kinases (EGFR, C-Met), serine/threonine kinases (Akt, GSK3-beta) as well as cytosolic (Caspases) and golgi resident proteases (furin). This work has resulted in the development of tools that have become invaluable in testing the efficacy of targeted therapeutic agents as well as in optimization of their dose, schedule and development of the most efficacious combination therapies.

Wednesday, 22 October 2008 08:00–09:45

WORKSHOP 2

Paediatric Oncology

11 INVITED

Update on the application of the EU paediatric regulation

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Immediately effective in all EU member states, the Paediatric Regulation (EC) 1901/2006 came into force about 18 months ago (26/01/2007). Its high-level goals are to facilitate the development and availability of medicinal products where there is a paediatric need, to ensure that such products are subject to ethical research of high quality, and to improve the information available on such medicinal products. The European Medicines Agency with the network of National Agencies is responsible for the scientific evaluation, authorisation and surveillance of medicinal products in Europe, and recently the paediatric development according to the Paediatric Regulation.

For each product to be authorised for the first time or, e.g., for additional indications, a Paediatric Investigation Plan (PIP) or a waiver request, has to be submitted by the pharmaceutical company. Such plans should include measures for the development and for the generation of data that are sufficient for authorisation, including formulation aspects, non-clinical studies and clinical trials. The plans have to define the necessary data on quality, safety and efficacy for use in the paediatric population (0−18 years). Submission of a PIP has to be by end of phase 1 trials in adults for new products. Then, the plan is discussed, modified, and agreed or refused by the EMEA's scientific Paediatric Committee. The EMEA Decision on the Committee's opinion is binding on the company, and a summary is published. The development is most often a combination of requirements for studies, and of waivers; studies may be deferred until more data are obtained in adults. Waivers may be granted for subsets in whom the condition does not exist, or when studies are not justified by an expected therapeutic benefit).

From August 2007 to April 2008, in total 178 applications (corresponding to 326 indications) for PIPs or waivers were reviewed by the Committee. About 20% of the applications were for waivers. Each PIP application corresponds to one active substance (or a combination), but a PIP usually covers more than one indication (e.g., high-grade glioma and neuroblastoma). 14% of the applications were for the therapeutic area of oncology. After excluding applications for waivers only, oncology plans were proposed for 18 active substances, of which 6 were non-cytotoxic and/or targeted. Among applications for substances specifically targeting molecules or pathways, some were for first-in-class products, and some with a known mechanism of action. Therefore, potential scenarios for paediatric development and use have to be defined, including generating the data where there is an unmet medical need. The clinical trials proposed by companies for 15 active substances for paediatric oncology development included 4 phase 1/2 studies, 10 single-arm, most often single-agent phase 2 studies, and 4 phase 3 studies; in total, 8 combination-therapy studies were proposed.

The limited opportunities for clinical trials especially in paediatric oncology, the need to avoid repeated studies in case of similar mechanism of action and use, the vulnerability of the paediatric patients who lack legal competence to consent, all have implications for the design and the analysis of trials, which should only be performed by trained investigators. Ethics Committees also need appropriate paediatric expertise to balance the benefits and risks of research in children. As for paediatric development in general, the possibility for extrapolation of efficacy from adult studies has to be considered for paediatric oncology and haematology. The overall aim is, however, to address potential paediatric uses and not just very advanced cancer stages. Thorough non-clinical studies and paediatric models are increasingly proposed in PIPs, but need to be further developed in respect of non-cytotoxic and/or targeted active substances.

12 INVITED

The Pediatric Preclinical Testing Program (PPTP): changing the paradigm for drug development

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Background: Development of new therapies for children with cancer presents challenges unique to this population. The incidence of cancer is relatively low; in the United States about 12,400 new cases are diagnosed annually in patients under 20 years old, the overall cure rate is approaching seventy percent, and in many patients that ultimately fail curative therapy, initial responses to current multimodality treatments are good. Thus, there are relatively few patients eligible for experimental drug evaluation, and greater than 400 cancer therapeutics are under development. The primary objective of the PPTP is to identify novel agents that will have significant activity against childhood cancer.

Methods: We have established and molecularly characterized 60 in vivo xenograft models and 23 cell lines representing most of the common cancers in children including neuroblastoma, sarcomas (osteosarcoma, Ewing, rhabdomyosarcoma), brain tumors (ependymoma, medulloblastoma, glioblastoma), kidney tumors (Wilms, rhabdoid) and acute lymphoblastic leukemia (ALL). Seventy five percent of the models were derived directly from patient specimens engrafted into mice, and 25 derived at relapse. In vivo we have evaluated 'blinded' the activity of 25 agents including standard cytotoxic agents used in the treatment of childhood cancer, novel agents in early clinical development, and several combinations of novel and standard agents.

Results: Molecular characterization (Affymetrix U133+2, 100K SNP) showed the models selected for the PPTP panels accurately recapitulated the molecular profiles of patient samples. Standard cytotoxic agents (cyclophosphamide, vincristine) demonstrated high activity against appropriate models, thus validating the screen. The screen has identified an antibody against the IGF-1 receptor (SCH717454), an Aurora A kinase inhibitor (MLN8237) and a picornavirus (SVV-001) as having high activity in various histotype panels.

Conclusions: The tumor panels established in the PPTP accurately recapitulate the molecular characteristics of their respective histotypes, and identify known active chemotherapeutic agents. Prospectively, the screen has identified novel agents with high activity that are being 'fast tracked' for pediatric clinical trials. Clinical evaluation of agents both active and inactive in the PPTP screen will determine the validity of this approach to selecting agents that warrant prioritization for pediatric testing.

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13 INVITED

KidsCancerKinome: a EU-FP6 project for preclinical kinase inhibitor evaluation as a tool to prioritize compounds for paediatric development

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KidsCancer Kinome will make a comprehensive analysis of the human protein kinase family. Protein kinases are already excellent targets for many small inhibitory molecules and antibodies designed for adult tumours. Six aggressive childhood tumours (neuroblastoma, medulloblastoma, rhabdomyosarcoma, osteosarcoma, Ewing sarcoma and acute lymphocytic leukaemia) will be addressed. These six tumours are responsible for 50% of childhood cancer deaths.

RNAi knockdown of kinase expression by viral shRNA libraries will be applied to test the human kinase gene family for tumour-driving kinases in cell lines. We first focus on the 'drugged kinases'. Effective lentiviral shRNA vectors are currently being tested for CDK2, AURKA+B, IGF1R, ALK and PIK3CA kinases in cell line panels of each of the 6 tumours. The next series of kinases will include KIT, MET, AKT3, FYN, MEK5+6, PDGFRA, PLK1 and RAF1.