Dear Colleagues,

With our newsletter November 2017 we would like to inform you about clinical trials at the NCT and new regulatory requirements. Topics for this newsletter are

- the INFORM Registry for the molecular characterization of childhood malignancies,
- trials performed in the framework of the German Cancer Consortium (DKTK) and the NCT 3.0 Proof of Concept Program (NCT 3.0), and
- updates regarding the Guideline for Good Clinical Practice and the EU Clinical Trial Portal.

For the latest news please also visit our homepage.

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

INFORM Registry has become "international"

The INFORM registry is a program for children with relapsed or progressive malignancies with no further standard of care therapy options. Tumor samples are analyzed by next-generation sequencing technologies and aberrations found for each single patient are weighted by an expert panel according to clinical relevance.

Recruiting of patients is exceeding expectations (Fig 1): Since beginning of 2015, almost 400 children and young adults from 48 German centers within the Society for Pediatric Oncology und Hematology (GPOH) have been registered, analyzed and documented. Furthermore, since June 2016, almost 90 international patients from seven countries (Fig. 1 and 2) have been registered and documented in the web-based database MARVIN. Three further countries are currently under preparation to participate in the INFORM registry (Fig. 2).

The data management of the NCT Trial Center serves as helpdesk for national and international users, is responsible for the quality of the database and provides data analyses.

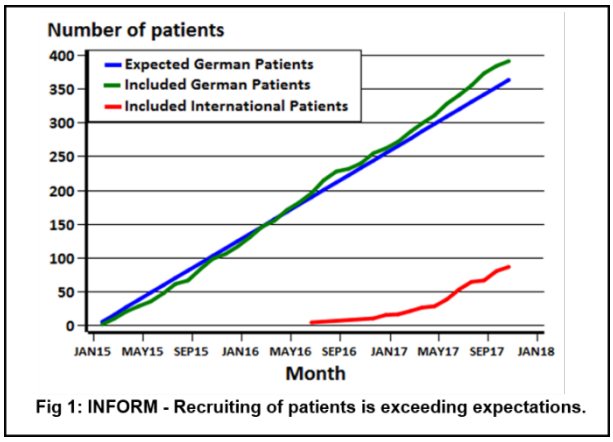

Fig 1: INFORM - Recruiting of patients is exceeding expectations.

More detailed information regarding the INFORM registry and its current status is provided on the homepages of INFORM and the NCT Trial Center, respectively.

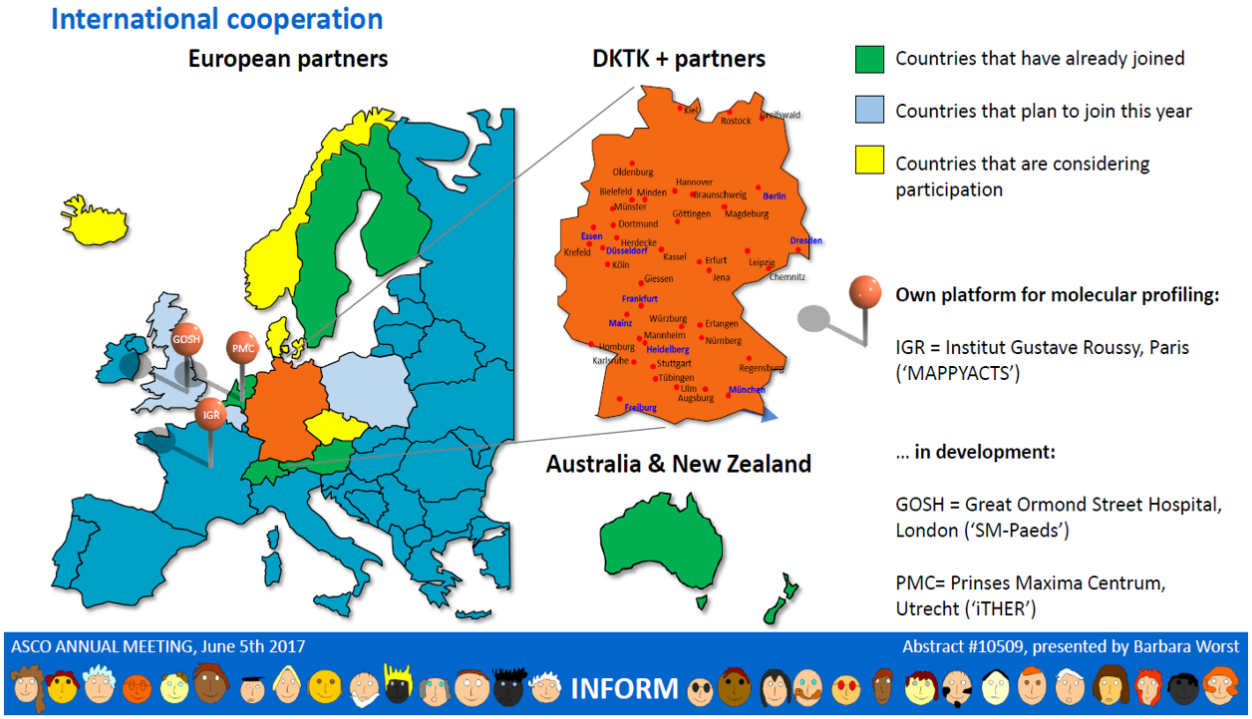

Fig. 2: INFORM – Participating sites in Germany and further countries already active or in preparation.

NOA-16 successfully completed clinical phase

NOA-16 is a first-in-human trial on the safety and immunogenicity of an IDH1 peptide vaccine in grade III-IV, *IDH1*R132H-mutant gliomas. The PI is Prof. Platten (DKFZ and Dept. of Neurology, University Hospital Mannheim).

The trial has been initiated in June 2015. Follow-up period of the last patient was completed in September 2017 – one year earlier than expected. Recruitment and treatment were performed in seven sites, which are all belonging to the German Cancer Consortium (DKTK).

Currently, the data management of the NCT Trial Center finalizes data entry into the central study database, generates queries and performs plausibility checks on trial data; statistical analysis is already in preparation. Final results are expected for spring 2018.

Within the trial, the IDH1 peptide vaccine – a 20mer peptide encompassing the R132H-mutated region – was administered subcutaneously to 33 patients. Eight doses of the vaccine were applied within a period of six months following radiotherapy and/or in parallel with Temozolomide chemotherapy.

The NCT Trial Center comprehensively supports the trial by project and data management and biostatistics. GMP manufacturing of the vaccine was carried out at Heidelberg University Hospital.

For details please refer to ClinicalTrials.gov and CTIS. NOA-16 is funded by DKTK and the NCT 3.0 Proof of Concept Program.

Several other trials of DKTK are in the final phase of preparation or already in approval process:

The trial **AMPLIFY-NEOVAC** will test the IDH1 peptide vaccine in combination with the checkpoint inhibitor avelumab.

The umbrella trial **N²M²** (NCT Neuro Master Match) assigning glioblastoma patients to particular subtrials based on DNA and RNA sequencing has recently been approved by the Paul Ehrlich Institute.

PMO-1601 is a phase II clinical trial to evaluate the efficacy of the small-molecule CDK4/6 inhibitor palbociclib in patients with locally advanced/ metastatic chordoma. Start of recruitment is anticipated for December this year.

NCT-PMO-1603/TOP-ART

NCT-PMO-1603/TOP-ART is a clinical trial based on the DKTK/NCT MASTER protocol using DNA and RNA sequencing. It is currently under final preparation for submission to ethics committees and the ‚Bundesinstitut für Arzneimittel und Medizinprodukte' (BfArM). This phase II trial will recruit patients with locally advanced or metastatic solid tumors that failed standard treatment and whose molecular tumor profiles show homologous recombination repair (HRR) defects.

The aim is to evaluate the efficacy of the combination of olaparib and trabectedin. In a randomized design the combination treatment with trabectedin and olaparib will be compared to conventional treatment of best physician's choice. Cross over will be allowed. The primary objective is to show superior disease control rate (DCR) of olaparib/trabectedin *vs*. physician's choice and investigate whether the PARP dependency of HRR-deficient tumors across entities can be exploited for therapeutic benefit.

Pre-Screening will be performed by Next Generation Sequencing within the NCT MASTER Program to select tumors with alterations (BRCAness) of DNA repair (among others, *BRCA1/2*, *CHEK2*, and *PALB2*).

The experimental combination regimen with repeat cycles of three weeks combines trabectedin and olaparib. DCR according to RECIST will be the primary endpoint at week 16.

Publications

Precision oncology program MASTER

Horak P, Klink B, Heining C, Groeschel S, Hutter B, Froehlich M, Uhrig S, Huebschmann D, Schlesner M, Eils R, Richter D, Pfuetze K, Georg C, Meissburger B, Wolf S, Schulz A, Penzel R, Herpel E, Kirchner M, Lier A, Endris V, Singer S, Schirmacher P, Weichert W, Stenzinger A, **Schlenk RF**, Schroeck E, Brors B, von Kalle C, Glimm H, Froehling S: **Precision oncology based on omics data: The NCT Heidelberg experience.** International Journal of Cancer 141 (5), 877-886, 2017.

Acute myeloid leukemia

Schlenk RF, Frech P, Weber D, Brossart P, Horst HA, Kraemer D, Held G, Ringhoffer M, Burchardt A, Kobbe G, Götze K, Nachbaur D, Fischer T, Lübbert M, Salih HR, Salwender H, Wulf G, Koller E, Wattad M, Fiedler W, Kremers S, Kirchen H, Hertenstein B, Paschka P, Gaidzik VI, Teleanu V, Heuser M, Thol F, Döhner K, Krauter J, Ganser A, Döhner H: **Impact of pretreatment characteristics and salvage strategy on outcome in patients with relapsed acute myeloid leukemia.** Leukemia 31 (5), 1217-1220, 2017.

Jaramillo S, Benner A, Krauter J, Martin H, Kindler T, Bentz M, Salih HR, Held G, Kohne CH, Gotze K, Lubbert M, Kundgen A, Brossart P, Wattad M, Salwender H, Hertenstein B, Nachbaur D, Wulf G, Horst HA, Kirchen H, Fiedler W, Raghavachar A, Russ G, Kremers S, Koller E, Runde V, Heil G, Weber D, Goehring G, Doehner K, Ganser A, Doehner H, **Schlenk RF:** **Condensed versus standard schedule of high-dose cytarabine consolidation therapy with pegfilgrastim growth factor support in acute myeloid leukemia.** Blood Cancer Journal 7 (5), e564, 2017.

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Nagel G, Weber D, Fromm E, Erhardt S, Lubbert M, Fiedler W, Kindler T, Krauter J, Brossart P, Kundgen A, Salih HR, Westermann J, Wulf G, Hertenstein B, Wattad M, Gotze K, Kraemer D, Heinicke T, Girschikofsky M, Derigs HG, Horst HA, Rudolph C, Heuser M, Gohring G, Teleanu V, Bullinger L, Thol F, Gaidzik VI, Paschka P, Dohner K, Ganser A, Dohner H, **Schlenk RF,** German-Austrian AML Study Group (AMLSG): **Epidemiological, genetic, and clinical characterization by age of newly diagnosed acute myeloid leukemia based on an academic population-based registry study (AMLSG BiO).** Annals of Hematology 2017.

Kayser S, Levis MJ, **Schlenk RF:** **Midostaurin treatment in FLT3-mutated acute myeloid leukemia and systemic mastocytosis.** Expert Review of Clinical Pharmacology 10 (11), 1177-1189, 2017.

Schlenk RF, Mueller-Tidow C, Benner A, Kieser M: **Relapsed/refractory acute myeloid leukemia: any progress?** Current Opinion in Oncology 29 (6), 467-473, 2017.

Schlenk RF, Krauter J, Raffoux E, Kreuzer KA, Schaich M, Noens L, Pabst T, Vusirikala M, Bouscary D, Spencer A, Candoni A, Sierra Gil J, Berkowitz N, Weber HJ, Ottmann O: **Panobinostat monotherapy and combination therapy in patients with acute myeloid leukemia, results from two clinical trials.** Haematologica 2017.

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Myelofibrosis

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Neuropathy

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Regulations

GCP Guideline: Risk Management and risk-based Quality Management are now obligatory

Revision of the Guideline for Good Clinical Practice (ICH-GCP) obligates the sponsor to perform and document risk management and risked-based quality management.

The NCT Trial Center has gained first experiences with documented risk Assessment of several trials that are currently in the preparation or submission process. Furthermore, the NCT Trial Center and colleagues from the DKFZ and the KKS Heidelberg work together to establish standard procedures and templates for these excessive tasks.

EU Clinical Trial Portal will be available in 2019

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 European Medicines Agency (EMA) this will be in the second half of 2019.

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