St. Anna Kinderkrebsforschung
CHILDREN'S CANCER RESEARCH INSTITUTE

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Press Release

Pediatric high-risk tumors: gene defect shortens survival and needs targeted treatment

(Vienna, 11.06.2021) **Neuroblastomas, the most common solid tumors outside the brain in children, are associated with poorer survival if they have genetic alterations in the *ALK* gene and belong to the high-risk group. This was shown by scientists from St. Anna Children's Cancer Research institute together with colleagues in an international collaboration. If such alterations are detected, it is conceivable that treatment with ALK inhibitors could be used as upfront therapy in future trials. The study was published in the renowned *Journal of Clinical Oncology*.**

Genetic alterations in the so-called *ALK* gene and the associated protein can fuel the growth of malignant nerve tumors in children. These tumors, namely neuroblastomas, are neoplasms outside the brain that arise from nervous tissue during embryonic development. In a very aggressive form of neuroblastoma (high-risk neuroblastoma), certain genetic alterations in *ALK* have now been identified for the first time as independent predictive markers of decreased survival. Affected children should therefore receive targeted treatment with an ALK inhibitor in future studies. This is the conclusion of a team from St. Anna Children's Cancer Research Institute (St. Anna CCRI) in collaboration with St. Anna Children's Hospital and research groups throughout Europe and Israel.

Better chances for survival thanks to targeted ALK inhibition?

ALK stands for "anaplastic lymphoma kinase", a protein that promotes tumor growth when activated. "Our results convincingly argue for the use of an ALK inhibitor together with chemotherapy and immunotherapy as initial treatment for high-risk neuroblastoma harboring an *ALK* mutation or amplification (i.e., massive replication of the affected DNA sequence). The presence of an *ALK* mutation or amplification worsens survival outcome of affected patients. These patients should therefore receive an ALK inhibitor as tailored therapy in future clinical studies", explains Univ.-Prof. Ruth Ladenstein, MD, MBA, cPM, co-senior author of the study and head of the "Studies & Statistics for Integrated Research and Projects (S^2IRP)" group at St. Anna CCRI.

Co-first author Ulrike Pötschger, PhD, senior statistician of the S^2IRP group, adds, "*ALK* alterations are also a risk factor for survival in a later phase of treatment, when patients receive immunotherapy to maintain previous treatment success." Prof. Ladenstein concludes, "This result strongly suggests that integration of ALK inhibitors throughout all phases of modern era high-risk neuroblastoma therapy is warranted."

ALK alterations are a relevant risk factor

This international, randomized phase III trial included 3,334 participants aged 12 months to 20 years with high-risk neuroblastoma. Of these, 762 were screened for an *ALK* mutation and 901 for an *ALK* amplification. ALK mutations were detected in 14 percent (106/762) and *ALK* amplifications in 4.5 percent (41/901) of these patients.

Overall, *ALK* alterations were a significant predictor for poorer survival in high-risk neuroblastoma (5-year overall survival: 48 vs. 67% with *ALK* alteration vs. no *ALK* alteration, p=0.03). This was also evident in the subgroup already treated with current standard high-dose chemotherapy (busulfan/melphalan) including anti-GD2 immunotherapy.

Furthermore, evaluation of *ALK* amplification alone was also associated with poorer long-term survival (5-year overall survival: 28 vs. 51% with *ALK* amplification vs. no *ALK* amplification, p<0.001), particularly in cases with metastatic *MYCN* amplified disease.
A subset of ALK mutations, namely those with a high "mutation dose" (i.e., clonal mutations; mutant allele fraction >20%) also proved to be a risk factor for poorer long-term survival (5-year overall survival: 34 vs. 59 vs. 49% for clonal *ALK* mutation vs. subclonal vs. no *ALK* mutation, p=0.018). *ALK* mutations with high "mutation dose" comprise approximately 10% of all high-risk neuroblastomas.

Strong European collaboration

This study was made possible thanks to a strong European collaboration, with a close cooperation between the Biological Reference Laboratories of the International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN), the contribution of the clinical centers of SIOPEN, and the close coordination between the principal investigators at St. Anna CCRI, Vienna, Austria, Newcastle University, UK and Institut Curie, Paris, France.
The biological analyses in this study were based on the expertise of the reference laboratories of the Biology Committee of SIOPEN, chaired by Gudrun Schleiermacher, MD, PhD, physician scientist and delegate director for translational research of the Integrated Pediatric Oncology Center SIREDO at Institut Curie, Paris, France. This team contributed to the discovery, in 2008, of the role of *ALK* alterations in neuroblastoma. It is now the strong collaboration between the SIOPEN biology reference laboratories that has enabled to demonstrate that ALK alterations are predictors of poor survival in children with high-risk neuroblastoma.

About high-risk neuroblastoma

Neuroblastomas are the most common pediatric solid tumors derived from nerve tissue outside the brain. High-risk neuroblastomas are tumors harboring a *MYCN* amplification, independent of age, or metastatic tumors in children aged twelve months or older. Unfortunately, the prognosis is still unsatisfactory, with only about half of the children with high-risk neuroblastoma surviving the disease in the long-term. Current standard treatment includes chemotherapy, surgery, autologous stem cell rescue, and isotretionin in combination with immunotherapy.

About the study

The international, randomized Phase III High-Risk Neuroblastoma trial (HR-NBL1), conducted by SIOPEN, enrolled a total of 3,334 patients between 2002 and 2019. Of these, 1,092 patients were included in the *ALK* analysis group, which did not differ in overall survival from the general study population. 132 institutions/hospitals in 19 different countries participated in the trial. Inclusion criteria included stage 2 to stage 4S neuroblastoma according to the International Neuroblastoma Staging System and *MYCN* amplification or stage 4 without *MYCN* amplification in patients aged over 12 months at diagnosis up to 20 years. Within the study, multiple randomized treatment arms consisting of chemotherapy, radiation, and immunotherapy were defined over different time periods.
A large proportion of children were older than 18 months at diagnosis (81%) and had reached an advanced stage of disease (88%, stage 4). *MYCN* amplification, a significant independent risk factor, was present in 47%.

Publikation

Frequency and prognostic impact of ALK amplifications and mutations in the European Neuroblastoma Study Group (SIOPEN) high-risk neuroblastoma trial (HR-NBL1)
Angela Bellini*, Ulrike Pötschger*, Virginie Bernard, Eve Lapouble, Sylvain Baulande, Peter F. Ambros, Nathalie Auger, Klaus Beiske, Marie Bernkopf, David R. Betts, Jaydutt Bhalshankar, Nick Bown, Katleen de Preter, Nathalie Clément, Valérie Combaret, Jaime Font de Mora, Sally L. George, Irene Jiménez Marta Jeison, Barbara Marques, Tommy Martinsson, Katia Mazzocco, Martina Morini, Annick Mühlethaler-Mottet, Rosa Noguera, Gaelle Pierron, Caroline Maria Rossing, Sabine Taschner-Mandl,

Nadine Van Roy, Ales Vicha, Louis Chesler, Walentyna Balwierz, Victoria Castel, Martin Elliott, Per Kogner, Geneviève Laureys, Roberto Luksch, Josef Malis, Maja Popovic-Beck, Shifra Ash, Olivier Delattre, Dominique Valteau-Couanet, Deborah A. Tweddle**, Ruth Ladenstein**, Gudrun Schleiermacher**

* Both authors contributed equally to this work and are to be considered as joint first authors
** All 3 authors contributed equally to this work and are to be considered joint senior authors

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Photo
Univ.-Prof. Dr. Ruth Ladenstein
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About St. Anna Children's Cancer Research Institute, CCRI
St. Anna CCRI is an internationally renowned multidisciplinary research institution with the aim to develop and optimize diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer. To achieve this goal, it combines basic research with translational and clinical research and focus on the specific characteristics of childhood tumor diseases in order to provide young patients with the best possible and most innovative therapies. Dedicated research groups in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics and clinical research are working together to harmonize scientific findings with the clinical needs of physicians to ultimately improve the wellbeing of our patients.
www.ccri.at www.kinderkrebsforschung.at

About St. Anna Children's Hospital
Established in 1837 in the former suburb of Schottenfeld, St. Anna was the first children's hospital in Austria and the third independent hospital in Europe dedicated exclusively to the health of children. St. Anna Children's Hospital has evolved into an institution that provides state-of-the-art medical care. Thus, in addition to its performance as a general children's hospital, the Center for Pediatrics and Adolescent Medicine has also been able to establish an excellent reputation throughout Austria and internationally over the past 40 years as a center for the treatment of pediatric hematologic disorders and tumor diseases (cancer).
www.stanna.at

Further Information:

Lisa Huto
Head of Marketing, Communication & Fundraising
St. Anna Kinderkrebsforschung /
St. Anna Children's Cancer Research Institute - CCRI
1090 Wien, Zimmermannplatz 10
P: +43 1 40470 - 4006
E: lisa.huto@kinderkrebsforschung.at

Mag. Anna Egger
Science Communication Manager, Editor
St. Anna Kinderkrebsforschung /
St. Anna Children's Cancer Research Institute - CCRI
1090 Wien, Zimmermannplatz 10
P: +43 1 40470 - 4067
E: anna.egger@ccri.at