and 5 without adequate details of treatment or outcomes) were excluded from the survival analysis which was restricted to 54 patients. At a median follow-up of 66 months, Kaplan-Meier estimates of 5-year progression-free survival and overall survival were 87.9% and 92.8% respectively. Traditional high-risk features such as age, residual tumor (>1.5cm^2) and leptomeningeal metastases (M+) did not emerge as significant prognostic factors for survival in this molecularly-characterized WNT-MB cohort. CONCLUSION: WNT-MB patients have excellent survival outcomes irrespective of traditional high-risk features suggesting the need for more tailored and refined risk-stratification with potential de-intensification of therapy. ACKNOWLEDGEMENTS: Brain Tumor Foundation (BTF) of India

MEDB-28. CDK9 IS A DRUGGABLE MEDIATOR SUSTAINING MYC-DRIVEN CIRCUITRY IN MEDULLOBLASTOMA

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BACKGROUND: Though long recognized as a master regulator of cell proliferation across a wide range of cancers, Myc has proven elusive to direct therapeutic targeting. The CDK9-containing PTEFb, complexed with either BRD4 or SEC, facilitates Myc-driven transcriptional programs and is necessary for sustaining expression of Myc itself. Advances in development of clinical-grade CDK9 inhibitors creates an opportunity to examine this as a rational therapy for Myc-driven medulloblastoma. METHODS: We used both RNAi depletion and a panel of pharmacologic agents to characterize the mechanistic and functional consequences of CDK9 inhibition in Myc-driven medulloblastoma. We used a combination of clonogenic assays and live cell imaging to assess the cytotoxic effects of CDK9 activity loss. We then performed a combination of CUT&RUN and RNA-seq to evaluate alterations to Myc binding and downstream Myc-driven transcriptional programs. Finally, we employed orthotopic xenograft models of medulloblastoma to assess CNS penetration, tolerability, and anti-tumor efficacy of lead CDK9i candidate compounds. RESULTS: Genetic or pharmacologic inhibition of CDK9 leads to a loss of Myc expression and downregulation of hallmark Myc-driven transcriptional programs. This corresponds to a loss of cell fitness, as measured by decreased proliferation and clonogenic potential. Clinically relevant CDK9 inhibitors show variable efficacy in vivo, but the CNS-penetrant zotiraciclib achieved a significant prolongation in xenograft survival. CONCLUSION: CDK9 catalytic activity represents a druggable vulnerability underpinning Myc-driven transcriptional programs. The development of CNS-penetrant CDK9 inhibitors may open new avenues for rational therapy in these high-risk medulloblastomas.

MEDB-29. APPLICATION OF ROTTERDAM POST-OPERATIVE CEREBELLAR MUTISM SYNDROME PREDICTION MODEL TO PATIENTS OPERATED FOR MEDULLOBLASTOMA IN A SINGLE INSTITUTION

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BACKGROUND: Post-operative cerebellar mutism syndrome (CMS) develops in up to 30% of children. The Rotterdam model (RM) predicts a 66% risk of CMS in patients with a score ≥100. However, our findings suggested that surgical experience contributes to CMS risk. The aim of this study was to retrospectively apply the RM and report incidence of CMS in high-risk patients from our institution. METHODS: Participants had to have first tumor resection at our institution and be enrolled on SJMB12 protocol (NCT01878617). All participants got structured serial neurologic evaluations. CMS, when present, was categorized into type 1 (complete mutism) and type 2 (paucity of speech with an inability to string 3-word sentence). Rotterdam score is calculated based on pre-operative imaging parameters and study neurologist (RBK) obtained it while blinded to CMS status. RESULTS: Of the 40 (14 female, 26 male) study participants, 4 (10%) had CMS (3 CMS1, 1 CMS2). Median age at tumor resection was 11.7 years (range 3.5-17.8). Tumor location was midline in 30 (75%), right lateral 6 (15%) and left lateral 4 (10%). Median Evans index was 0.3 (0.2-0.4) and 34 (85%) were ≥0.3 (indicative of hydrocephalus); 5 participants needed ventricular shunt. Median tumor volume was 50 cm3 (2-180.6). Gross total resection was achieved in 35 (87.5%), near total in 4 (10%) and subtotal in 1. Twelve tumors were SHH, 7 WNT, and 29 NWNS. Median RM score was 90 (25 – 145). Eighteen participants had a score of ≥100 and 16.7% of these (n=3) had CMS. Scores for the 4 with CMS were 85, 125, 145 and 145. CONCLUSION: At our institution, the incidence of CMS in those that had RM of ≥100 was much lower than reported risk of 66%. This data supports our hypothesis that neurosurgical experience remains a significant risk factor in the development of CMS.

MEDB-30. SUBCLASSIFICATION OF GROUP 3/4 MEDULLOBLASTOMA AS A POTENTIAL PROGNOSTIC BIOMARKER TO REDUCE THE DOSE OF CRANIOSPINAL IRRADIATION IN PATIENTS WITH METASTATIC TUMORS: A JAPANESE PEDIATRIC MOLECULAR NEURO-ONCOLOGY GROUP STUDY

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BACKGROUND: In patients with medulloblastoma, one of the most significant challenges is to reduce the dose of craniospinal irradiation (CSI) to minimize neurological sequelae in survivors. Molecular characterization of patients treated using lower-dose CSI rather than standard therapy is important for further reducing the treatment burden. METHODS: We conducted DNA methylation analysis using an Illumina Methylation EPIC array to investigate molecular prognostic markers in 38 patients with medulloblastoma who were registered in the Japan Pediatric Molecular Neuro-Oncology Group and were treated using lower-dose CSI rather than standard-dose radiation therapy. RESULTS: Among the patients, 23 were classified as having a "standard-risk" and 15 as having a "high-risk" according to the classic classification based on tumor resection rate and presence of metastasis, respectively. The median follow-up period was 71.5 months. The median CSI dose was 18 Gy in both groups, and 10 patients in the "high-risk" group received a CSI dose of 23.4 Gy or 24 Gy. Molecular subgrouping revealed the "standard-risk" cohort included 5 WNT, 2 SHH, and 16 Group 3/4 cases; all 15 patients in the "high-risk" cohort had Group 3/4 medulloblastoma. Among the patients with Group 3/4 medulloblastoma, 13 of the 16 "standard-risk" patients were subclassified as subtypes I, IV, VI, and VII, which were associated with a good prognosis according to the novel sub-subclassification among Group 3/4 medulloblastomas. However, only 6 of the 15 "high-risk" patients were included in the subtypes. The good prognostic subtype cases among "high-risk" cohort were all survived without recurrence, in contrast to a worse prognosis (5-year progression free survival=33.3%; p=0.01) of the other cases. CONCLUSION: Although these findings require validation in a larger cohort, the present findings suggest that the novel sub-subclassification of Group 3/4 medulloblastoma may be a promising prognostic biomarker for reducing the dose of CSI in patients with metastatic medulloblastoma.

MEDB-31. THE CLINICAL SIGNIFICANCE OF EXTENT OF RESECTION IN MEDULLOBLASTOMA

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Medulloblastoma (MB) patients determined to have a sub-total resection (STR), defined by >1.5cm^2 post-surgical tumour residuum, receive intensified treatment regimes, but recently the designation of STR as a high risk feature is being questioned. We aimed to assess the clinical correlates of ex-