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Considerations in PK-PD of Antibodies

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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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Pharmacometrics to Improve Treatment of Cancer in Children

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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.

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Optimising Phase I Trials With Modelling and Simulation Using Pharmacometrics

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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**

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Basics of BRAF

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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.

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Melanoma Therapy − Realising the Potential in Targeted Therapy

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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