124 INVITED

Considerations in PK-PD of Antibodies

C. Kloft[1]. [1]*Freie Universitaet Berlin, Institute of Pharmacy, Department Clinical Pharmacy, Berlin, Germany*

Due to their attractive characteristics (e.g. high specificity and affinity to their target), monoclonal antibodies (mAb) present an innovative class of biopharmaceuticals with increasing clinical importance. However, in some cases only a certain fraction of patients benefits from these "targeted therapies" and the pharmacokinetics (PK) of mAbs is unique compared to small molecule drugs: Their binding/elimination characteristics comprise multiple pathways, in particular the often observed parallel linear and nonlinear elimination. Furthermore, PK is also influenced by the pharmacodynamics (PD) and vice versa in terms of binding to the target (concept of "target-mediated drug disposition", TMDD). Several PK and PD parameters have been reported to be related to patient characteristics, e.g. the different clearances to body size. However, systematic investigations are still sparse. Hence, a thorough understanding of the underlying mechanisms of drug disposition, target binding, drug-target complex internalisation and trafficking inside the cell in various sub-cellular compartments and target dynamics and well as the impact of patient/treatment/study characteristics is required. In future, pharmacometrics as science to effectively integrating mechanistic knowledge in pharmacokinetics and pharmacodynamics, as well as combining approaches of cross-disciplinary interaction (e.g. pre/clinical oncology and modelling & simulation) might streamline drug development (also of novel mAb-derived classes) and increase the risk/benefit ratio of therapeutic use in the individual patient.

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125 INVITED

Pharmacometrics to Improve Treatment of Cancer in Children

A.D.R. Huitema[1]. [1]*Slotervaart Hospital/Netherlands Cancer Institute, Pharmacy & Pharmacology, Amsterdam, The Netherlands*

Many ethical and practical constraints limit clinical trials in pediatric oncology. Therefore, it is imperative to use clinical trial designs and analysis techniques which efficiently use all available information to establish dosing strategies and treatment regimens. Population pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation is very suitable for this purpose. PK/PD modeling and simulation has been used in the design and analysis of clinical trials and for further optimization of treatment regimens in pediatric oncology. In most studies only PK is used as the outcome of the study. Using appropriate scaling methods the exposure in children can be estimated and a dose can be derived based on target drug exposures (for instance based on adult data). For pharmacokinetic scaling several methods have been used to account for body size and maturation related changes in drug exposure. These methods include fairly empirical scaling methods, including the use of different age/weight groups, allometric scaling methods to account for body size effects and whole body physiology based pharmacokinetic modeling approaches. For example, the intravenous form of busulphan has been developed using a population PK scaling approach. In contrast, studies with PK and PD as endpoint are very scarce. For example, for topotecan in pediatric neuroblastoma patients, a PK/PD model incorporating PK, hematological toxicity and tumour size has been developed to derive an optimal administration schedule. In these PK/PD studies, part of the observed variability in PD may be explained by PK variability. However, in the absence of PK data, which is often very hard to collect in pediatric oncology, K/PD models relating dose to PD, may be very useful. In conclusion, as advocated by regulatory bodies, population PK/PD modeling and simulation is very useful in all stages of clinical development of drugs in pediatrics and especially in oncology to overcome some of the ethical constraints imposed by clinical trials in this population.

126 INVITED

Optimising Phase I Trials With Modelling and Simulation Using Pharmacometrics

I. Trocóniz[1], N. Vélez de Mendizabal[1], E. Romero[1], M. Garrido[1]. [1]*University of Navarra, Pharmacy and Pharmaceutical Technology, Pamplona, Spain*

The science of pharmacometrics plays an important role in all the stages of drug development. In early clinical development pharmacometrics offers the possibility to integrate all available information to better understand the new compound and better optimize phase I clinical trials.
There are several aspects that have to be taken into consideration at the time to design an early clinical trial. Those aspects are not limited to the dose range, number of patients and sampling measurement times. Proper knowledge of the specific biopharmaceutic, pharmacokinetic (PD), and pharma (PD)-/toxicodynamic properties of the new drug is required and provides the basis for case specific study designs.
The most efficient way to handle information from various sources (PK, PD, etc) is by developing a (semi-) mechanistic PK/PD/Disease model integrating pre-clinical data, clinical data if available, published data, etc. Such a PK/PD/Disease model will then be used to simulate a variety of scenarios and select those resulting most promising. Important questions such as the optimal dose, dosing regimen, and pharmacokinetic profile can be explored and answered by computer simulations in relation to surrogate markers like tumour shrinkage or percentage of patients suffering severe neutropenia. An important characteristic in drug response is the substantial variability found between individuals. To be most efficient, the PK/PD/Disease models should incorporate variability in their parameters and residual error in the observations, which can be achieved analyzing data under population modelling approach.
Examples to be presented will cover a variety of applications of pharmacometrics in designing early clinical trials: (i) coupling ex vivo human PD data with animal PK information to predict the first dose in humans, (ii) prediction of combination studies based on monotherapy data, and (iii) optimization of improved sustained drug delivery systems.

Scientific Symposium (Sun, 25 Sep, 09:00−11:00) **Melanoma Therapy − Realising the Potential in Targeted Therapy**

127 INVITED

Basics of BRAF

R. Marais[1]. [1]*Institute of Cancer Research, Signal Transduction Team, London, United Kingdom*

BRAF is a protein kinase that is mutated in about half of human melanoma cases. BRAF is normally activated downstream of the small G-proteins of the RAS family, but its mutation in melanoma results in constitutive activation which drives constitutive signalling through the MEK/ERK pathway, thereby stimulating proliferation. Oncogenic BRAF plays a fundamental role in melanoma development. We have developed mouse models of melanoma driven by oncogenic BRAF. Critically, we have found that while BRAF mutations can be founder events in melanoma, by itself oncogenic BRAF is not sufficient to drive full melanomagenesis and our mouse models provide an exceptional opportunity to study the gene-gene and gene-environment interactions in melanoma. We are complementing our mouse studies with gene expression approaches to determine the role played by BRAF in melanoma progression. Through this approach, we have found that BRAF drives melanoma invasion and metastasis by downregulating expression of the cGMP-specific phosphodiesterase PDE5A and the implications of this will be discussed. Finally, we are also investigating the regulation of metabolism in melanoma cells and have found that whereas metformin blocks the growth of melanoma cells that express oncogenic RAS, it accelerates the growth of melanoma cells expressing oncogenic BRAF. This difference appears to be mediated by the protein kinase RSK, the upregulation of VEGF and the consequent induction of angiogenesis.

128 INVITED

Melanoma Therapy − Realising the Potential in Targeted Therapy

K. Flaherty[1]. [1]*Massachusetts General Hospital, Oncology, Boston, USA*

Therapy for advanced melanoma has progressed slowly over the past three decades. The successful translation of therapies targeting signal transduction pathways that are activated by oncogenes in other cancers has provided a model for molecularly targeted therapy. RAS mutations were

discovered 26 years ago in melanoma, and are found in 20% of melanoma cases. However, targeting mutant RAS with drugs remains an elusive goal. The identification of *BRAF* mutations in 2002 was the watershed event that turned the attention of the melanoma field to this concept. Seven years passed between the identification of BRAF mutations and the validation of this target in melanoma patients with a potent and specific BRAF inhibitor, PLX4032. As phase II and phase III single-agent trials have been completed with the aim of establishing single-agent BRAF inhibition as a new standard of care for the BRAF mutated subpopulation, attention now turns to understanding mechanisms of resistance and rational combination approaches. Current efforts are focused on combining other targeted therapies with BRAF inhibitors in the subgroup of patient who have BRAF mutations.
Subsequent to the discovery of BRAF mutations, KIT mutations have been described in a small subset of melanomas; a significant finding since KIT inhibitors are already clinically available based on their efficacy in gastrointestinal stromal tumour, where KIT mutations are more commonly found. In ocular melanoma, three genetic discoveries in the past two years point to the way to new therapeutic approaches in that historically treatment-refractory subset of patients as well. For the first time, there is a clear strategy for how to build toward increasingly efficacious therapies for advanced melanoma, with the hope that even greater advances lie ahead in the next few years.

129 INVITED

Combining TKI's in Melanoma: Which Rationale, How and When

A. Ribas[1]. [1]*UCLA Medical Center, Jonsson Comprehensive Cancer Center, Department of Medicine Hematology/Oncology, Los Angeles, USA*

The field of melanoma treatment has been dramatically changed with the clinical development of highly specific driver oncogene inhibition of mutated BRAF or c-kit. In both cases, the presence of a driver mutation in the oncogenic kinase is the pre-requisite for a tumour response, and tumour responses are frequent when treating patients with metastatic melanoma bearing the mutant kinase.
The type I BRAF inhibitors vemurafenib (PLX4032/RG7204) and GSK2118436 provide a very high rate of initial response rates in patients with $BRAF^{V600E}$ mutant melanoma. However, the sustained clinical activity is limited primarily by the development of acquired resistance leading to tumour progression.
Mechanisms of acquired resistance fall into two broad groups that predict for secondary responses when adding agents that block the resistance mechanisms. One is the reactivation of the mitogen-activated protein kinase (MAPK) pathway, either through secondary mutations in NRAS or upregulation of COT, or mutations in MEK. These escape mechanisms may be targeted by the addition of a MEK or an ERK inhibitor. Another broad mechanism of acquired resistance is mediated by alternative survival pathways downstream of receptor tyrosine kinases (RTK) like PDGFRb or IGF1R, which may be targeted by the addition of inhibitors to PI3K or AKT. Such combination studies could treat and/or prevent acquired resistance to single agent BRAF inhibitors.
Another possibility to increase the duration of responses combination of targeted oncogenic inhibitors and immunotherapy. The ability of BRAF inhibitors to induce regression of melanoma in a high proportion of patients with $BRAF^{V600E}$ positive melanoma could provide several benefits with the potential to synergize with tumour immunotherapy: i) Increased expression of melanosomal tumour associated antigens upon MAPK pathway inhibition. ii) Release of tumour antigens by dying melanoma tumour cells resulting in increased antigen cross-presentation to CTLs. iii) Modulation of the anti-apoptotic environment in cancer cells upon BRAF inhibition to become more sensitive to the pro-apoptotic effects of CTLs. These immune sensitizing effects, together with the intratumoral infiltration by lymphocytes upon treatment with anti-CTLA4 antibodies, would increase the pool of TILs able to respond to released tumour antigens inside tumours. The clinical testing of combinations of BRAF inhibitors and anti-CTLA4 antibodies or other immune modulators is underway.
In conclusion, the understanding of molecular mechanisms of oncogene signaling in melanoma have opened the door to a new generation of highly active therapies for this disease, and understanding the mechanisms of resistance and the interaction with the immune system can expand the benefits of these therapies.

130 INVITED

TKI's, BRAF Inhibitors and the Problem of New Toxicities Such as Keratoacanthoma and Induction of Invasive SCC

C. Robert[1], C. Mateus[1], L. Boussemart[1], N. Kamsu Kom[1], L. Lacroix[1], A. Eychene[2], J. Wechsler[1], G. Tomasic[1], N. Dumaz[3]. [1]*Institut Gustave Roussy, Department of Dermatology, Villejuif,* [2]*Institut Curie, Inserm, Orsay,* [3]*St Louis, Inserm, Paris, France*

New targeted therapies of cancer induce multiple and various skin side effects. One particularly intriguing and concerning of these cutaneous adverse events is the emergence of skin tumours during therapy with drugs targeting RAF proteins. Indeed, all drugs targeting RAF proteins can induce benign, borderline (keratoacanthomas) or malignant tumours originating from keratinocytes (Squamous Cell Carcinomas, SCC).
The mechanism underlying this phenomenon is probably linked to the paradoxical activation of the MAPkinase pathway by this drugs in the cells that are not mutated for BRAF. Additional somatic event like EGFR activation in the hair follicles, UV-induced RAS or TP53 mutations or viral proteins might be necessary to lead to a fully transformed cell.
Until now, we did not observe any metastatic evolution of these skin tumours and the treatment consists in surgical resection of the skin lesions. However, when observing the effects of RAF inhibitors on the skin and on keratinocytes *in vitro*, one can address the question of the potential risk of developing such neoplasms also in other organs elsewhere in the body. Caution has to be taken and the physiological bases of these induced cancers should be deeply explored before RAF inhibitors are used in the adjuvant setting.

Scientific Symposium (Sun, 25 Sep, 09:00−11:00)
Molecular Genetics in Lymphoma − Current Knowledge and New Insights From High-Throughput Technologies

131 INVITED

Chronic Lymphocytic Leukaemia (CLL)

T. Zenz[1]. [1]*NCT/DKFZ & University Hospital Heidelberg, Translational Oncology & Department of Internal Medicine V, Heidelberg, Germany*

Copy number alterations and mutations of key tumour suppressors as *ATM* or *TP53* have been described in chronic lymphocytic leukemia (CLL). Nonetheless, recurrent mutations are relatively rare in CLL and ongoing whole genome sequencing approaches are expected to yield novel mutations contributing to the pathogenesis of CLL. Ideally, our improved understanding of molecular lesions in CLL could be used to develop genotype specific approaches and to exploit the disease specific mutations by directly targeting these or consecutive pathway dependencies.
Currently genotype specific treatments in CLL are considered in ultra-high risk patients with 17p (*TP53*) deletion. In the future, patients with *TP53* mutations (in the absence of 17p deletion) may be considered in a similar risk category.
In order to advance the field further, it will be crucial to build stronger models of CLL subgroups. In these models it will be important to consider genetic risk groups (e.g. *TP53* mutation and 17p deletion, unmutated *IGHV*) alongside clearer clinical subgroups. CLL may be an ideal disease where pretreatment (genomic aberrations, *TP53* mutation, *IGHV* status) and post treatment factors (MRD level, response depth and duration) could be integrated into novel models. While most current approaches consider pretreatment factors, it should be possible to design combinatorial models. Our understanding of the genetic make-up of CLL is likely to increase as more whole genome sequencing data becomes available. This will undoubtedly lead to new insights and questions with regard to biological basis as well as clinical treatment approaches.

132 INVITED

Mantle Cell Lymphoma (MCL)

Abstract not received

133 INVITED

Diffuse Large Cell Lymphoma (DLCL)

A. Rosenwald[1]. [1]*University of Würzburg, Wurzburg, Germany*

Diffuse large B-cell lymphoma (DLBCL) is heterogeneous biologically and clinically. Over the last decade, high-throughput technologies have helped to define two major subtypes of DLBCL based on their gene expression