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

S. Fulda[1]. [1]*Goethe-University Frankfurt, Institute for Experimental Cancer Research in Pediatrics, Frankfurt, Germany*

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

F. Pignatti[1], U. Hermes[2], B. Jonsson[3]. [1]*European Medicines Agency (EMA), Safety and Efficacy Sector, London, United Kingdom;* [2]*Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany;* [3]*Läkemedelsverket, Uppsala, Sweden*

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.

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[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,