

San Martino, Genoa, Italy. <sup>2</sup>Epidemiology and Biostatistics, IRCCS-Istituto Giannina Gaslini, Genoa, Italy

**AIMS:** We report a cohort of YCMB cases homogeneously treated with HDCT in two Italian institutions, and the prognostic impact of histology and genetics retrospectively evaluated. **METHODS:** All YCMB (aged  $\leq 3$  years) treated with upfront HDCT in the period 1998-2019 were included, reclassified according to the WHO2021 classification of CNS tumours. Mutational status of PTCH1, SUFU, and TP53 was analysed in selected cases. Histology and genetics were correlated with survival, secondary tumours (STs), and cancer predisposition syndromes (CPSs). **RESULTS:** Fifty-three patients were enrolled (62.3% male), median age 2.2 years. 21 had classic (CMB), 15 desmoplastic/nodular (DMB), 11 MBEN and 6 large-cell/anaplastic (AMB/LCMB) medulloblastoma. Metastases were present in 18. Genomic pattern showed SHH-TP53wt in 29 cases, non-WNT/non-SHH in 22; 2 were SHH-TP53mut. Induction chemotherapy (VCR/HDMTX, HDVP16, VCR/HDCTX and HDCARBO) was followed by 2-3 HDCT courses; irradiation reserved to cases with metastatic disease and/or residual tumours. 22 patients never received irradiation. SHH-TP53wt cases had significantly less metastasis ( $p=0.002$ ), while non-WNT/non-SHH received more often irradiation ( $p<0.0001$ ). OS at 5, 10, and 20 yrs was 0.73, 0.70 and 0.57 respectively in the entire cohort; stable at 0.85 (at 5, 10, and 20 yrs) in SHH-TP53wt patients while 0.58, 0.51 and 0.17 in the non-WNT/non-SHH. PFS at 5, 10, 20 yrs was stable at 0.89 in SHH-TP53wt and remained 0.35 in non-WNT/non-SHH. 13/53 patients presented Gorlin Syndrome; 1 had familial MB. 16 STs were reported in 14 cases; life-threatening, irradiation-related STs mainly in non-WNT/non-SHH cases. In SHH-TP53wt benign tumours or related to CPS were reported. **CONCLUSIONS:** This is one of the first series of YCMB treated with HDCT without stratification for stage and histology. The long follow-up highlights the frequency/types of associated CPS and STs; the latter, in non-WNT/non-SHH, were treatment-related and life-threatening.

#### MEDB-36. CLINICAL AND MOLECULAR HETEROGENEITY WITHIN MYC AND MYCN AMPLIFIED MEDULLOBLASTOMA

Edward Schwalbe<sup>1,2</sup>, Janet Lindsey<sup>1</sup>, Rebecca Hill<sup>1</sup>, Stephen Crozier<sup>1</sup>, Sarra Ryan<sup>1</sup>, Daniel Williamson<sup>1</sup>, Marcel Kool<sup>3,4</sup>, Till Milde<sup>3,5</sup>, Stefan Pfister<sup>3,5</sup>, Simon Bailey<sup>1</sup>, Steven Clifford<sup>1</sup>; <sup>1</sup>Wolfson Childhood Cancer Research Centre, Newcastle University, Newcastle upon Tyne, United Kingdom. <sup>2</sup>Dept. of Applied Sciences, Northumbria University, Newcastle upon Tyne, United Kingdom. <sup>3</sup>Hopp Children's Cancer Center Heidelberg (KiTZ); German Cancer Research Center (DKFZ), Heidelberg, Germany. <sup>4</sup>Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands. <sup>5</sup>Heidelberg University Hospital, Heidelberg, Germany

MYC and MYCN are the most commonly amplified oncogenes in medulloblastoma. Their overall association with a poor prognosis has supported their adoption as high-risk disease biomarkers in trials. However, emerging evidence suggests that certain patients with MYN/MYCN focally-amplified tumours can achieve long-term survival and therefore may suffer unnecessary late-effects associated with intensified therapies. To investigate this heterogeneity, we characterised the molecular and clinico-pathological features of curated cohorts of MYC (n=64) and MYCN (n=95) amplified tumours, drawn from >1000 diagnostic cases, and assessed their associations with disease outcome. Within the MYCN-amplified cohort, survival was related to molecular group; patients with MYCN<sub>Grp3</sub> or MYCN<sub>Grp4</sub> tumours with no other clinico-pathological risk factors (subtotal resection (STR), metastatic disease, LCA pathology) were intermediate-risk (n=25; 70% 5-year PFS). In contrast, a very-high-risk group was defined by positivity for MYCN<sub>SHH</sub>, STR and/or LCA (n=64; 32% 5-year PFS). 22/35 assessable MYCN<sub>SHH</sub> harboured TP53 mutations; 9/12 with data were germline. MYC<sub>Grp3</sub> represented the majority (46/58; 79%) of molecularly-grouped MYC-amplified tumours. Importantly, while radiotherapy receipt conferred a modest survival advantage, for MYC-amplified tumours with additional clinico-molecular risk factors (LCA, metastasis, STR, Grp3), survival was dismal, irrespective of radiotherapy receipt. A very-high-risk group of MYC-amplified tumours was identified (n=51; 10% 5-year PFS), defined by positivity for  $\geq 1$  additional risk factors (STR, LCA and/or metastasis). Alternatively, membership of subgroups II/V defined a smaller, very-high-risk patient group (n=28; 7% 5-year PFS). Long-term survival was seen in the majority of remaining MYC-amplified tumours negative for these specified features (61% 5-year PFS; high-risk). MYC and MYCN-amplified medulloblastomas are biologically heterogeneous with diverse clinical outcomes. Molecular subgroup assignment and established clinical features are critical for their improved stratification. Patient subgroups identified may be eligible for therapy de-escalation; in contrast, the very-high-risk patient groups are incurable using current therapies and urgently require novel experimental treatment strategies upfront.

#### MEDB-37. CHEMOTHERAPY RESPONSE PREDICTION BY MOLECULAR RISK FACTORS IN METASTATIC CHILDHOOD MEDULLOBLASTOMA

Denise Obrecht<sup>1</sup>, Michael Ludwig Bockmayr<sup>1,2</sup>, Brigitte Bison<sup>3</sup>, Stefan M. Pfister<sup>4,5</sup>, Dominik Sturm<sup>4,6</sup>, Felix Sahm<sup>4,7</sup>, David T. W. Jones<sup>4,8</sup>, Martin Sill<sup>4,6</sup>, Katja von Hoff<sup>9</sup>, Martin Benesch<sup>10</sup>, Nicolas U. Gerber<sup>11</sup>, André von Bueren<sup>12</sup>, Carsten Friedrich<sup>13</sup>, Torsten Pietsch<sup>14</sup>, Ulrich Schüller<sup>15,2</sup>, Martin Mynarek<sup>1,16</sup>, Stefan Rutkowski<sup>1</sup>; <sup>1</sup>Pediatric Hematology and Oncology, University Hospital Hamburg-Eppendorf, Hamburg, Hamburg, Germany. <sup>2</sup>Research Institute Kinderkrebs-Zentrum Hamburg, Hamburg, Hamburg, Germany. <sup>3</sup>Department of Diagnostic and Interventional Neuroradiology, University Hospital Augsburg, Augsburg, Germany. <sup>4</sup>Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany. <sup>5</sup>Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany. <sup>6</sup>KiTZ Clinical Trial Unit (ZIPO), Department of Pediatric Hematology and Oncology, Heidelberg, Germany. <sup>7</sup>Department of Neuropathology, University Heidelberg, and, CCU Neuropathology, German Cancer Research Center (DKFZ), and, German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany. <sup>8</sup>Pediatric Glioma Research Group, German Cancer Research Center (DKFZ), Heidelberg, Germany. <sup>9</sup>Department for Pediatric Oncology and Hematology, Charité – University Medical Center, Universitätsmedizin Berlin, Berlin, Germany. <sup>10</sup>Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria. <sup>11</sup>Department of Pediatric Oncology, University Children's Hospital Zürich, Zürich, Switzerland. <sup>12</sup>Department of Pediatrics, Obstetrics and Gynecology, Division of Pediatric Hematology and Oncology, University Hospital of Geneva, Geneva, Switzerland. <sup>13</sup>Department of General Pediatrics and Pediatric Hematology/Oncology, University Children's Hospital, Oldenburg, Germany. <sup>14</sup>Institute of Neuropathology, Brain Tumor Reference Center of the German Society for Neuropathology and Neuroanatomy (DGNN), University of Bonn, DZNE German Center for Neurodegenerative Diseases, Bonn, Germany. <sup>15</sup>Department of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. <sup>16</sup>Mildred Scheel Cancer Career Center HaTriCS<sup>4</sup>, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

**BACKGROUND:** Childhood metastatic medulloblastoma (MB) frequently receive postoperative chemotherapy (CT) before craniospinal irradiation. Some MB show stable (SD) or progressive disease (PD) upon CT. Identification of biomarkers for non-response might allow therapy-modifications. **METHODS:** Patients registered to the German HIT-MED database (2001–2019) were eligible if they were 4-21 years old at diagnosis of a M2/M3-metastasized MB, received therapy in analogy to the MET-HIT2000-AB4 protocol, had centrally reviewed response assessment after 2 cycles HIT-SKK-CT and DNA-methylation analysis was available. DNA-methylation-based tumor classification and whole chromosomal (WC) losses/gains were derived from DNA-methylation arrays. **RESULTS:** 51/163 (31.3%) patients (median age: 9.8 $\pm$ 4.4 years, median follow-up: 6.2 $\pm$ 4.0 years) presented SD/PD during/after HIT-SKK-CT and were classified as non-responder. Response to CT had high predictive value for PFS/OS (5-year PFS responder: 67.9 $\pm$ 4.8%, non-responder: 26.1 $\pm$ 6.6%,  $p<0.01$  / 5-year OS responder: 80.0 $\pm$ 4.2%, non-responder: 45.9 $\pm$ 8.0%,  $p<0.01$ ). Patients with nonWNT/nonSHH-MB subtype II (response: 7/13), subtype III (response: 6/19) and/or MYC-amplification (n=27, overlap subtype II/III: n=11/8, response: 14/27) were less likely to respond, while all 6 of WNT, 8/9 SHH-TP53-wildtype and 1/1 SHH-TP53-mutant responded (Mann-Whitney-U-test  $p=0.04$ ). Further,  $\geq 2$  WC losses/gains of chromosome 7/8/11 was associated with superior response (n=29/32, others: n=83/131, Mann-Whitney-U-test  $p<0.01$ ). We identified a very-high-risk-cohort (any two criteria of:  $< 2$  WC losses/gains of chromosome 7/8/11, MYC-amplification, MB subtype II, III, V, or VIII, n=94), and a standard-risk-cohort (WNT or any  $\geq 2$  WC losses/gains of chromosome 7/8/11, n=37) with 40 vs. 8% non-response and 44 $\pm$ 5/60 $\pm$ 5 vs. 79 $\pm$ 7/87 $\pm$ 6% 5-year PFS/OS ( $p<0.01$ / $p<0.01$ ), respectively. Non-response in n=32 non-VHR/non-SR-patients was 32% with a 5-years PFS/OS of 60 $\pm$ 10/77 $\pm$ 8%. **CONCLUSION:** Molecular information can be helpful to predict response to chemotherapy. Upon validation, this may contribute to improve treatment stratification in metastatic MB.

#### MEDB-38. SIGNIFICANCE OF CSF CYTOLOGY AND NEUROLOGIC DETERIORATION IN RELAPSED MEDULLOBLASTOMAS IN THE GERMAN HIT-REZ-97/2005 STUDIES AND THE HIT-REZ-REGISTER

Sebastian Tschirner<sup>1</sup>, Jonas E. Adolph<sup>1</sup>, Christine Gaab<sup>1</sup>, Stephan Tippelt<sup>1</sup>, Ruth Mikasch<sup>1</sup>, Martin Mynarek<sup>2,3</sup>, Stefan Rutkowski<sup>2</sup>, Thorsten Pietsch<sup>4</sup>, Brigitte Bison<sup>5</sup>, Monika Warmuth-Metz<sup>6</sup>, Stefan M. Pfister<sup>7,8</sup>, Till Milde<sup>7,9</sup>,