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

B. Jonsson. *Medical Products Agency, Uppsala, Sweden*

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

S. Lowe. *Cold Spring Harbor Laboratory, Cancer Research, New York, USA*

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

xenographs. As an alternative approach we have applied the power of mouse genetics to produce animal models that recapitulate the genetics and pathobiology of human malignancies to study treatment responses of tumors treated at their natural site. One model we have focused on is the Em-myc transgenic mouse. These mice overexpress the c-myc oncogene in B-cells, and develop malignancies that resemble human Non-Hodgkin's lymphomas. Using methods for rapidly producing Eμ-myc lymphomas with compound genetic lesions and experimental strategies that parallel clinical trials, we have characterized biologic and genetic determinants of drug resistance in vivo. These studies have identified potential mechanisms of drug sensitivity and resistance, and highlight the relationship between tumor cell genotype and its response to cancer chemotherapy. They also suggest rational strategies to reverse drug resistance in some tumor types.

13 INVITED

Patient and cell line derived human tumor xenograft models – preclinical/clinical correlations

H.H. Fiebig. *Oncotest GmbH, Institute for Experimental Oncology, Freiburg, Germany*

For all major solid human tumor types experimental models have been developed by engrafting patient tumors or permanent human cell lines into immunodeficient mice. Transferring the NCI 60-cell line panel – the largest cell line panel used for drug discovery – *in vivo* into nude mice resulted in sc growth in 47/58 cases (Fiebig et al 1989), or 49/60 cases (Plowmann et al. 1997), respectively. My group implanted more than 1600 solid tumors directly from patients, leading to more than 400 permanent xenograft models. The take rate was highest (38–51%) for melanomas, lung and colon cancers. 60 xenografts were characterized in detail by comparing histology, and 10 surface markers over 10 *in vivo* passages with the original patient tumor. More than 90% showed very similar histology and marker profiles. From 100 xenografts the histology, sensitivity to standard cytotoxic agents, 35 molecular drug targets and expression profiles of 34.000 genes (Affymetrix chips HU133) were determined and compared with the occurrence in the *in vivo* growing NCI-60-cell line panel. 85% of the NCI cell lines showed an undifferentiated or very poorly differentiated histology *in vivo* without the typical tumor architecture seen in e.g. adenocarcinomas of the colon or lung in contrast to the patient's and the patient derived xenograft models. Many cell line-derived xenografts grow faster than patient-derived ones. For colon xenografts, comparison of gene expression profiles showed some differences in cell line-derived models to patient derived xenografts in typical colon associated genes. Activity of standard cytotoxic agents (regression) was observed in cell line-derived xenografts only with alkylating agents, but not with Vinca-alkaloids, Adriamycin, VP16, 5-FU and Methotrexat. In the Freiburg xenograft panel we obtained regressions for 12 clinical active standard agents except 5-FU from which mice tolerate only 25% of the human dose. The response of the same tumors treated in the nude mouse and in the patient was investigated in 42 combinations and 38 single agent therapies. The xenografts showed a very similar response as the same tumor in the clinic, in 90% (19/21) for remission and in 97% (57/59) for resistance. The high correct predictivity validates the xenograft system for drug development. More recently, also target-directed compounds effected remissions and T/C values <10%, e.g. EGF-R-, VEGF- and HSP-90-inhibitors EMD72000, Erbitux, Avastin and 17-AAG. Modulation of the respective targets *in vivo* has been demonstrated. Patient derived xenograft models established in nude mice reflect very well the clinical situation except for metastasis and they are excellent models for tumor biology studies and for the discovery of target directed novel antitumor agents.

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WORKSHOP 3

Mechanistic combinations

14 INVITED

Combined targeted agents with cytotoxic chemotherapy

L. Gianni, G. Bianchi, G. Mariani, S. Cresta. *Istituto Nazionale Tumori, Division of Medical Oncology A, Milan, Italy*

The availability of targeted drugs interfering with signal transduction and/or intracellular signaling has led to the investigation of the potential for using them in combination with conventional chemotherapy that still is the leading therapeutic option for medical treatment of cancer patients. The possibility for combination stands on several considerations. The cellular targets of chemotherapeutic and of targeted drugs are different, supporting the concept that combinations would not lead to cross-resistance, while expected toxicity would not be overlapping. Indeed, perturbation of signals involved in regulation of growth, survival, invasion and metastasis could be associated with enhanced sensitivity to chemotherapeutic drugs and eventually lead to synergistic antitumor effects. The possibility of combining chemotherapy and targeted drugs has been extensively explored in several cellular and animal models. In most cases, the combination of cytotoxic agents and drugs targeting erbB receptors, farnesyl-transferase, m-TOR, PTEN, proteasome, VEGF and VEGF-receptors, PDGFR and many other signaling pathways including those involved in apoptosis has indicated at least additive and often synergistic results. Such experimental evidence has served as a basis for designing clinical studies for many such combinations. Most molecular targeted agents could be combined with most cytotoxic agents at full or nearly full doses. In most instances, continuous exposure to the targeted drugs was associated with concomitant delivery of monochemotherapy or classical combination chemotherapies. Less frequently, the targeted drugs were given sequentially after the delivery of the planned chemotherapy. Outcome of these trials have sometimes posed problems of enhanced or unexpected toxicity, although tolerability of the combinations has rarely been a limiting factor. The clinical antitumor activity and efficacy has offered mixed results. In some case, most notably that of combinations of anti-erbB2 drugs and chemotherapy, significantly improved efficacy and possibly syergism was documented. In other examples, the preclinical evidence supporting supra-additive effects was not confirmed in the clinic. The mixed success of the approach is possibly related to the emerging awareness that in most cases the presence of the target is not the only variable dictating the sensitivity to the targeted agent(s). The future success of combinations of cytotoxic agents and targeted drugs will likely depend on the clarification of what makes the target competent of the tumor survival, and in which cases. That clarification will restrict the applicability of targeted drugs, but, at the same time, expand the possibility of exploiting and measuring expected synergisms from the application of these new combinations in selected subgroups of patients.

15 INVITED

Radiation with targeted agents

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Two fundamental principles should guide the extrapolation of preclinical data with radiation and anticancer agents to the clinical situation as follows:

1. The mechanisms by which each agent produces its antitumor effect must be understood.
2. The extent to which the preclinical model mimics the human situation in those aspects relevant to the mechanisms of the agents must be known.

This presentation will review examples relevant to the combination of radiation with targeted agents with these two principles in mind. Specifically, we will review the extent to which the response of tumors to radiation is governed by the sensitivity of the tumor cells versus the sensitivity of the endothelial cells comprising the vasculature. The answer to this question will determine the efficacy and way in which radiation should be combined with antiangiogenic agents. Also of relevance to the combination of radiation with antiangiogenic drugs is the extent to which transplanted tumors reflect human spontaneous tumors in their reliance on neovasculature. We will show that preclinical models with transplanted tumors are likely to "overpredict" the efficacy of antiangiogenic therapy in the clinic because rapidly growing transplanted mouse tumors have a total reliance on the neovasculature whereas this is not the case with most human tumors. Second, we will review the extent to which preclinical models mimic the clinical situation when radiation is combined with hypoxic cell radiosensitizers or hypoxic cytotoxins. In this context many studies, particularly with hypoxic cell radiosensitizers, were conducted at doses of radiation and drugs that did reflect the clinical situation, and which let to inappropriate expectations in the clinic. Third, we will examine the extent to which short-term assays using apoptosis or tumor shrinkage are relevant to the response of human tumors to combinations of radiation with therapies designed to enhance tumor cell apoptosis.

16 INVITED

Targeted agent with targeted agents

P. Houghton. *St Jude Children's Research Hospital, Molecular Pharmacology, Memphis, USA*

Dysregulation of signaling cascades involved in cellular proliferation and survival is a hallmark of many human cancers, and thus presents potentially selective targets for therapeutic intervention. Agents that target signaling pathways dysregulated during transformation and tumor progression are entering clinical trials. However, with the exception of imatinib, other