Dear Colleagues,

With our newsletter June 2017 we would like to inform you about updates regarding clinical trials at the NCT. Topics for this newsletter are:

- **REMOTUX,** a phase II study with cetuximab in patients with metastatic colorectal cancer, successfully completed
- **Sickle-cell disease registry** of the GPOH
- **Ethics and Laws are in Flux** – News with reference to laws and regulations

For the latest news you can also visit our homepage.

Do you plan to perform a clinical study or do you have questions about services of the NCT Trial Center or the contents of this newsletter?
Please contact us!

We hope you will enjoy the reading,

Your NCT Trial Center

Your partner for clinical trials of the NCT and DKFZ

Clinical Trials

REMOTUX trial completed

The REMOTUX trial was an investigator-initiated, prospective, open-label, single-arm, monocentric phase II study to assess the *in vivo* metabolic response during treatment with the EGFR-monoclonal-antibody cetuximab in patients with KRAS/RAS wild-type gene status diagnosed with metastatic colorectal cancer. The study was conducted at the NCT Heidelberg and was coordinated by the NCT Trial Center. Sponsor of the trial was the University Hospital Heidelberg, the principal investigator was Dr. Anne Katrin Berger.

Metabolic changes of the tumor were assessed during two ^{18}F-FDG PET-CT scans, where tracer uptake is measured using standardized uptake values (SUV): The first scan was conducted at baseline followed by a second scan on day 14 after the run-in with cetuximab (days 1 and 8). Subsequently, patients were treated according to the Folfiri-cetuximab regimen as a first-line regimen for metastatic colorectal cancer. The primary endpoint of the study was the clinical response according to RECIST, which was assessed by routine CT scans on day 56 versus baseline. The primary goal of the study was to establish whether or not relative changes in SUV had any predictive relevance for early clinical response. Secondary objectives included the assessment of progression-free and overall survival, the clinical response rate, antivascular/ antiangiogenic effects of cetuximab, as well as a safety analysis.

Between February 2011 and November 2014, a total of 40 adult patients were treated with cetuximab, followed by a two-year follow-up period. The last patient finished follow-up in December 2016, after which the NCT Trial Center assembled and validated all study data and performed a detailed statistical analysis. The final study report according to ICH GCP E3 was sent to the Competent Authorities at the end of April 2017.

The study was supported by Merck KGaA.

Berger AK, et al. (2012) *BMC Cancer* **12**, 108

Sickle-cell disease registry active and recruiting

In 2016 the "Deutsche Kinderkrebsstiftung" decided to fund the sickle-cell disease registry. Thereafter Dr. Kunz and Dr. Tagliaferri from the Center for Child and Adolescent Medicine and members from the NCT Trial Center discussed how other centers could be included and how tasks might be divided most efficiently.

In December 2016 all members of the GPOH had been contacted and had been asked for participation. This was followed by individual follow-ups, consulting and negotiations of the respective centers as well as the concerned local ethics committees. Owing to the efficient division of work and excellent communication within the interdisciplinary, five members team of both institutions as well as the smooth support by the legal department, after only 4 months 38 centers agreed to participate. In April 9 centers had already registered their first patients.

The sickle-cell disease is one of the most common hereditary diseases. Most severe complications can be avoided if the disease is detected early and treated appropriately. The sickle-cell disease registry aims at providing a solid evidence base to incorporate it into the routine newborn screening. Furthermore the data will be used to describe the epidemiology of the sickle-cell disease in Germany.

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http://www.sichelzellkrankheit.info/

Publikationen

„Between worlds: phase 0- or clinical trial with nutritional supplement ?"

The NCT Trial Center published together with Prof. Platten (Medical Director of the Neurological University Hospital Mannheim and Head of the clinical cooperation unit of Neuro Immunology and Brain Tumor Immunology at the DKFZ) an article about the properties of phase 0 trials in general and the study idea for a nutritional supplement with anti-tumoral effect developed for this purpose. This study idea initially seemed to fulfil the legal requirements but finally could not be implemented.

Dr. Daniela Schilling, Prof. Dr. Michael Platten, Dr. Andreas Eisenmenger, *pharmazeutische medizin 2016* der DGPharMed, Jahrgang **18**, Heft 3, November

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Regulations

Ethics and Laws are in Flux

Clinical trials are performed on a broad basis of laws and guidelines. Currently we are experiencing an intense change in treatment options and types of studies in oncology as well as in relevant legal standards. In this newsletter we would like to inform you about the most important innovations:

4th AMGÄndG - Amendment of the MA (Medicines Act)

The 4th MA-Amendment was adopted end of 2016 and became effective on 24th December 2016 already in parts. The changes regarding clinical trials included in the amendment refer to national implementation of rules for the application of the EU-regulation 536/2014 (as previously reported). The EU-regulation 536/2014 is expected to enter into force in the fall of 2018, as EMA states. In parallel most of the new rules of the MA will also become effective in fall 2018. Significant changes affecting clinical trials in humans are: Specifications for the integration of ethics committees under the new EU approval procedure for trials with clinical drugs, registration procedures for ethics committees, code of procedure and organizational chart as well as changes to the procedures for the approval and the prerequisites for clinical trials. The German GCP-regulation will be overridden to a large extent at this moment, accordingly with an appropriate transitional period.

KPVVO - Ordinance for the Code of Procedures in Clinical Trials

This Ordinance (see draft of 22 March 2017) lays down the details of the registration procedure for ethics committees, the time limits for validation, assessment and decisions of trial applications for registered ethics committees, the sharing of fees and the criteria for a business organizational chart as well as the prerequisites for requesting for additional information from the sponsor in the upcoming EU approval procedure according to EU-regulation 536/2014. After the adoption of the ordinance, the ethics committees are called upon to officially register for the new EU procedure and then jointly draw up an organizational chart, according to which, for example, a new study application is allocated to a competent ethics committee in Germany then.

Pilot Phase for EU-Regulation 536/2014 in Germany

Since 1 October 2015 the German federal authorities and currently 33 ethics committees offer sponsors, as one of the first EU countries, the opportunity to test the new deadlines and procedures in dependence on the approval procedure of the EU-regulation 536/2014, without running the risk of having disadvantages in their approval of clinical trials. The results of several completed procedures are encouraging. The ambitious time limits of the EU regulation have even been undercut mostly. However, rather "easy" cases have been submitted so far. It is worth here to gain experience.

Federal Cabinet adopts new radiation protection act (RPA)

The draft of the new RPA has been set up and is put to vote in Bundestag and Bundesrat.

It is targeted to adopt the law before the parliamentary elections this year. The new rules apply to both the implementation of the new Euratom-directive as well as to changes affecting clinical studies with x-rays, ionizing radiation and radionuclides. The draft includes new regulations, now with time limits and

more detailed procedural rules, for the approval of so-called companion diagnosis and independent research on human under this law, the so-called full procedure. The current regulations affecting radiation and x-ray protection ordinances will be replaced completely.

CIOMS Ethical Guideline for Clinical Trials

In February 2017 the Council for International Organizations of Medical Sciences (CIOMS, founded in 1949 by WHO and UNESCO) finalized the revision - debated for years - of the International Ethical Guidelines for Health-related Research Involving Humans of 2002. The 120-page document claims to become the new basis for anyone who carries out clinical trials, observational studies, epidemiological studies or bio banking. It contains chapters on all aspects of study design and implementation, education and consent, on compensation for study participants and up to the role of ethics committees.

New Curriculum of the German Medical Association (BÄK) for Investigators

In October 2016 the Medical Association together with the Ethics Committees of the Federal States Medical associations (LÄK) as well as the Working Party of the Medical Ethics Committees of the Federal Republic of Germany e.V. (AKmedEK) decided new curricular training requirements for investigators/ sub investigators or principal investigators and members of an investigational group in clinical trials under Medicines Act/Regulation (EU) No. 536/2014 and Medical Device Act. These are now divided into three parts and set requirements for basic course, intermediate course and refresher course for the above mentioned group of persons. The ethics committees already examine qualifications according to these requirements. The KKS Heidelberg has updated its training offer accordingly. Physicians who want to participate in clinical trials should promptly catch up on the new requirements and participate in good time in any necessary training in order to avoid delays in study participation.

Conclusions

All this sounds complicated but actually it is not. However, the changes are extensive and therefore significant in daily routine. It's worth to adjust to the changes at an early stage.

The NCT Trial Center will be pleased to inform you in detail about the upcoming changes.

Image courtesy of Stuart Miles at FreeDigitalPhotos.net

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