NCT Trial Center News

Dear Colleagues,

With our newsletter June 2018 we would like to inform you about

- Umbrella und Basket Designs in NCT´s clinical trials, especially
- the academic, EU-wide clinical basket trial 'Basket of Basket' under the umbrella of Cancer Core Europe,
- start of the NCT-PMO-1601 trial in patients with chordoma,
- approval of the AMPLIFY-NEOVAC trial combining a mutation-specific vaccine and an immune checkpoint inhibitor in glioma patients,
- the successfully completed CTLA-4 trial that applied Ipilimumab in patients with metastatic melanoma,
- the KiTZ Clinical Trial Unit (ZIPO), as well as
- current issues on regulations including authorities´ workshops on adaptive study concepts, the EU General Data Protection Regulation, and news regarding the EU Clinical Trials Regulation / EU Portal.

The NCT Trial Center supports clinical trials performed under German Drug Law (AMG) or Medical Devices Act (MPG) by conducting trial-related duties of the sponsor, in particular project management, data management and biometry.

Do you plan to perform a clinical trial 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 at the NCT and DKFZ

Clinical Trials

NCT´s clinical trials make use of Umbrella und Basket Designs

Based on scientific progress in the fields of molecular biology and immunology as well as on the development of new targeted therapies within the last years, adaptive designs are increasingly used in oncological trials of the NCT (please also refer to 'Regulations'):

In the umbrella trial **N^2M^2** (NCT Neuro Master Match) glioblastoma patients are assigned to particular subtrials based on DNA and RNA sequencing and thus, to particular targeted therapies. The trial has been initiated this month.

The EU wide basket trial **INFORM2 NivEnt** for relapsed malignancies in childhood is currently being prepared by the KiTZ Clinical trial Unit (ZIPO, also refer to 'Current Issues' of this newsletter) for approval within the central European approval process (VHP-Plus) for authorities and ethics committees.

Cancer Core Europe – Basket of Basket

Under the umbrella of Cancer Core Europe (CCE), the Vall d'Hebron Institute of Oncology (VHIO) prepares as legal sponsor an academic, EU-wide clinical basket trial, at which DKFZ and NCT Heidelberg with University Hospital take part: *Basket of Basket - A Modular, Open-label, Phase II, Multicenter Study to Evaluate Targeted Agents in Molecularly Selected Populations with Advanced Solid Tumours*. The project is supported financially and with drug supply by Roche and with molecular diagnostics, bioinformatics and data management by CCE partners. The trial was submitted to the

central European approval process (VHP-Plus) on March, 29th 2018. After its completion, the national applications with Competent Authorities and Ethics Committees will take place around June 2018. Details about CCE, its aims and partners are to be found at CCE´s webpage.

NCT-PMO-1601 started successfully

As scheduled the NCT-PMO-1601 trial – a study for patients suffering from a CDKN2A/B-deficient Chordoma – started recruitment in December 2017. Chordomas are categorized as bone tumors, although they do not originate from bone tissue. They derive from remnants of the Chorda dorsalis and therefore usually occur at the base of the cranium and/or coccyx. The standard treatment is the resection and/or radiation therapy. At an advanced stage, alternative therapy options are available with cytostatic chemotherapy or targeted approaches (Imatinib/Lapatinib), - however, the remission rates achieved with these treatment options are very low. The NCT-PMO-1601 phase II study investigates the efficacy of the CDK4/6 inhibitor Palbociclib in patients with locally advanced or metastatic chordoma. This study will show whether the dependence of CDKN2A/B-deficient Chordomas on CDK4/6-is therapeutically applicable. Study centers are Heidelberg, Essen and Ulm. Four patients have been included in the trial so far.

AMPLIFY-NEOVAC (NOA-21) approved

AMPLIFY-NEOVAC is a trial of the German Cancer Consortium (DKTK) and the Neurooncology Working Group of the German Cancer Society (NOA). The trial has recently been approved by the Paul Ehrlich Institute and the responsible Ethics committee. It will be initiated and start recruitment within the next weeks.

This randomized, open-label, 3 arm, phase I trial will test a mutation-specific IDH1 peptide vaccine in combination with the checkpoint inhibitor Avelumab. 48 patients with recurrent IDH1R132H-mutated gliomas with an unfavorable molecular profile (no 1p/19q co-deletion, nuclear ATRX loss) progressive after radio- and chemotherapy eligible for re-resection, will be enrolled. Patients will receive an IDH1 peptide vaccine alone, in combination with the anti-PD-L1 antibody Avelumab, or Avelumab alone. Planned re-resection will take place after 6 weeks of therapy and therapy will be continued after re-resection. Resected tumor tissue will be extensively analysed for molecular and immunonological parameters.

Key outcome parameters will be safety and immunogenicity based on peripheral and intratumoral immune analyses. Extensive exploratory analyses include efficacy, dependent on predictive molecular immune and imaging biomarkers, such as increased mutational load.

The Coordinating Investigator is Prof. Michael Platten, DKFZ and Mannheim University Hospital; Co-Investigators are Prof. Wick (DKFZ und Heidelberg University Hospital) und Prof. Steinbach (University Hospital Frankfurt/M.).

The NCT Trial Center comprehensively supports the preparation of this trial. GMP manufacturing of the vaccine is carried out at the Wirkstoffpeptidlabor Tübingen, which is also part of the DKTK. Recruitment will be performed in Heidelberg and 8 other clinical sites, which are part of the DKTK and/or the NOA. The trial is funded by DKTK and Avelumab is supplied by Pfizer.

CTLA-4 successfully completed and published

The successfully completed CTLA-4 NY-ESO-1 study included 25 patients with metastatic melanoma and pre-existing immune response against NY-ESO-1, who were treated for 12 weeks with Ipilimumab. The results have been published [Haag et al., Eur J Cancer. 2018]: Disease control rate according to irRC (immune-related response criteria) was 52%, irPR (immune-related partial response) was observed in 36% of patients. Progression-free survival according to irRC was 7.8 months, according to RECIST criteria 2.9 months. Median overall survival was 22.7 months; the corresponding 1-year survival rate was 66.8%. Thus, Ipilimumab demonstrated clinically relevant activity within this biomarker-defined population.

Current Issues

KiTZ Clinical Trial Unit (ZIPO)

The **'Hopp Children's Cancer Center at the NCT Heidelberg' (KiTZ)** is a joint institution of the Heidelberg University Hospital and the German Cancer Research Center (DKFZ). As a therapy and research center for oncologic and hematologic diseases in children and adolescents, the KiTZ is committed to scientifically exploring the biology of childhood cancer and to closely linking promising research approaches with patient care – from diagnosis to treatment and aftercare.

The aim of the **KiTZ Clinical Trial Unit (ZIPO)** is to identify target structures for personalized therapies using state-of-the-art molecular diagnostics methods. For this purpose, new phase I/II clinical trials are being developed and new therapeutic approaches tested. With this individualized approach, the study unit assumes a pioneering role in Germany. The KiTZ Clinical Trial Unit is headed by Olaf Witt.

Tasks of the KiTZ Clinical Trial Unit are:

- Treatment within phase I/II clinical trials using targeted medicines and other therapies,
- Molecular diagnostics,
- Consultation and second opinions, and
- Development and international coordination of innovative phase 1-3 studies.

Access to novel therapy approaches: In the KiTZ Clinical Trial Unit, a multidisciplinary team looks after young cancer patients for whom standard treatment procedures were unsuccessful. Whenever possible, these children and adolescents have access to new treatment options under controlled conditions in clinical trials.

Translation into new studies: New therapeutic approaches discovered in the pre-clinical program are being transferred to clinical research. A team of the KiTZ Clinical Trial Unit, which consists of specialized physicians, statisticians, project managers, and data managers, develops innovative study protocols in cooperation with the Department of Statistics of the DKFZ and the NCT Study Center and coordinates its own academic studies within the existing pediatric oncology networks at national and international level.

Regulations

Authorities´ workshops on adaptive study concepts

Adaptive study designs are increasingly used in oncological clinical research due to the scientific progress of recent years in molecular biology and immunology and in the development of new, targeted therapies.

The sometimes highly complex umbrella, basket and platform designs place high demands on applicants and investigators as well as on ethics committees and competent authorities.

The challenges and prerequisites for a safe and meaningful conduct of such studies were discussed intensively at the end of 2017:

On 20 Nov. 2017 a `BfArM im Dialog` event took place on the topic: 'Complex study designs, umbrella studies, basket studies and other complex study approaches – a challenge for all involved'.

A PEI-DKTK workshop entitled 'Adaptive study concepts for innovative cancer therapies: Regulatory challenges in basket and 'umbrella studies' took place a week later.

Results and resulting issues will be addressed in coming events. Further information can be found in the following links and publications:

- BfArM im Dialog – Complex study designs (in German)
- PEI-DKTK Workshop – Adaptive study concepts for innovative cancer therapies (in German)
- Keller-Stanislawski *et al.*: Umbrella-, Basket-Studien und adaptive Studienansätze – Aspekte des Genehmigungsverfahrens der klinischen Prüfung. Bulletin zur Arzneimittelsicherheit, Ausg. 2 Juni 2017, 28f. (in German)
- Fruhner *et al.*: Analysis of integrated clinical trial protocols in early phases of medicinal product

development. Eur J Clin Pharmacol (2017) 73:1565–1577

Standards defined in the EU General Data Protection Regulation (EU GDPR) have to be considered in informed consents

The EU GDPR, which enters into force as from May 25th, 2018, defines a standardized and high level for data protection within the EU.

For clinical trials, this is of special interest for informed consents that have to be adapted – also for trials that are already recruiting and treating patients.

The German ethics committees ('Arbeitskreis der Medizinischen Ethikkommissionen') have published preliminary recommendations how to proceed with active trials (in German).

The NCT Trial Center compiles current information and recommendations of different stakeholders like competent authorities and ethics committees. It develops together with colleagues from other departments proposals for text templates.

EU Clinical Trial Portal will be available in 2020

The EU Clinical Trials Regulation 536/2014 regulates approval, conduct und oversight of clinical trials throughout the EU. It is already into force and will become effective as soon as the EU portal will be available. According to the latest information of the German Higher Competent Authorities (Bundesoberbehörden) this will be at the beginning of 2020.

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http://www.nct-heidelberg.de/forschung/nct-core-services/nct-trial-center.html