NCT Trial Center News

Dear Colleagues,

With our newsletter at the end of 2018, we would like to inform you about NCT clinical trials and about news on regulatory aspects. Topics include:

- PMO-1603 TOP-ART, a phase II study of locally advanced or metastatic solid neoplasia regardless of histological entity, launched in several German centers
- N^2M^2, a successfully launched umbrella study, in which glioblastoma patients are included in one of five sub studies depending on specific molecular markers or – in the absence of these markers – are randomized into one of three other sub studies
- PERDAM, a recently launched meta-study evaluating measurable residual disease as surrogate parameter for therapy response in AML
- TEAM, a study using an innovative Matched Threshold Crossing approach to sample size calculation
- 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

PMO-1603 TOP-ART (EudraCT 2017-001755-31) Patient recruitment opens

The PMO-1603 TOP-ART study has recently been activated in 3 of 11 German centers. This randomized, open-label, multicenter Phase II study is part of the "Program for Precision Medicine in Oncology (PMO)" launched at the NCT and supervised by Prof. Richard Schlenk and Prof. Stefan Fröhling. Several studies have already been launched in the framework of this program. In this study, the NCT Trial Center conducts project management, data management and biometry. In addition, we coordinate externally joint service providers (e.g. pharmacy, pharmacovigilance, monitoring). All participating sites are members of the German Cancer Consortium (DKTK). The study is financially supported by the pharmaceutical companies Astra Zeneca and PharmaMar, who also provide the investigational medicinal product.
The TOP-ART study investigates the active ingredients olaparib and trabectedine, with the aim of evaluating synergistic effects. This experimental therapy will be compared to standard of care according to current oncological therapy guidelines. A total of 102 patients with locally advanced or metastatic solid neoplasias are to be included regardless of histological entity. The primary endpoint is the rate of controlled tumor disease after 16 weeks.

N^2M^2 Studie (EudraCT No. 2015-002752-27) successfully launched

The N2M2 (NCT Neuro Master Match) study by the Neuro-Oncology Working Group in the German

Cancer Society (NOA-20) is a study for brain tumor patients with an innovative Umbrella Design. The NCT Trial Center fosters this study since application, design and financial planning and contract design with project management, data management and biometrics until reporting and publication. In the N2M2 study, patients with newly diagnosed glioblastoma and non-methylated MGMT promoters are assigned to one of five sub-studies by using global methylation analysis, panel and exome sequencing and expression analysis, and the corresponding established confirmation proceedings. In the absence of characteristic changes, patients are randomized in one of the other three sub studies, including the standard arm (with temozolomide). The feasibility of the process has successfully been proven last year in more than 40 patient tissues (Pfaff, Kessler et al. Neuro Oncol 2018[1]).

This allows patients, based on up-to-date molecular information from the tissue removed immediately before the study, to undergo individualized therapy in combination with radiation without standard chemotherapy. In May 2018, N2M2 was initiated in Heidelberg. More study centers followed. A total of 13 Neuro-Oncology Centers across Germany are taking part in the study. Twenty-five patients have already been included in the screening phase. The study concept has recently been published (Wick et al. Neuro Oncol 2018[2]).

1 https://www.ncbi.nlm.nih.gov/pubmed/29165638

2 https://www.ncbi.nlm.nih.gov/pubmed/30277538

PERDAM (ClinicalTrials.gov Identifier NCT03549351) – Meta-study to evaluate measurable residual disease as surrogate parameter for therapy response started at AML

The standard of therapy for patients with acute myeloid leukemia (AML) has been largely unchanged for years, and prognosis remains unfavorable especially in elderly patients. In the PERDAM study, patients' risk profile after CR achieved by induction therapy will be evaluated both by established genetic markers and by "measurable residual disease" (MRD). This biomarker endpoint is measurable at an early time point. If it is meaningful enough to replace survival endpoints, promising new therapies could be identified more quickly.

The PERDAM study evaluates if MRD values measured during therapy are related to overall survival and can thus be used as early surrogate parameters. For this, MRD is determined by multi parameter flow cytometry in samples taken after induction therapy and after completion of consolidation therapy. Samples will be taken from more than 1,000 patients participating in other randomized trials. Measurements are carried out in reference laboratories in Heidelberg and Dresden. AML patients participating in a randomized trial of the Study Alliance Leukemia (SAL) and the HEidelberg LEukemia NEtwork are eligible for PERDAM.

TEAM (EudraCT 2017-005158-12): Innovative matching approach to sample size calculation in submission process

The TEAM study (also targeting AML), is now going through the planning and submission process with significant support by the NCT Trial Center team. This multicenter Phase II study examines the efficacy of a combination of high-dose cytarabine, gemtuzumab ozogamicin (GA) and the proteasome inhibitor bortezomib (B) as compared with historical controls.

Approximately 50 study patients will receive one cycle of combination therapy with Gemtuzumab Ozogamicin, cytarabine and Bortezomib. Using the Matched Threshold Crossing Approach[1], treatment response (CR/CRi) in these patients will be compared with historical controls drawn from two large-scale meta-analyses and matched in age as well as several molecular genetic factors. If the results are promising, a randomized Phase III study is intended.

As part of the submission process the BfArM carried out an inspection, during which the NCT Trial Center was also assessed. This inspection afforded the opportunity to re-evaluate the experience gained so far with Risk Based Quality Management (RBQM) approaches.

[1] Relapsed/refractory acute myeloid leukemia: any progress? Schlenk et al., Curr Opin Oncol. 2017 Nov;29(6):467-473. doi: 10.1097/CCO.0000000000000404. Review.

Kontakt: studienzentrale@nct-heidelberg.de, Tel.: 06221 / 56 6294, INF 350 (OMZ), 69120 Heidelberg
http://www.nct-heidelberg.de/forschung/nct-core-services/nct-trial-center.html

Publications

A phase I trial investigating the Aurora B kinase inhibitor BI 811283 in combination with cytarabine in patients with acute myeloid leukaemia. Döhner et al., Br J Haematol. 2018 Nov 19. doi: 10.1111 / bjh.15563. [Epub ahead of print]

Cohort Profile: the EPI-CT study: A European pooled epide miological study to quantify the risk of radiation-induced cancer from paediatric CT. Bernier et al., Int J Epidemiol. 2018 Nov 2. doi: 10.1093 / ije / dyy231. [Epub ahead of print]

Phase I / II study on cytarabine and idarubicin combined with escalating doses of clofarabine in newly diagnosed patients with acute myeloid leukaemia and high risk for induction failure (AMLSG 17-10 CIARA trial). Krauter et al. Br J Haematol. 2018 Oct;183(2):235-241. doi: 10.1111 / bjh.15546.

Improving consolidation therapy in acute myeloid leukemia - a tough nut to crack. Schlenk RF, Jaramillo S, Müller-Tidow C., Haematologica. 2018 Oct;103(10):1579-1581. doi: 10.3324 / haematol.2018.200485

Measurable residual disease monitoring by NGS before allogeneic hematopoietic cell transplantation in AML. Thol et al., Blood. 2018 Oct 18;132(16):1703-1713. doi: 10.1182 / blood-2018-02-829911. Epub 2018 Sep 6.

A Face-Aging App for Smoking Cessation in a Waiting Room Setting: Pilot Study in an HIV Outpatient Clinic. Brinker et al., J Med Internet Res. 2018 Aug 15;20(8):e10976. doi: 10.2196 / 10976

Midostaurin: A Multiple Tyrosine Kinases Inhibitor in Acute Myeloid Leukemia and Systemic Mastocytosis. Schlenk RF, Kayser S., Recent Results Cancer Res. 2018;212:199-214. doi: 10.1007 / 978-3-319-91439-8_10.

Adding dasatinib to intensive treatment in core-binding factor acute myeloid leukemia-results of the AMLSG 11-08 trial. Paschka et al, Leukemia. 2018 Jul;32(7):1621-1630.

Phase I dose-escalation trial investigating volasertib as monotherapy or in combination with cytarabine in patients with relapsed / refractory acute myeloid leukaemia. Ottmann et al., Br J Haematol. 2018 Jun 8. doi: 10.1111 / bjh.15204. [Epub ahead of print]

Management of patients with acute promyelocytic leukemia.Kayser S, Schlenk RF, Platzbecker U., Leukemia. 2018 Jun;32(6):1277-1294

What's new in consolidation therapy in AML? Schlenk RF, Müller-Tidow C, Seminars in Hematology. In Press, Corrected Proof, Available online 29 August 2018

Midostaurin added to chemotherapy and continued single agent maintenance therapy in acute myeloid leukemia with FLT3-ITD. Schlenk RF, et al. Blood accepted

Regulations

Experience report on the GCP Addendum

Since 14.06.2017, the Integrated Addendum on ICH-GCP (R2) has become mandatory in the EU. Meanwhile, the first experiences with the wider requirements are available. The implementation of risk-based quality management (RBQM) for sponsor and study has the greatest impact on the planning and conduct of clinical trials. The requirements listed in Chapter 5.0 require practical implementation as early as planning a clinical trial and run through all phases until statistical analysis and reporting. They demand closer interaction between all parties involved than before. The NCT Trial Center works intensively to adapt and prepare processes and establish a software-based risk-based quality management for the entire life cycle of studies.

Recently, the first experiences from BfArM inspections during trial application have been received. Those inspections are carried out regularly (also at Heidelberg University Hospital) since a short time.

Corresponding conference contributions from inspectors support the inspection requirements experienced: Risk assessment, coordinated risk indicators, their controlling and an ongoing risk management plan, including possible CAPAs, as well as the interaction of all parties involved are inten-

sively questioned. This requires well-coordinated processes with appropriate SOPs and a clear responsibility split, a communication plan and finally new data management tools for centralized monitoring. Not all of this is new, but now requires a structured, documented approach. Nevertheless, individual lecturers speak of far-reaching changes for conducting clinical trials. The overall goal of RBQM is not to react on issues only after they occurred. Instead, potential sources of error should be identified at an early stage, risks avoided and critical processes closely controlled.

[1] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf

[2] Corrective And Preventive Actions

Revision of radiation protection law

At its meeting on 19 October 2018, the Federal Council (Bundesrat) adopted the Regulation on the Revision of Radiation Protection Law, which amends both the Radiation Protection Act (StrlSchG) and the Radiation Protection Ordinance (StrlSchV). The new regulation mainly concerns occupational safety and medical protection and aims to increase practicality for users. The majority of the regulation is due to come into force on 31 December 2018.

[1] https://www.bundesrat.de/SharedDocs/drucksachen/2018/0401-0500/423-18(B).pdf?__blob=publicationFile&v=1

Kontakt: newsletter.studienzentrale@nct-heidelberg.de, Tel.: 06221 / 56 6294, INF 130.3, 69120 Heidelberg
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