Pinealoblastoma (PB) is an aggressive embryonal brain tumor comprising 1% of pediatric CNS tumors. The clino-molecular heterogeneity and developmental origins underlying PB are poorly understood; therefore, we have assembled a molecular cohort of histologically defined PBs (n=43) with corresponding outcome data. Methylation profiling revealed four molecularly and clinically distinct PB subgroups, including two novel entities. Mutational and transcriptional analysis identified characteristic molecular features of each subgroup, such as mutations in the miRNA processing pathway or FOXR2 proto-oncogene overexpression. Furthermore, subgroups exhibited differences in propensity for metastasis, cytogenetics, and clinical outcomes. To dissect PB developmental origins and resolve PB subgroup biology, we have employed a combination of single-cell genomics and genetically engineered mouse modeling. We created a single-cell transcriptional atlas of the developing mouse pineal gland across 11 timepoints and are currently integrating these data with single nucleic RNA-seq data of human PB (n=25). Single-cell analysis of the developing pineal gland revealed three distinct populations of pinealocytes, referred to as early, mid and late pinealocytes, which segregate by developmental trajectories that lie along a single latent trajectory. Preliminary results implicate significant associations between PBs and the early pinealocyte population as well as subgroup-specific differences in intratrumor heterogeneity. Furthermore, this knowledge has informed the downstream generation of high throughput proteomics datasets. Preclinical results held his head. CT scan and MRI revealed a large mass in the right frontal lobe with midline shift. Subtotal tumor resection was done. Histological and immunohistochemical analyses was consistent with ETANTR in one laboratory and substantiates early pinealocytes as the probable cell-of-origin for this PB subgroup.

ETMR-07. ETANTR: A RARE TUMOR IN A RESOURCE-LIMITED SETTING
Jolanta Haymayan 1, Manushak Aravanyan 2, Anna Aravanyan 2, Ruzanna Panyan 1, Samvel Ikanayn 1, Samvel Dzamelian 1, Garik Hovhannisyan 1, Parandzem Khachaturyan 2, Georgy Tamanyan 2, and Samvel Bardakchyan 2, 1Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof, R, Yeolyan, Yerevan, Armenia, 2Harrington Institute of Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

INTRODUCTION: Embryonal tumor with abundant neuropil and true rosettes (ETANTR) is a rare aggressive brain tumor with low survival rates. There are about 80 cases reported in the literature since 2000 when it was first described. There is no standard treatment scheme for ETANTR yet. CASE REPORT: A 2 years old boy presented with a month-long of headache and inability to hold his head. CT scan and MRI revealed a large mass in the right frontal lobe with midline shift. Subtotal tumor resection was done. Histological and immunohistochemical analyses was consistent with ETANTR in one laboratory and substantiates early pinealocytes as the probable cell-of-origin for this PB subgroup.

ETMR-09. THE ROLE OF RADIATION FOR EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES
Akhide Kondo, Mario Suzuki, Junya Fujimura; Juntendo University, Tokyo, Japan

BACKGROUND: Embryonal tumor with multilayered rosettes (ETMR) is a challenging tumor. The prognosis of the patients suffering from this tumor is extremely poor. We have survival cases of more than 12 months. However, the stage of illness is different. In this setup, we have reviewed our treatments in this study. TREATMENT COURSE: We have two cases. Both have relapsed after the same chemotherapy after the same radiation therapy. After the recurrence we used protocols that were included extended resection, second radiation therapy with bevacizumab. METHODS: We compared molecular biological evaluations for the initial and recurrent tumors. The resection rate at the time of second removal and the intensity of radiation therapy intensity were compared: RESULTS: We succeeded to remove the tumors with the confirmation of intraoperative MRI. No apparent differences could be seen in molecular biological characters of tumors before and after treatment. There was a difference between the period until radiation therapy and the irradiation methods. CONCLUSIONS: This tumor is untreatable only by resection. We need the second radiation therapy with bevaczumab. It was presumed that tumor should be irradiated quickly with appropriate irradiation field and dose.

ETMR-10. EARLY FOCAL RADIOTHERAPY AND TEMOZOLOMIDE FOLLOWING COMPLETE RESECTION APPEAR SUPERIOR TO INTENSIVE CHEMOTHERAPY AND DELAYED RADIOTHERAPY IN CHILDREN WITH EMBRYONAL TUMORS WITH MULTILAYERED ROSETTES (ETMR)
Lise Mary1, Johannes Gojo1, Andreas Pery1, Amedeo Azzi1, Karin Dieckmann1, Christine Haberl1, Thomas Czech1, and Irene Slavc1, 1Medical University of Vienna, Department of Pediatrics and Adolescent Medicine, Vienna, Austria, 2Medical University of Vienna, Department of Neurosurgery, Vienna, Austria

BACKGROUND: Embryonal tumor with multilayered rosettes (ETMR) is a rare, aggressive embryonal central nervous system tumor characterized...
by LIN28A expression and alterations in the C19MC locus. ETMRs predominantly occur in young children, have a dismal prognosis, and no definitive treatment guidelines have been established. We report on our experience in nine consecutive patients. METHODS: Between 2006 and 2017, nine patients were diagnosed with ETMR. Median age was 25 months (5–38); seven were treated for primary diagnosis, two referred with progressing tumors, seven diagnosed prospectively, two retrospectively, five were located supratentorially, the remaining one in the brainstem. RESULTS: Seven patients had a gross total resection, one a partial resection and one a biopsy at initial diagnosis, followed by second resections at progression. Six patients were treated with intensive chemotherapy regimens including high-dose chemotherapy in three patients and all recurred after a median of 6 months (range 2–11) and all except one patient who died after high-dose chemotherapy, succumbed to their disease after a median of 13 months (range 7–28). Two patients were treated with gross total tumor resection, early focal radiotherapy and concomitant temozolomide followed by temozolomide and intrathecal therapy for one year and both are in continuous complete remission 31 and 46 months after diagnosis. CONCLUSION: Gross total resection followed by early focal radiotherapy, temozolomide, and intrathecal chemotherapy seem to be superior to intensive chemotherapy including high-dose chemotherapy. Steady progression was observed in both patients with initial biopsy and PR only despite intensive therapy. Radiotherapy at recurrence/progression was not successful.

ETMR-11. A CASE OF PRIMARY DIFFUSE LEPTOMENINGEAL PRIMITIVE NEUROECTODERMAL TUMOR Masahiro Sugawa,1 Keita Terashima,1 Yukihito Matsukawa,1 Takehiro Minatogawa,1 Hiroshi Ioshiki,1 Shinji Muromoto,1 Meri Uchiyama1, Kenichi Sakamoto,2 Yoshishiro Gocho,1 Tomoo Osumi,2 Yoko Shioda,1 Chikako Kiyotani,3 Motohiro Kato1, Daikuse Tomizawa,1 Kenichi Usami,4 Hideki Ogawa3, Yoshiaki Tsutsumi,3 Masayuki Nakano,4 Takako Yoshio,1 and Mikimasa Katori,1 1Department of Radiology, National Center for Child Health and Development; 2Department of Neurosurgery, National Center for Child Health and Development; 3Department of Radiology, National Center for Child Health and Development; 4Department of Pathology, National Center for Child Health and Development, Tokyo, Japan

BACKGROUND: Primary diffuse leptomeningeal primitive neuroectodermal tumor (PDL PNET) is a rare embryonal brain tumor which arises primarily in the meninges without an intraparenchymal mass. Few previous reports of this condition exist, and the clinical outcomes are poor. We herein report a case of a child with PDL PNET and present a cursory review of the literature. CASE: A 3-year-old female patient was seen at a local clinic due to vomiting, headaches, and seizures. As a head MRI revealed hydrocephalus but no mass, acute encephalopathy was initially diagnosed. She received steroid pulse therapy, but the symptoms progressed to hallucination and lethargy. Another MRI at the 1-month follow-up revealed diffuse leptomeningeal enhancement. Thereafter she was transferred to our hospital. A spine MRI revealed spinal dissemination. She underwent a dura mater biopsy, and the pathological analysis led to the diagnosis of PDL PNET. Following chemotherapy and radiotherapy, hydrocephalus resolved, and the external ventricular drainage was removed. A follow-up MRI showed that the leptomeningeal enhancement decreased during the four cycles of chemotherapy without radiotherapy. The patient is scheduled to receive high-dose chemotherapy as consolidation therapy. CONCLUSION: PDL PNET is extremely rare, and its diagnosis is often delayed. Treatment of PDL PNET is very difficult due to its aggressive course, and surgical resection is impossible. Early diagnosis may help improve outcomes.

ETMR-12. EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES: A SINGLE CENTER EXPERIENCE Satomi Yoshihara,1 Michiru Sugawara,1 Michiaki Okuwa,1 Yuki Arakawa1, and Makoto Mori,1 1Department of Pediatric Hematology/Oncology, Saitama Children's Medical Center, Saitama, Japan

BACKGROUND: Embryonal tumor with multilayered rosettes (ETMR) is a rare embryonal brain tumor which predominantly occurs in the central nervous system and is usually diagnosed in children aged <2 years. Currently, because no defined treatment strategy has been reported, treatment regimens are often extrapolated from other embryonal tumors. Therefore, data collection of ETMR cases is important for further understanding ETMR. Here, we present our experience with four patients with ETMR. MATERIAL AND METHODS: Patients were diagnosed at a pathological institute. METHODS: From 1993 to 2016 at Sattama Children's Medical Center were included. Their clinical data were retrospectively analyzed. RESULTS: This study included four cases of ETMR (one male and three females). The mean age at diagnosis was 29.3 months (range 15–37 months). Presenting symptoms included seizures, headache, vomiting, and headache. The mean maximal tumor diameter was 42.5 mm. The tumor locations included frontal lobe, temporal lobe, occipital lobe, cerebellum, and brainstem. Gross total resection was achieved in two cases. Fluorescence in situ hybridization analysis demonstrated amplification of C19MC (Xq11–q12), one chromosome in all cases, and diffuse positive expression was observed in the immunohistochemical staining for LIN28A. Systemic postoperative chemotherapy was administered to all patients. Three patients received intrathecal therapy and three were irradiated. The mean overall survival and progression-free survival were 43.3 and 42 months, respectively.

ETMR-13. NFI GENES IN ETMR TUMORIGENESIS AND NEURODEVELOPMENT Jens Rump1,2, Sandor Lambo1, Jonathan Lim1, Monika Maurer1, Stefan Pfafter1,3, Linda Richards1, Marcel Kool1,2, Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands, Queensland Brain Institute, University of Queensland, Brisbane, Australia, 1Sattama Children's Medical Center, Tokyo, Japan, 2Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Embryonal tumors with multilayered rosettes (ETMRs) are aggressive pediatric brain tumors with a universally poor prognosis. These tumors are commonly characterized by amplification of C19MC, but other miRNA-related aberrations, such as Dicer mutations or MIR17HG amplifications, are also observed. Nevertheless, it remains unknown how these aberrations are driving the tumorigenesis. We applied miRNA target prediction to investigate the downstream targets shared by these aberrations and normal brain development and tumorigenesis. The network of one NFI family of transcription factors were found to be top candidates shared by both miRNA clusters. These genes are expressed at very low levels in ETMRs, in contrast to other brain tumors. During normal brain development these genes are expressed in radial glial progenitors and are required for the transition of proliferation to differentiation. Since radial glial progenitors are the potential cell-origin of ETMRs, we hypothesize that downregulation of NFI is required for the proliferative, undifferentiated state of ETMRs. Indeed, mouse models with deletion of an Nfi family member display sustained proliferation and delayed differentiation of radial glial progenitors during development. This leads into brain overgrowth, which has also been observed in humans with intellectual disabilities caused by NFI haplosufficiency. When multiple Nfi family members are simultaneously deleted in mice, the proliferation of vincristine-resistant ETMR-like cells is enhanced, and both neurogenesis and gliogenesis are inhibited, resulting in a neurodevelopmental disorder similar to that of human ETMR tumors. Hence, downregulation of NFI genes resulting from miRNA alterations could contribute to the developmental state and possibly tumorigenesis of ETMRs.

ETMR-14. TREATMENT OF EMBRYONAL TUMOURS WITH MULTILAYERED ROSETTES (ETMR) WITH CARBOPLATIN-ETOPOSIDE INDUCTION AND TANDEM HIGH-DOSE CHEMOTHERAPY WITHIN THE PROSPECTIVE HIT-TRIALS AND REGISTRIES Boit-Ole Juhanke1, Marco Gessi2, Nicolas Ulrich Gerber3, Carsten Friedrich4, Christine Haberer2, Martin Mynarek2, Brigitte Bösön3, Rolf-Dieter Kortmann2, Monika Warmuth-Metz2, Ulrich Schüller4, Stefan Michael Pfafter1,5, Torsten Pietsch1,6, Marcel Kool2,7, Stefan Rutkowski2, Katja von Hoff1

1Clinic for Paediatric Haematology and Oncology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, 2Neuropathology Unit, Division of Pathology, Fondazione Policlinico Universitario “A. Gemelli” IRCCS, Catholic University, Rome, Italy, 3University Children's Hospital Zürich, Zürich, Switzerland, 4Children's Clinic, University Medical Centre Rostock, Rostock, Germany, 5Division of Neuroradiology and Interventional Neuroradiology, Medical University of Vienna, Wien, Austria, 6Institute for Diagnostic and Interventional Neuroradiology, University Hospital Würzburg, Würzburg, Germany, 7Clinic for Radiotherapy, Leipzig University Medicine, Leipzig, Germany, 8Institute of Neuroradiology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, 9Department of Pediatric Hematology and Neuro-Oncology • December 2020