Abstracts

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GRP3-MYC amplification and relapse in infant medulloblastoma (MB): a global multi-cohort study

Stacey Richardson1, Debbie Hicks1, Melissa Gough1, Jemma Castle1, Stephen Cross2, Miguel Garcia-Ariz2, Idota Martin-Guerrero2, Sabine LA Plasschaert3, Franck Bourdeaut3, Christelle Dufour4, Julien Masliah-Planchon4, Francesca R Buttarelli4, Maria-Luisa Garre4, Veronica Biasoni5, Maura Massimino4, Yonehiro Kanemura5, Vijay Ramaswamy5, Amar Gajjar1, Paul Northcott4, Giles Robinson5, Andrey Korshunov1,5,6, Stefan M Pfister1,2,16, Martin Mynarek17, Stefan Rutzowski17, Edward C Schwalbe1,2,18, Simon Bailey1, Steven C Clifford1, 1Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom, 2Biocruces Bizkaia Health Research Institute, Barakaldo, Spain, 3Kinderoncologe, Primes Máxima Centrum voor kinderontologie, Utrecht, Netherlands, 4SIREDO Oncology Center (Pediatric, Adolescent and Young Adults Oncology), Institut Curie, Paris, France, 5Département de Cancérologie de l’Enfant et de l’Adolescent, Gustave Roussy, Paris, France, 6Unité de Génétique Somatique, Institut Curie, Paris, France, 7Department of Neurology and Psychiatry, Sapienza Universita di Roma, Rome, Italy, 8Pediatric neurooncology, IRCCS Istituto G. Gaslini, Ospedale Pediatrico Gaslini, Genova, Italy, 9Dipartimento di Ematologia ed Oncoematologica Pediatrica, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy, 10Department of Biomedical Research and Innovation, Institute for Clinical Research, NHO Osaka National Hospital, Osaka, Japan, 11Department of Neurosurgery, NHO Osaka National Hospital, Osaka, Japan, 12Programme in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, ON, Canada, 13Division of Neuro Oncology, Department of Oncology, St Jude Children’s Research Hospital, Memphis, TN, USA, 14Division of Brain Tumor Research, Department of Developmental Neurobiology, St Jude Children’s Research Hospital, Memphis, TN, USA, 15Clinical Cooperation Unit Neuropathology (B500), German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), and National Center for Tumor Diseases (NCT), Im Neuenheimer Feld 280, 69120, Heidelberg, Germany, 16Hopp Children’s Cancer Center Heidelberg (KiTZ), Division of Pediatric Neuro-Oncology (B062), German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany, 17Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, 18Department of Applied Sciences, Northumbria University, Newcastle upon Tyne, United Kingdom

BACKGROUND: Clinical studies in infant medulloblastoma (iMB; <5 years) have, to date, focussed on modestly-sized or national trials cohorts...
and have not directly compared therapeutic approaches or placed these in the context of dedicated biomarker studies, to inform future treatment strategies. METHODS: We assembled a multi-national cohort of molecularly and clinically-annotated iMBs (<5 years at diagnosis; n=646), the largest to date. We investigated molecular pathology, treatments received, and relationships to outcome within this population. RESULTS: The SHH group (iMB_{SHH} n=267, 40%) predominated, encompassing SHH-1 (37.7%, median age 2.0 years), SHH-2 (47.0%, 1.4 years) and SHH-3 (14.4%, 3.0 years) WHO subgroups. MBEN histology was significantly enriched in SHH-2, and SUFU mutation and MYCN amplification in SHH-1 and SHH-3, respectively. Notably, TP53 mutations were identified in all subgroups; in SHH-1 and SHH-2 (each n=3) tumours lacked features typically associated with TP53-mutated SHH-3 (LCA histology and MYCN amplification) and did not have a worse survival. Upfront radiation-sparing treatments were used in 132/267 children and comprised regimens founded on intraventricular methotrexate (IVT-MTX; 54.5%), high-dose (HDCTx; 22.0%) or standard-dose (23.5%) chemotherapy. Across all radio-naive iMB_{SHH}, non-DN/MBEN histology (HR 2.76, CI 1.26-6.01, p=0.011) and SHH-1 (vs SHH-2, HR 2.51, CI 1.25-5.01, p=0.009) conferred worse PFS in univariable analysis; subgroup was the only independently prognostic risk-factor (multivariable analysis; SHH-1 HR 2.65, CI 1.27-5.51, p=0.009). 3-year OS for HDCTx recipients was very favourable in SHH-1 (100%) and SHH-2 (93.3%), and subgroup-dependent for IVT-MTX (SHH-1; 76.4%, SHH-2; 100%, p=0.009). In CSI-treated iMB_{SHH} (n=49), non-DN/MBEN histology (HR 10.23, CI 2.22-47.04, p=0.003) and MYCN amplification (HR 7.35, CI 2.01-26.87, p=0.003) conferred worse PFS. CONCLUSION: iMB_{SHH} outcomes in this cohort are dependent upon WHO subgroup, histology and therapy received. These findings provide an evidence-based foundation for selection of cohorts and therapies for prospective assessment in forthcoming iMB_{SHH} clinical trials (e.g. SIOP-CONNECT-YC-MB-LR).