Wednesday 29 September 08:00–09:45

WORKSHOP 1

Marketing approval for anticancer agent – the perspective of a worldwide co-ordination!

8 INVITED

The FDA perspective on marketing approval for anticancer agent

A. Farrell. *USA*

Abstract not received.

9 INVITED

The EMEA perspective on marketing approval for anticancer agent

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In 2004, the number of Member States of the EU increased by ten, a new regulation governing the licensing of medicinal products was adopted and a revision of the CPMP Notes for Guidance on anticancer products was initiated.
Increased heterogeneity within the Union as regards medical culture and regulatory traditions is therefore foreseen. Additionally, in the new legislation the concept "Conditional Approval" (CA) is introduced, referring to temporary authorisation, subject to annually reviewable conditions. While it may be assumed that CA conceptually will be similar to Fast Track Approval in the US, the "Implementing Regulation" is still on a draft level.
These changes in the regulatory environment will most likely in no way affect the standard criteria that govern the licensing of anticancer drugs. As referral to "Exceptional Circumstances" in the past has been used as a means to license drugs early, the possibility for CA might also in practice have limited effects. It is recognised, however, that while it is easy to reach agreement as regards benefit–risk based on well conducted randomised and reference controlled studies with relevant measures of efficacy and safety, this is not the case if these criteria are not fulfilled. Here differences in valuation and, e.g. clinical culture are more important.
As regards standard criteria, convincingly demonstrated effects on overall survival and/or PFS have for long been accepted as proof of efficacy within the EU. It is recognised that, in most cases, it is impossible (given the constraints of the conduct of clinical trials in man) to prove that PFS is a valid surrogate for patient benefit. However, it has been accepted that if there are clearly active next-line therapies, the possibility to detect effects on overall survival may be diminished to such a degree that only accepting survival as a valid end point would not be in the interest of patients.

10 INVITED

The Industry perspective on marketing approval for anticancer agent

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The process of discovery and development and the subsequent registration of novel anticancer agents remains a significant challenge in spite of the tremendous progress that has been made in the understanding of the molecular biology of cancer and the identification of more selective anti cancer drug targets. The progress of new knowledge about cancer as a targetable process provides opportunities for, as well as demands, novel approaches to the oncology drug development pathways. The traditional approaches to early phase devlopment may now not serve as well as in the past and novel phase 1 designs utilising patients selected on the basis of expression of specific targets with evidence of activated downstream pathway signatures based on a much more detailed understanding of the biology will be needed. These trials will resemble more closely the early pharmacodynamic (PD)trials performed in other therapeutic areas that utilise intrapatient dose escalation titrated against molecular or physiologic PD markers. Understanding the dynamic changes in these cancer pathways and their associated pathways will allow rapid hypothesis generation and testing of combination therapies much earlier than traditionally seen. Investigators will present challenging novel designs to IRBs and regulatory authorities that will require almost realtime dynamic adjustment of dose, schedule, and possibly combination partner in a much more rapid fashion. Dose and schedule can be selected based on PD markers or non invaisive imaging of the functional status of the various physiologic hallmarks of cancer rather than RECIST criteria Serial exploration of hypotheses will need to be accounted for in the design of these protocols and will require a very flexible attitude to dynamic protocol amendments. The process of drug development will converge on a learning and confirming approach where data analyses performed on early sets of patients can be the basis for confirmation in second trials. This may be particularly true for identification of baseline signatures of response(eg a mutated oncogene plus evidence of activation of a selected normal pathway) that may apply in subsets across the traditional histotypes normally considered in oncologic nosology. More careful characterisation of patients likely to respond will require co ordinated development and approval of the needed companion diagnostics. The rapid evolution of new standards of care for first, second and later lines of therapy will present challenges with regard to standards of approval especially when long term survival data will not be available or confounded by alternative treatments.

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WORKSHOP 2

Preclinical models

11 INVITED

Overview of the models currently in development

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In 1999, the National Cancer Institute (NCI/NIH) confronted the critical need for improved model systems to inform basic, clinical, epidemiologic, and translational research. The ability to manipulate the germline of mice, and the unprecedented store of data about genetic alterations implicated in human cancer prompted the NCI to implement a collaborative project of mouse cancer modeling. The resulting program, the Mouse Models of Human Cancers Consortium (MMHCC), has expertise in basic, translational, clinical, and epidemiological research, and mouse genetics. The initial 19 member groups were recently increased to 24 to accommodate an expanded set of goals that are designed to leverage advances in many technologies, particularly *in vivo* imaging, computational modeling, and simulation.
The 300-member MMHCC cooperates with the NCI Center for Bioinformatics (NCI CB) to evolve an integrative systems approach to human cancer research, providing the informatics platforms to blend descriptive cancer model information with comparable human disease data. The NCI CB maintains the Cancer Models and Cancer Images Databases, to which any researcher may submit data. This ensures that the databases reflect the experience of all cancer researchers who explore how well model systems inform human cancer therapy, prevention, early detection, imaging, and population science. The eMICE website (*http://emice.nci.nih.gov*) is the interface to the NCI's preclinical models programs, resources, databases, and the NCI Mouse Repository.
The MMHCC members collaborate with the NCI to convene numerous roundtables and other open forums to promote state-of-the-art mouse cancer science, especially its application to cancer therapy. One important forum is The Pre-Clinical Trials Roundtable, at which representatives from academia and the private sector address policy and scientific issues that pertain to application of model systems, especially genetically engineered mice, to the development and testing of interventions. Later this year, the NCI-MMHCC will launch the Imaging Sciences Roundtable to promote collaborations among academic and private sector researchers who employ various *in vivo* imaging techniques to examine changes in tissues as cancers emerge, progress to invasive tumors and metastases, and respond to interventions or recur. More importantly, the Roundtable will encourage the application of real-time cell-based imaging strategies to intact living systems.

12 INVITED

Linking cancer genetics to cancer therapy

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Defects in apoptosis underpin both tumorigenesis and drug resistance, and because of these defects chemotherapy often fails. Understanding the molecular events that contribute to drug-induced apoptosis, and how tumors evade apoptotic death, provides a paradigm to explain the relationship between cancer genetics and treatment sensitivity and should enable a more rational approach to anticancer drug design and therapy. Conventional approaches to identify determinants of drug sensitivity and resistance often rely on human tumor cell lines treated in vitro or as ectopic