far discontinued treatment. A reduction in spleen size was seen in all 22 remaining patients (100%). All 14 patients with leukocytosis at baseline have experienced a marked reduction in their WBC count. Of the 25 *JAK2*V617F-positive patients, 8 (32%) have experienced a greater than 50% reduction in granulocyte mutant allele burden.

INCB018424: Summary of abstract presented at the 2008 American Society of Hematology meeting. INCB018424 (ATP mimetic from Incyte) is a potent, selective inhibitor of JAK 1 and 2. Over 100 patients were enrolled with a mean exposure to drug of >5 months. Twenty percent of patients had received INCB018424 for >9 months. INCB018424 is generally well tolerated with the primary toxicity being dose-dependent grade 3 or 4 reversible thrombocytopenia which occurred in 0%, 18% and 32% of patients dosed with 10 mg BID, 50 mg QD or 25 mg BID. INCB018424 was associated with a rapid reduction of splenomegaly with 50% or greater reduction being observed in 35% of patients dosed with 10 mg BID or 50 mg QD, and 59% of patients dosed with 25 mg BID regimens. Improvements were also seen with constitutional symptoms: night sweats, pruritis and fatigue. There was a dose-dependent weight gain, most pronounced in patients with the lowest body mass index values at baseline. Profound reductions in inflammatory cytokines were observed by the first evaluation at week 2 in virtually all patients, and were maintained during therapy.

CEP-701: Summary of abstract presented at the 2009 European Hematology Association meeting. CEP-701 (ATP mimetic from Cephalon) was studied in *JAK2*V617F-positive MF, in a phase 2 clinical trial, at MD Anderson Cancer Center. Patients were treated with CEP-701 at an initial dose of 80 mg twice daily. A total of 22 patients were treated. Responses were seen in 6 patients (27%) and consisted of reduction in spleen size alone in 3 patients, transfusion independency in two patients, and reduction in spleen size together with improvement in neutrophils and platelets in one patient. Main toxicities were anemia (grades 3−4: 18%), thrombocytopenia (grades 3−4: 18%) and diarrhea (all grades: 68%; grades 3−4: 9%). CEP-701 is currently being evaluated by other centers in the US in *JAK2*V617F-positive MF, PV and ET.

In addition to the three I described above, many other anti-JAK2 ATP mimetics or HDAC inhibitors are either being evaluated or soon will be:

1. XL019 (ATP mimetic from Exelixis; completed and not to be pursued further; MF and PV)
2. CYT387 (ATP mimetic from Cytopia; study scheduled to open soon at the Mayo Clinic; MF)
3. AZD1480 (ATP mimetic from AstraZeneca; recruiting in the US and France; MF),
4. SB1518 (ATP mimetic from S*BIO; recruiting in Australia and USA; MF, leukemia and lymphoma).
5. ITF2357 (HIDAC inhibitor from Italfarmaco; phase 2 study completed in Italy; JAK2V617F-positive MF, PV or ET),
6. MK0683 (also known as vorinostat; HDAC inhibitor from Merck; ongoing in Europe; PV and ET)
7. LBH589 (also known as panobinostat; HDAC inhibitor from Novartis; scheduled to open soon in the US; MF)

80 INVITED

HDACs inhibitors for lymphoid neoplasias

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Epigenetic modulation involving the regulation of histone acetylation is proving to be a valid antineoplastic strategy, leading to the first FDA approval of the histone deacetylase inhibitor (HDACi), vorinostat, for cutaneous T-cell lymphoma. Acetylation of nucleosomal histones leads to silencing of tumor suppressor and pro-apoptotic elements of critical importance to lymphocyte regulation; this deacetylation is controlled by histone deacetylase (HDAC) activity. The growing understanding of the role of class II and III deacetylases, which regulate the post translational acetylation of proteins, and their inhibition by various agents will also be reviewed, particularly with regard to lymphoid malignancies. Inhibition of histone and protein deacetylase activity has been shown to affect tumor cell differention, growth arrest, and apoptosis in multiple cell types; we will review several of the pathways, with a focus upon DNA damage response elements, as well as effects of these drugs upon proinflammatory cytokines and the microenvironment.

A review of the pharmacology, preclinical single agent and combination activity of various HDAC inhibitors across the range of lymphoid malignancies, from acute lymphoblastic leukemia through B and T cell lymphomas on to multiple myeloma as well as the potential role of HDAC inhibitors in allogeneic transplant (given the sensitivity of activated lymphoid cells to these agents) will be presented.

Scientific Symposium (Mon, 21 Sep, 16:15−18:15)
How to select a new drug in paediatric oncology

82 INVITED

How to select a new drug in paediatric oncology

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Each year, 15000 children are diagnosed with cancer in Europe: 75% are cured with current multimodality treatments while 3000 die. Paediatric malignancies are rare diseases representing only 1% of all cancers in human. However, cancer remains the first cause of death by disease over 1 year of age in Europe and new innovative therapies are urgently needed. The paediatric oncology community has been working together during the last 40 years through clinical research networks that achieved major progress in the cure of children with cancer. New safe and effective anticancer drugs need now to be introduced in standard treatments. The European Paediatric Medicines Regulation is currently changing the landscape of paediatric drug development in Europe, and children with cancer may benefit eventually. However, there are some risks and pitfalls that must be anticipated to assure that children with cancer will benefit from the EU regulation.

The development of targeted therapies based on a better knowledge of tumour biology has opened avenues and hope for many refractory cancers in adults such as kidney and liver cancer. Those compounds must be studied in children as well. There are more than 500 new anticancer compounds in clinical development and many more in industry pipelines since oncology became the first area for drug development. Selection and prioritization of compounds to be evaluated in children is the major challenge, within the new frame set up by the EU regulation. Indeed, cancer is rare in children. More than 60 different diseases from rare to extremely rare tumours are observed in the paediatric population. In addition, biology will dissect further paediatric malignancies with regard to therapies as biology has already dissected/fragmented frequent adult cancers in rarer sub-groups that deserve different types of treatment, as illustrated by breast cancer. Understanding biology of the different paediatric cancers, identifying altered pathways and genetic alterations that are functionally involved is crucial and represents the first step to select compounds of interest. Relevant preclinical models of paediatric tumours, either transplantable or transgenic, are needed to validate druggable targets using compounds. Then, extrapolation from adults to children may speed up the initial phases of dose-finding in the paediatric population while innovative study designs are clearly mandatory to evaluate targeted therapies and their biomarkers in rare diseases such as paediatric malignancies. Thus, the choice of anticancer drugs to be evaluated in children should be based on the paediatric needs identified through biology and state of the art for the treatment of each paediatric cancer. A strong and fruitfull partnership in between the Paediatric Oncology Community, the Pharmaceutical Industry and the Regulatory Bodies is mandatory to assure that the best expertise is accessible to establish the more appropriate strategies for new drug developments for children with cancer.

83 INVITED

Phase I and II trial methodology

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The conduct of early clinical trials in paediatrics poses some unique challenges. Balanced against this is a need to continue to develop anti cancer agents in children. In recent years new European legislation has mandated the investigation of all new drugs in children when marketing authorisation is being sought. This is leading to greater numbers of drugs being available to test. In a relatively small pool of patients this in itself poses challenges. The efficient use of children in such studies becomes increasingly important and study design therefore critical.

This talk will look at the methodological techniques that need to be considered when undertaking Phase I/II studies. Whilst many issues are generic, the availability of existing adult trial data does result in the need to modify some design methods and these will be highlighted. The critical importance of study design and selection of appropriate and informative patients will be discussed.

Early clinical trials in children do pose their own challenges, but experience suggests that cooperative networks can deliver these trials in a timely fashion with good quality data and high levels of safety.