new paradigm in early phase oncology drug development. This presentation focuses on practical aspects and early learnings from the on-going Phase I collaborative study.

357 INVITED

The Regulatory Perspective of Co-Development of Investigational Agents

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For some anticancer agents, it is expected that combinations are needed not only to optimise anti-tumour activity, but that they are actually necessary in order to obtain meaningful antitumour activity. The European Medicines Agency (EMA) has recently set up an Oncology Working Party to expand the current guideline for the development and evaluation of cancer drugs [1]. The guideline focuses on both exploratory and confirmatory studies for different types of agents. The current revision will address a number of topics, including the use of biomarkers as an integrated part of the drug development and the co-development of new compounds [2].
The rationale for using each drug in a combination should always be established based on appropriate nonclinical and clinical models. Furthermore, from a regulatory perspective, there is a need to establish the contribution not only of the combination of new agents but also of each individual agent in a combination. Concerning the latter, exploratory and confirmatory studies should aim to establish the benefit-risk balance of each individual agent intended to be used in combination with other agents, based on objective criteria of efficacy and safety. Incorporation of a reference treatment arm to enhance assay sensitivity is encouraged.
If based on exploratory clinical or nonclinical data it can be established convincingly that one or more agents do not have sufficient antitumour activity on their own, it maybe possible to further develop these agents using designs that only aim to establish the benefit-risk of these agents when used in combination. For instance, if based on convincing pharmacological and non-clinical data, one or more drugs have no or minimal antitumour activity on their own but are expected to enhance the anti-tumour activity of other drugs (for example, preventing the development of resistance), monotherapy phase 2 and phase 3 studies for the enhancing drugs may not be required. Similarly, when based on well powered phase 2 trials it can be shown that any drugs have each insufficient anti-tumour activity as single agents, but that the combination achieves sufficient antitumour activity to warrant further investigation, the design of phase 3 trials may omit monotherapy treatment arms. As the same targets may have a different impact in different malignancies, the role of each agent in a combination may need to be reassessed when exploring new indications.
The European regulatory requirements on co-development of investigational agents are currently under discussion. Until further guidance becomes available, regulatory advice is recommended in co-development programs.
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] European Medicines Agency. Concept paper on the need to revise the guideline on the evaluation of anticancer medicinal products in man. 2010; Available from: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500096730.

Special Session (Mon, 26 Sep, 17:00–18:00)
How to Write and Review a Good Article?

358 INVITED

The Point of View of a Statistician

L. Collette[1]. [1]*EORTC Headquarters, Statistics Department, Brussels, Belgium*

A mass of new medical information is published every day, bringing various levels of scientific evidence, unfortunately not always objectively presented,

therefore the need to develop a critical thinking to assess their merit. The reasoning involved in this process is, from the statistical point of view, very similar to the steps one takes when designing and conducting a clinical trial to its end.
Whether you write or read a scientific paper, start by identifying the objectives, then read the methods and the results, and then make your own judgment about their value before reading/writing the discussion and conclusion. Make this with a fresh mind, free of prior beliefs and with logic and objectivity!
Be mindful that bias may be introduced at every step of a clinical experiment:
– By construction (if e.g. endpoints or follow-up assessments systematically favor one group, or by selection of a suboptimal comparator)
– In the conduct (selection bias, selective reporting of events, operational bias − this one comes when intermediate results are divulged that influence the further conduct of the experiment)
– In the data analysis (sub-grouping, data dredging, hindsight bias − a natural human tendency to try to confirm prior beliefs, disconfirmation bias − the opposite tendency to scrutinize more the results that go against prior beliefs)
– In the presentation of the results (when more focus is given to the significant findings, even if they are secondary/exploratory; when effect estimates are not reported thus clincal significance cannot be assessed)
– In the interpretation of the results (a tendency to confirm prior beliefs and to see causality)
– In the publication of the results (publication bias: a tendency to make more publicity for positive results than for negative results).

Modern clinical trials are becoming increasingly complex due to the increasing economical pressure and to the growing scientific knowledge. Trials that use adaptive designs, surrogate endpoints or sophisticated pharmaco-genomic classifications are at particularly high risk of bias. In reading articles, be mindful that intermediate endpoints may not always be surrogates for long term clinical benefit; that adaptive designs carry the risk of operational bias or require appropriate safeguards and that the risk of false positive findings must be controlled by appropriate measures whenever analyses in subgroups or interim analyses are conducted.
Find current reporting guidelines on www.equator-network.org

359 INVITED

How to Get Good Evidence Based Information

Abstract not received

Tuesday 27 September 2011

Scientific Symposium (Tue, 27 Sep, 09:00−11:00) Relieving Symptoms of Hormonal Therapies in Patients With Breast Cancer

360 INVITED

Endocrine Symptom Assessment in Women With Breast Cancer

K. Ribi Brega[1], J. Bernhard[1]. [1]*IBCSG International Breast Cancer Study Group, Quality of Life Office, Bern, Switzerland*

Background: Toxicity and tolerability profiles of endocrine treatments in breast cancer trials are usually derived from physician-recorded adverse events. However, there is some evidence that these proxy rating do not adequately reflect endocrine symptom burden experienced by women with breast cancer.
Objective and Methods: The objective is to give an overview of measures used to assess self-reported symptoms related to endocrine therapy in women with breast cancer, to summarise major findings of clinical trials including self-reports of endocrine symptoms and their impact on quality of life (QoL), and to discuss implications for clinical practice.
Results: Several valid tools are available to assess self-reported endocrine symptoms in breast cancer clinical trials. These tools encompass subscales of commonly used cancer-specific QoL measures (e.g. Functional Assessment of Cancer Therapy − Endocrine Subscale; FACT-ES) or checklists specific to endocrine or menopausal symptoms (e.g. Breast Cancer Prevention Trial (BCPT) Symptom Checklist). In contrast, the Checklist for Patients on Endocrine Therapy (C-PET) was developed for the individual assessment of patients' experience with endocrine treatment at clinical visits in order to facilitate communication between the patient and the treatment team. Prevalence rates for most endocrine symptoms are higher when self-reported compared to physician ratings published in pivotal clinical trials. Studies that assessed subjective endocrine symptoms focused on treatment comparisons rather than on the associations between endocrine symptoms and QoL measures. Regarding the impact of endocrine treatment on QoL, findings are not consistent.
Conclusion: The use of endocrine agents, particularly aromatase inhibitors like anastrozole, letrozole and exemestane will extend in earlier stages of disease and for longer periods of time. It's therefore important to collect data on patients' self-reported symptom burden from clinical trials. This information is relevant to inform women about the potential physical sequelae of different endocrine agents, to interpret the association between symptoms and QoL, and to symptom management.

361 INVITED

Evidence-based Management of Symptoms Related to Endocrine Treatment

Y. Wengström[1]. [1]*Karolinska Institutet, Neurobiology Care Sciences and Society Division of Nursing, Stockholm, Sweden*

Endocrine treatment will be a major part of breast cancer therapy for postmenopausal women with hormone-sensitive early breast cancer for years to come, the safety and long-term tolerability of the treatment are therefore important considerations. Like all adjuvant therapies, endocrine treatment has symptoms and side effects associated with their use, many of which resemble symptoms common to menopause. There is a great need to support patients to tolerate and effectively manage and/or prevent these symptoms. Educating patients about anticipated symptoms and side effects may help them understand, accept, and cope with treatment long-term. This presentation reviews symptoms and side effects associated with different adjuvant endocrine treatments and highlight some strategies to manage them effectively. It also highlights the importance of patient education regarding endocrine therapy and involvement in treatment decisions, which may lead to better long-term adherence and ultimately to better outcomes.

362 INVITED

Identification and Management of Treatment-Related Symptoms for Breast Cancer Patients Receiving Adjuvant Endocrine Therapy

L. Fallowfield[1]. [1]*University of Sussex, Brighton East Sussex, United Kingdom*

Data from several multi-national clinical trials have demonstrated that adjuvant endocrine treatment significantly reduces the risk of recurrence and death in women with ER+ breast cancer. It is however difficult to determine which patients actually need treatment: many with early stage disease will be cured of their cancer by adequate surgical and radiation therapy. Consequently some women may receive adjuvant hormone therapy for 5−10 years and experience considerable iatrogenic harms without deriving any discernable benefit. Some of the rarer harms e.g. thromboembolic events and endometrial cancer maybe life-threatening. More commonly experienced harms that are quality of life threatening include: vaso-motor complaints, loss of libido, vaginal dryness and arthralgias. If these are left untreated they can compromise adherence to therapy. We need to minimise the impact of these troublesome side-effects by careful monitoring and prompt implementation of ameliorative interventions. Some of the methods for managing symptoms are reviewed and areas that demand more research to demonstrate efficacy will be outlined.

363 INVITED

Non-compliance in the Adjutant Endocrine Treatment of Women With Breast Cancer

P. Peyman Hadji[1]. [1]*Philipps-University of Marburg, Gynaecology Onkology and Endocrinology, Marburg, Germany*

Enhanced therapeutics and treatment options have improved outcomes of patients with endocrine responsive early breast cancer. Contribution from both physicians and patients is necessary to translate this progress for the overall population into benefit for the individual patient. To ensure the latter one, potential and actual adverse events and respective management options as well as the importance of compliance need to be addressed and discussed openly with empathy and self confidence before and during the course of therapy.
Oral therapies are used increasingly in the treatment of all cancers, especially breast cancer accommodating most women's preferences for tablet therapies. For that reason, patient compliance with recommended treatment is crucial to successful outcomes. However, a 2003 study among 2,378 women with early stage breast cancer revealed that overall adherence to tamoxifen decreased to 50% by the fourth year of therapy. These results were confirmed by more recent studies for patients prescribed tamoxifen or anastrozole. Reasons for non-adherence