NCT Trial Center News

Dear Colleagues,

with our 2020 summer newsletter, we would like to inform you about NCT clinical trials and news on regulatory aspects. Topics include:

- DERANO/HPV-Registry Study
- COGNITION-GUIDE, a phase II umbrella study
- RECOVER Study, a randomized open label phase-II clinical trial
- News from the field of laws and regulations

You will always find news on our homepage.

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

DERANO/HPV-Registry Study

Decitabine Treatment in HPV-Induced Anogenital and Head and Neck Cancer Patients after Radiotherapy or as Novel Late Salvage

The open-label, single-center phase I study “Decitabine Treatment in HPV-Induced Anogenital and Head and Neck Cancer Patients after Radiotherapy or as Novel Late Salvage” (DERANO) has been open for recruitment since October 2019. The study is designed to investigate the safety and tolerability of the DNA methyltransferase inhibitor decitabine in patients with HPV-induced anogenital and head and neck cancer in two patient strata.

In stratum 1, patients who have received definitive chemoradiotherapy as part of standard therapy and who are at high risk of disease recurrence can be included.

Patients with non-curable and progressive disease having received all standard, nationally approved systemic therapies may be treated in stratum 2 as a late salvage approach.

In total, 18 Patients (9 in each stratum) are planned to be included in the trial over a recruitment period of 2 years. The duration of the trial for each patient is expected to be 6 months. This includes two 28 day cycles of study treatment plus a four months follow-up.

Primary endpoint is the incidence of dose limiting toxicities (DLTs) during the first two cycles of study treatment (up to day 56). Moreover, additional safety endpoints including the frequency and severity of adverse events (AE), serious adverse events (SAE), and changes in laboratory parameters will be assessed. Secondary objective of the study is to evaluate preliminary signs of efficacy of the study treatment.

In order to fulfil the trial’s inclusion criteria the tumour must have a positive HPV-status. This will be assumed if both HPV DNA and immunohistochemical overexpression of p16INK4a is detected in tumour tissue. The HPV status of the tumour will be determined in advance, e.g. within the HPV registry study. Before inclusion in the DERANO-study, the positive HPV-status will be confirmed via routine pathology. The primary aim of the HPV registry study is to systematically determine the prevalence of HPV infections, for which a causative role in tumor development is assumed, in patients with carcinomas of the anogenital tract and oropharynx at the Heidelberg University Hospital. It is planned to enroll a total of 400 patients in the HPV registry study.

After completion of the DERANO study, patients who are also included in the HPV-registry study will ideally be followed up within the HPV registry study. This takes place within the framework of routine tumor follow-up according to guidelines and includes, among other things, the collection of data on overall and progression-free survival.

COGNITION-GUIDE

Phase II Umbrella Trial
Implementation of Precision Oncology in Early Breast Cancer

Since 2017, two molecular diagnostic platforms (registry studies) for breast cancer patients have been set up at the NCT Heidelberg, which are coordinated by Prof. Andreas Schneeweiss, Prof. Peter Lichter u. Prof. Richard Schlenk. The aim is to implement genome-based targeted therapeutic approaches in everyday clinical practice and to further facilitate translational scientific companion programs.
While the CATCH study is geared towards advanced, metastatic disease, COGNITION aims to integrate precision medicine into everyday clinical practice in the early disease stages. Due to the potentially curative treatment situation, the latter strategy is directed towards patients with high risk of relapse with poor response towards standard-of-care neoadjuvant treatment, which enables comprehensive genomic characterization of the therapy-resistant residual tumor. The COGNITION-GUIDE treatment study is closely linked to the COGNITION diagnostic register and allows the therapeutic translation of the biomarker profiling within a 9-arm phase II study concept using targeted substances. A total of 240 patients will be enrolled into the umbrella study to evaluate the efficacy and patient benefit of precision oncology in early-stage breast cancer. The NCT trial center is involved in project management, data management and biometrics and further coordinates external service providers (e.g. pharmacy, pharmacovigilance, monitoring).

RECOVER

A Randomized Open label Phase-II Clinical Trial with or without Infusion of Plasma from Subjects after Convalescence of SARS-CoV-2 Infection in High-Risk Patients with Confirmed Severe SARS-CoV-2 Disease

To date, the lack of an effective treatment against SARS-Cov-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infections poses a major challenge for the control of COVID-19 (Coronavirus Disease 2019) worldwide. Different therapeutic strategies are currently under investigation. Beside potential vaccines and drugs, the plasma therapy using convalescent plasma (CP) of COVID-19 patients following recovery from the disease has been suggested as a promising therapeutic option. Indeed, CP treatment has been proposed to decrease mortality in patients in previous epidemics / pandemics such as Spanish flu, MERS-CoV, Ebola etc.), and recent reports indicate that treatment with anti-SARS-Cov-2 CP might improve the clinical course of the disease – especially in high-risk patients. However, a definitive evidence is still missing.

The RECOVER trial aims to investigate the effect of this therapeutic approach in four groups of high-risk SARS-CoV-2-infected patients: group 1, pre-existing or concurrent hematological malignancy or stem cell transplantation and/or active cancer therapy (incl. chemotherapy, radiotherapy, surgery) within the last 24 months or less; group 2, chronic immunosuppression not meeting the criteria of group 1; group 3, age ≥ 50 - 75 years and lymphopenia < 0.8 x G/l and/or D-dimer > 1µg/mL meeting neither the criteria of group 1 nor group 2; group 4, age ≥ 75 years meeting neither the criteria of group 1 nor group 2).

174 patients will be enrolled, at 10 – 15 clinical sites in Germany. Patients will be randomized 1:1 in two arms, to receive either the available viral or supportive therapy only (standard of care arm), or anti-SARS-Cov-2 convalescent plasma in addition to the available standard therapy (interventional arm). Patients are treated with respectively 240 - 340 ml of anti-SARS-Cov-2 CP at day 1 and 2 post-randomisation. A cross-over from the standard of care arm to the experimental arm is possible at day 10, in case of no clinical improvement or worsening of the clinical condition.

The trial was initially submitted to the local ethic committee as a monocentric trial on April 17th, 2020

and was approved within two days. Approval of PEI followed on May 4th, 2020. Eight other clinical sites were submitted on July 9th, 2020 and the site at the Internal Medicine V: Hematology, Oncology and Rheumatology of the University Hospital Heidelberg was initiated on July 31st, 2020. Site activation is planned for August 2020. RECOVER is co-financed by the BMBF program on emergency research funding for COVID-19 and the funds of Heidelberg University Hospital. Coordinating Investigator is Prof. Carsten Müller-Tidow, University Hospital Heidelberg, Internal Medicine V: Hematology, Oncology and Rheumatology.

Regulations

ICH E8 (R1) and ICH E6 (R3) & Eudralex Vol 10 are adapted to EU CTR.

The ICH published the final concept for revision 3 of the ICH GCP E6 on 18 November, E6-R3 Final Concept Paper 2019. The action proposed is a full rewrite and reorganization of the ICH E6(R2) Guideline entitled Good Clinical Practice (GCP).

In the two decades since ICH E6 was first drafted, clinical trials have become more complex with respect to trial design, use of technology, quantity of data collected and involvement of central testing facilities or other service providers.

The development of E6(R3) will address the complexities of clinical trials in the current global regulatory climate. The new guideline will retain its focus on good clinical practice and will refer to relevant critical-to-quality factors similar to those identified in the E8(R1) Revision of General Considerations for Clinical Studies.

The draft of the ICH E8(R1) Guideline "General Considerations for Clinical Trials" May 2019 Step 2b of the ICH process, https://www.ema.europa.eu/en/ich-e8-general-considerations-clinical-studies. Comments from the draft's public consultation have been available since April 2020. The modernization of the ICH E8 Guideline is the first step in the "GCP Renovation" started in 2017.

E6(R2) included a focus on a proportionate, risk-based approach to the design and conduct of clinical trials. E6(R3) will be designed to further advance this concept and to encourage relevant parties to utilize this approach. The proposed rewrite will include more specific discussions and refinement to E6 principles in the context of different trial types and data sources, and will no longer address only classic prospective drug studies but also, for example, registry studies.

There are new joint recommendations of the BfArM and the PEI on application observations (AWBs) in accordance with Section 67 (6) AMG and on the display of non-interventional safety tests (NIS/PASS) in accordance with Section 63f AMG of 20 December 2019, Joint Recommendations, Text in German

EU CTR 536/2014 is expected to be applied (from mid) 2021, after the audit is scheduled for the end of 2020.

See EMA homepage for new information about CTR EMA: Clinical Trial Regulation.
https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

Reference to COVID-19 pages of

EMA
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19

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

Bundesinstitut für Arzneimittel und Medizinprodukte: Coronavirus SARS-CoV-2.
https://www.bfarm.de/DE/Service/Presse/Themendossiers/Coronavirus/_node.html

Paul-Ehrlich-Institut: Coronavirus SARS-CoV-2
https://www.pei.de/DE/newsroom/dossier/coronavirus/coronavirus-inhalt.html

Britain to leave the EU by the end of 2020

After the British government missed the deadline for extending the transition period, the UK will now leave the EU by the end of 2020, with or without a new agreement to work with the EU. Individual studies in the NCT, where D and GB cooperate, are affected.
EMA: UK withdrawal from the EU on 31 January 2020.
https://www.ema.europa.eu/en/news/uk-withdrawal-eu-31-january-2020

Applications for clinical trial can be submitted electronically

Applications for approval of a clinical trial can now be submitted electronically via the Common European Submission Portal (CESP).
The CESP submission replaces sending an application in paper form and sending CDs or DVDs to the federal authorities.

Documents can still be submitted in paper form and/or on a data carrier.

In the present pandemic situation, the BfArM asks that notices of change, which are necessary due to the pandemic and must therefore be processed appropriately, be submitted electronically via the European CESP portal.

Validity of Medical Device Regulation (MDR) postponed by one year

On 26 May 2020, Regulation (EU) 2017/745 on medical devices should be applied in all Member States of the European Union.

Due to the COVID-19 outbreak, the European Commission has now postponed the validity of the MDR until 26 May 2021.

At national level, the Bundestag adopted the law on the adaptation of medical device law to Regulation (EU) 2017/745 and Regulation (EU) 2017/746 (Medical Devices-EU Adaptation Act – MPEUAnpG) on 28 April 2020.

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