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: From January 2006 to June 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, two infratentorially, 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 reoccurred 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 Sugawa1, Keita Terashima1, Yukihito Matsukawa1, Takahiro Motomiya1, Yoshihiko Ishioda1, Shintaro Sato2,3, Kenichi Sakamoto1, Yoshihiro Gocho1, Tomoo Osumi2, Yoko Shioda1, Chikako Kiyotani1, Motohiro Kato1, Daisuke Tomizawa1, Kenichi Usami4, Hideki Ogwara4, Yoshibaki Tsutsui1, Masayuki Nakano5, Takako Yoshiohara1, and Kimikazu Matsumoto1.1Children’s Cancer Center, National Center for Child Health and Development, Tokyo, Japan, 2Department of Neurosurgery, National Center for Child Health and Development, Tokyo, Japan, 3Department of Radiology, National Center for Child Health and Development, Tokyo, Japan, 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 after one month and she was referred to our hospital. A spine MRI revealed spinal dissemination. She underwent intrathecal chemotherapy consisting of vincristine, cyclophosphamide, and etoposide, cispatin, and intrathecal methotrexate injections twice monthly after the initial presentation. The progressive hydrocephalus was managed with external ventricular drainage. Two weeks after the first cycle of chemotherapy, 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 further research is needed to confirm these results.

ETMR-13. NFI GENES IN ETMR TUMORIGENESIS AND NEURODEVELOPMENT Jens Ruml1, Sander Lambo1, Jonathan Lim1, Monika Mauermann1, Stefan Pfister1, Linda Richards1, Marcel Kool1, 2Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands, 1Queensland Brain Institute, University of Queensland, Brisbane, Australia, 2Max Planck Institute for Developmental Biology, 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 most frequent 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-of-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 haploinsufficiency. When multiple Nfi family members are simultaneously disrupted in mice, the progression of vincristine-induced hydrocephalus is decreased, and gliogenesis are inhibited, resulting in a neuropathology similar to that of human ETMR tumors. Hence, downregulation of NFI genes resulting from miRNA aberrations could contribute to the developmental state and possibly tumorigenesis of ETMRs.

ETMR-14. TREATMENT OF ETMR TUMOURS WITH MULTILAYERED ROSETTES (ETMR) WITH CARBOPLATIN-ETOPOSIDE INDUCTION AND TANDEM HIGH-DOSE CHEMOTHERAPY WITHIN THE PROSPECTIVE HIT-TRIALS AND REGISTRIES Bettina-olie Jahnke1, Marcio Gessi2, Nicolas Ulrich Gerber3, Carsten Friedrich4, Christine Haberer1, Martin Mynarek5, Brigitte Bisons6, Rolf-Dieter Kortmann7, Monika Wurmuth-Metz8, Ulrich Schüller9, Stefan Michael Pfister9,10, Torsten Pietsch11, Marcel Kool1,10, Stefan Rutkowski1, Katja von Hoff1.

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ETMR-15. USE OF HIGH-DOSE CHEMOTHERAPY FOR TWO CHILDREN WITH EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES
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Embyonal tumor with multilayered rosettes (ETMR) is a new entity defined in the 4th revised edition of the WHO classification of tumors of the central nervous system. It is a high-grade, radiation-resistant, embryonal tumor with multilayered rosettes, and chemotherapy is considered to be necessary for ETMR. The efficacy of chemotherapy for ETMR in Japan has not been established. Here, we report different clinical courses for two children with localized ETMR treated with the Sr. medulloblastoma-96 (SMB96) regimen, which consists of four cycles of high-dose chemotherapy with autologous peripheral blood stem cell transplantation. For both children, the diagnosis of ETMR, C19MC-altered was confirmed after gross total tumor resection. Multihapten chemotherapy was administered following conventional irradiation and a local boost. One month after completion of the treatment, one patient experienced local recurrence but has been in remission for over 2 years after tumor resection and stereotactic irradiation with a CyberKnife and treatment every three weeks with bevacizumab. The other patient also experienced local recurrence after the third cycle of chemotherapy and several times thereafter. Although she again underwent tumor resection and local irradiation, her tumor grew larger and invaded. Because her prognosis was very poor, her parents chose only palliative care. Based on our experience, we believe that continuous chemotherapy at conventional doses is preferred over intensive dose chemotherapy such as SMB96. However, the number of reports on chemotherapy for ETMR is still small, and a prospective multicenter trial is needed to establish effective chemotherapy for ETMR.

ETMR-17. SINGLE-CELL TRANSCRIPTOME ANALYSIS OF ETMR PATIENT SAMPLES
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Brain tumors are comprised of cells with heterogeneous genetic and transcriptional states, resulting in substantial phenotypic diversity. This diversification is particularly evident in embryonal tumors, for which therapies urgently need to be included in an upfront setting. We present data showing the effect of DFMO (5,6-difluoromethylornithine) in ETMR, an ODC1 inhibitor known to reduce gins and ETMR-specific oncogenic pathways. These timely results provide unparalleled insights into the molecular underpinnings of the phenotypic heterogeneity observed in ETMR. Analyses aimed at further integrating malignant cell type abundances with genetic alterations and clinical annotations, and therapeutic targeting of malignant cell populations using in-vitro models are currently ongoing.

ETMR-18. TARGETING LIN28 IN ETMR WITH ODC1 INHIBITOR DFMO
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Embryonal tumor with multilayered rosettes (ETMR), is an aggressive brain tumor primarily occurring in young patients (<4 years of age) and characterized by C19MC amplification and Lin28 overexpression. These genetic hallmarks have been shown to participate in driving ETMR in a C19MC-Lin28-MYCN circuit. Reducing Lin28 disrupts this circuit and reduces cell viability in ETMR models. Investigation of therapeutic agents targeting this pathway is required to provide new treatment options for this deadly disease. We present data showing the effect of DFMO (5,6-difluoromethylornithine) in ETMR, an ODC1 inhibitor known to reduce Lin28 in neuroblastoma. DFMO treatment of the ETMR cell line BT-183 resulted in a significant reduction of intracellular Lin28 protein levels (P<0.05) as indicated by flow cytometry. In concert with this reduction in Lin28, there was a significant reduction in viable cells (P<0.05), and the number of CD133+ cells were reduced 2-fold (P<0.05). Highthroughput drug testing of BT-183 identified a number of additional therapeutic agents with potential therapeutic efficacy for ETMR and combining these with cytototoxic agent DFMO demonstrated the potential use of these drugs in combination. These in vitro data were complemented by testing of DFMO in an in vitro stereotactic xenograft ETMR model, with inhibition of tumor burden monitored by bioluminescent imaging of the tumors. Together this work demonstrates that Lin28 targeted agents such as DFMO in combination and integrating these types of agents into treatment strategies for ETMR may lead to better outcomes.