Short Study Report for Health Authorities

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Name of Sponsor/Company: EORTC	Individual study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
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Title of the Study	*Personalized Risk-Adapted Therapy in Post-Pubertal Patients with Newly Diagnosed Medulloblastoma (PersoMed-I)* *1634 protocol v5.0 20241021.pdf*	
Investigators & Study Centres		

	Randomization status			
	Screened failure (N=9)	Randomized (N=10)	Not randomized (N=1)	Total (N=20)
	N (%)	N (%)	N (%)	N (%)
Study Site				
Universitaetsklinikum Tuebingen- Crona Kliniken	1 (11.1)	2 (20.0)	0 (0.0)	3 (15.0)
Universitaetsklinikum - Essen	2 (22.2)	1 (10.0)	0 (0.0)	3 (15.0)
Universitaetsklinikum Hamburg-Eppendorf KE - University Cancer Center	1 (11.1)	1 (10.0)	0 (0.0)	2 (10.0)
Charite - Universitaetsmedizin Berlin - Campus Mitte	0 (0.0)	1 (10.0)	0 (0.0)	1 (5.0)
Universitaetsklinikum Bonn	1 (11.1)	0 (0.0)	0 (0.0)	1 (5.0)
Ludwig-Maximilians-Universitaet Muenchen - Campus Grosshadern	0 (0.0)	1 (10.0)	0 (0.0)	1 (5.0)
UniversitaetsMedizin Mannheim	0 (0.0)	1 (10.0)	0 (0.0)	1 (5.0)
Universitaetsklinikum Regensburg	0 (0.0)	1 (10.0)	0 (0.0)	1 (5.0)
University Hospital Frankfurt -Senckenberg Institute of Neurooncology	0 (0.0)	1 (10.0)	0 (0.0)	1 (5.0)
CHU de Toulouse - Institut Claudius Regaud - IUCT oncopole	1 (11.1)	0 (0.0)	0 (0.0)	1 (5.0)
Hospital Clinic de Barcelona	0 (0.0)	0 (0.0)	1 (100.0)	1 (5.0)
P3063-Universitaetsklinikum Tuebingen- Crona Kliniken	1 (11.1)	0 (0.0)	0 (0.0)	1 (5.0)
Peter Maccallum Cancer Institute	1 (11.1)	0 (0.0)	0 (0.0)	1 (5.0)
Princess Alexandra Hospital - University Of Queensland	1 (11.1)	0 (0.0)	0 (0.0)	1 (5.0)
Royal North Shore Hospital	0 (0.0)	1 (10.0)	0 (0.0)	1 (5.0)

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Publication (reference)	*The overall study data have not been published yet, however, publications about part of the data are:* Hertler C, Felsberg J, Gramatzki D, Le Rhun E, Clarke J, Soffietti R, Wick W, Chinot O, Ducray F, Roth P, McDonald K, Hau P, Hottinger AF, Reijneveld J, Schnell O, Marosi C, Glantz M, Darlix A, Lombardi G, Krex D, Glas M, Reardon DA, van den Bent M, Lefranc F, Herrlinger U, Razis E, Carpentier AF, Phillips S, Rudà R, Wick A, Tabouret E, Meyronet D, Maurage CA, Rushing E, Rapkins R, Bumes E, Hegi M, Weyerbrock A, Aregawi D, Gonzalez-Gomez C, Pellerino A, Klein M, Preusser M, Bendszus M, Golfinopoulos V, von Deimling A, Gorlia T, Wen PY, Reifenberger G, Weller M. Long-term survival with IDH wildtype glioblastoma: first results from the ETERNITY Brain Tumor Funders' Collaborative Consortium (EORTC 1419). Eur J Cancer. 2023 Aug;189:112913. doi: 10.1016/j.ejca.2023.05.002. Epub 2023 May 8. PMID: 37277265.	
Phase of development	Observational study	
Studied period	Date of first enrolment: 05/07/2015 Date of last enrolment: 12/04/2022 Clinical cut-off date: N/A Date of early termination, if any N/A	

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Substantial changes to the protocol	On 14 January 2021, the first scientific amendment was approved. This amendment included a risk/benefit assessment related to COVID-19, which was added to the COVID appendix M. Additionally, the conditions for administering the COVID-19 vaccine within the study were described. The second amendment was approved on 20 April 2021. The amendment involved splitting the initial unified Patient Information Sheet and Informed Consent (PISIC) into two separate documents: Patient Information and Informed Assent for post-pubertal patients under the legal age of consent. Parental/Legal Guardian Information and Informed Consent for patients under the legal age of consent. The third amendment was approved on 25 February 2022. This amendment involved several changes to the protocol and Patient Information Sheet and Informed Consent (PISICs) based on feedback from competent authorities and ethics committees. The specific changes included: Redefining the inclusion criteria to specify the definition of post-pubertal patients.Removing patients with ermline alterations of TP53, PTCH, SUFU, BRCA2, and PALB2 from the inclusion criteria and changing them to exclusion criteria. Clarifying that the administration of Sonidegib should not be interrupted. The fifth amendment was approved on 17 March 2023. This amendment added a France-specific exclusion criterion to the clinical trial protocol, which excluded patients who were under tutorship or curatorship or deprived of liberty. The seventh amendment was submitted and approved on 10 October 2023. This amendment involved relaxing the eligibility criteria to improve the accrual rate. Specifically, it included the pooling of the Group-3 subgroup with Group-4. On 21 October 2024, nineth amendment was approved. It included information on the use of Vincristine, Lomustine, and Sonidegib for CTR compliance, updates on the regulatory status of cytotoxic drugs, and the addition of Sonidegib in the experimental arm for SHH mutated patients. It also outlines extra end-of-study rules, procedures for study suspension or termination, and early termination of recruitment, along with follow-up and analysis procedures and changes to the CRF and data management. Amendments 4, 6 and 8 were for administrative purposes only.	

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Objective(s)	Primary objective was to compare progression-free survival (PFS) by central review of a personalized intensity-modulated therapy (experimental arm; sonidegib) vs. standard therapy in the SHH-activated subgroup in post-pubertal patients with newly diagnosed standard risk medulloblastoma. Secondary objectives were • To compare PFS by central reviewer in the WNT & Group 4 subgroups • To compare PFS by local investigator in the 3 molecular • subgroups • To compare overall survival (OS) in the 3 molecular • subgroups • To evaluate safety and tolerability profile • To evaluate short- and long-term health-related quality of life (HRQoL) with a particular emphasis on the social functioning scale • To evaluate issues linked to survivorship (fear of recurrence, having problems with insurance/mortgage, work opportunities, life plans/goals and relationships with family or friends) • To evaluate short- and long-term neurocognitive function (NCF) • To evaluate short- and long-term endocrine function • To assess the incidence of second malignancies	
Methodology	This study was a multicentre, randomized, controlled, open label phase II trial.	

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Number of patients Number planed (Statistical design)	In the SHH subgroup, which constitutes 70% of the study population, A total of 128 eligible patients (64 per arm) had to be randomized, For the WNT subgroup and Group 3 & Group 4 subgroup, each representing 15% of the population, 28 patients per subgroup had to be randomized, including 3 M1 and 25 M0 patients. Only M0 patients had to be randomized between the standard and experimental arms, while M1 patients would be observed. The total number of per-protocol (PP) patients is 184, and with an estimated 10% non-PP rate, 205 intent-to-treat (ITT) patients were expected to be randomized.	
Number analysed	The study was closed anticipatively for poor accrual. 20 patients were registered (only SHH). 10 SHH patients were randomized (5 in each treatment arm) 5 out of 10 SHH patients were included in the per protocol population 5 patients out of 10 SHH were included in the safety population 0 WNT and group 3 & group 4 patients were recruited.	

Diagnosis and main criteria for inclusion	**Inclusion Criteria** **<u>At Registration:</u>** • Written informed consent must be given according to ICH/GCP and national/local regulations. For patients under the age of legal consent, consent must be obtained from the parent(s) or legal representative. • FFPE tumour tissue from surgical resection and whole blood for central pathology review must be available. **<u>At Enrolment/Randomization:</u>** • Newly diagnosed, histologically proven, genetically classified, centrally confirmed medulloblastoma. • Molecular subtypes include medulloblastoma, SHH-activated, M0-1; WNT-activated, M0-1; Group 3 & Group 4, M0-1. • Histologic subtypes include classic (CMB), desmoplastic/nodular (DNMB), with extensive nodularity (MBEN), and large cell/anaplastic (LCA). • Adults (≥18 years) in WNT-activated, Group 3, and Group 4 medulloblastoma. • Post-pubertal patients (<18 years, M0 only) or adults (18 years or above, M0 or M1) in SHH-activated medulloblastoma. • Patients (<18 years) must have a radiologically confirmed bone age of minimum 15 years for females and 17 years for males. • Clinical status within 2 weeks of randomization/enrolment: Karnofsky 50-100, NANO-score 0 to 9. • No CNS metastasis on MRI (cranial and spinal) and no evidence of extra-CNS metastasis. **Exclusion Criteria** **At Registration:** • Prior treatment for medulloblastoma. • Unavailability of central review pathology results. **<u>At Enrolment/Randomization:</u>** • Known prognostic markers (MYC/MYCN amplification and/or TP53 germline alteration) in post-pubertal patients. • Inability to start radiotherapy within 56 days after surgery • Significant sensorineural hearing deficit as defined by pure tone audiometry. • Any medical contraindication to radiotherapy or chemotherapy. • Hypersensitivity to contrast medium for MRI or towards the active substance of any study drugs or their excipients. • Current use of BCRP substrates such as mitoxantrone, methotrexate, topotecan, imatinib, or irinotecan. • Concurrent severe or uncontrolled medical disease that would compromise the safety of the patient or the ability to complete the study.

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	• Prior or second invasive malignancy, except certain low-risk cancers. • Known history or current evidence of active Hepatitis B or C, or HIV infection. • Presence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol.	

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Treatment Test product, dose and mode of administration (batch number if applicable). Duration of treatment.	**<u>Radiotherapy</u>** Radiotherapy is administerdfor craniospinal irradiation and boost irradiation. For adult SHH M0-1, adult WNT M0, and adult Group 3 & Group 4 M0, radiotherapy to the cranio-spinal axis was administered at 35.2 Gy in 22 daily fractions of 1.6 Gy, followed by a boost to the posterior fossa/tumour site of 19.8 Gy in 11 daily fractions of 1.8 Gy, totaling 55.0 Gy in 33 daily fractions. For post-pubertal SHH M0, the dose was 23.4 Gy in 13 daily fractions of 1.8 Gy, with a boost of 30.6 Gy in 17 daily fractions, totaling 54.0 Gy in 30 daily fractions. The standard arm consisted of 33 radiotherapy days, while the experimental arm consisted of 30 radiotherapy days. **<u>Lomustine</u>** Lomustine was part of the maintenance chemotherapy regimen. Lomustine was administered orally at a dose of 75 mg/m² on Day 1 of a 6-week cycle. Up to 6 cycles were administered during the maintenance chemotherapy phase. **<u>Cisplatin</u>** Cisplatin is administered in the maintenance chemotherapy regimen. Cisplatin was administered intravenously at a dose of 70 mg/m² on Day 1 of a 6-week cycle. Up to 6 cycles were administered during the maintenance chemotherapy phase. **<u>Vincristine</u>** Vincristine was included in both concomitant and maintenance chemotherapy. Vincristine was administered intravenously at 1.5 mg/m² (maximum 2 mg) every second week during radiotherapy and on Days 1 and 15 of a 6-week cycle during maintenance chemotherapy. Up to 6 cycles were administered during the maintenance chemotherapy phase. **<u>Sonidegib</u>** Sonidegib was used in the experimental arm for SHH-activated medulloblastoma. It was included in both concomitant and maintenance chemotherapy Sonidegib was administered orally at a dose of 200 mg per day, starting from the first day of radio-chemotherapy until the last day of maintenance therapy. Sonidegib was administered continuously from the first day of radio-chemotherapy until the end of maintenance chemotherapy (i.e. up to 6 cycles of standard drugs).	
Reference therapy, dose and mode of administration (batch number if applicable)	N/A	

Criteria for evaluation	The criteria for evaluation include several key aspects: MRI and CSF Cytology: MRI assessments were used to evaluate brain and spine lesions, with specific criteria for CR, PR, SD, and PD. CSF cytology was also used to assess response, requiring negative results for CR if tumour cells were present at baseline. Neurologic Exams and Steroid Use: Neurologic exams were performed as per protocol, and stable or improving conditions were required for CR and PR. Steroid use should be stable or less than baseline for CR and PR. Extra-CNS Disease and Serum Markers: For extra-CNS disease, no new sites of disease should have been be present for CR and PR. Serum or CSF markers like AFP and βhCG had to be within normal range for CR.
Efficacy	Progression-Free Survival (PFS): PFS was the primary endpoint of the trial and had to be assessed by central review using Response Assessment in Paediatric Neuro-Oncology (RAPNO) criteria. PFS as defined as the time from the date of randomization until the date of the first objective progression according to RAPNO criteria, as determined by the local investigator and reviewed within one week by a panel of central reviewers, or the date of the patient's death, whichever occurs first. Patients without evidence of progression would be censored at the last date of disease follow-up assessment. Overall Response Assessment: The response had to be assessed by central review using RAPNO criteria categorized into Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD) based on specific criteria. Overall Survival was defined as the time calculated from the date of randomization up to the date of death from any cause. For patients who were still alive or lost to follow-up at the time of analysis, survival would be censored at the last follow-up visit date. Event-Free Survival (EFS) was defined as the time from the date of randomization until the date of the first objective progression according to RAPNO criteria, the date of the patient's death, or the occurrence of a new primary malignancy, whichever occurs first. Patients who did not experience any of these events would be censored at the date of their last follow-up visit. This definition ensured that EFS captures not only disease progression but also other significant events that impact patient outcomes.

Safety	For the safety analysis: All adverse events were recorded, and the investigator assessed whether these events were drug-related. The collection period for adverse events started from registration and continued until five months after the last treatment intake or administration. The study used the International Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, for adverse event reporting. The highest CTCAE grading per cycle and per patient was computed for the analysis. Serious Adverse Events (SAEs) were defined by the Good Clinical Practice Guideline and had to be immediately reported. SAEs included events that resulted in death, were life-threatening, required hospitalization, resulted in disability, or were medically important. The cause of death had to be reported, and toxic death was defined as death due to adverse events that are not confirmed as unrelated. Adverse Events of Special Interest (AESI) included neurological, auditory, cognitive, kidney, endocrine, and radiotherapy-associated adverse events.
Neurocognition/Quality of Life	Neurocognitive Function Evaluation The neurocognitive function (NCF) evaluation had to use a core testing battery that includes the HVLT-R (Part A Free recall, Part B Delayed recall, Part C Delayed recognition), TMT (Part A and Part B), COWA, MOS scale, and the Schmahmann CCAS scale. These tests had to be administered in one session by a certified examiner. The schedule for NCF assessments was 14 days prior to enrolment, on Day 1 of cycle 3, at the end of treatment, and annually for five years during follow-up. Quality of Life Evaluation Quality of life (QoL) had to be assessed using the EORTC QLQ-C30 and QLQ-BN20 questionnaires. The QLQ-C30 included functional and symptom scales, as well as a global health status/QoL scale. The QLQ-BN20 focused on symptoms specific to brain tumour patients. Additionally, the core survivorship questionnaire (QLQ-SURV111) had to be used. The schedule for HRQoL assessments was aligned with patient visits, and the questionnaires had to be completed at the hospital.
Fertility sub-study	Fertility sub-study The Fertility sub-study had to involve administering a fertility questionnaire to patients participating in mandatory project 1A (Oncofertility Care and Outcomes) at diagnosis, end of treatment, and subsequently at 12 months, 36 months, and 60 months after

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	the end of treatment. For patients participating in optional project 1B (Assessment of Fertility Analysis), fertility counselling and potential assessments, including blood samples and reproductive hormone analysis, had to be conducted at the same time points.	
Statistical methods	Statistical Methods for Analysis The primary endpoint, Progression-Free Survival (PFS), had to be analyzed using a stratified Log-Rank test adjusted for stratification factors assessed at randomization, specifically in the SHH subgroup. The hazard ratio (HR) had to be calculated using Cox's proportional hazards model, and Kaplan-Meier survival curves would be presented with summary statistics. For all analyses, a significance level of 0.05 would be used, and 95% confidence intervals would be estimated where applicable. Event-Free Survival (EFS) and Overall Survival (OS), had to be assessed using Kaplan-Meier curves and unstratified Log-Rank tests. The treatment HR would be calculated by an unstratified Cox's proportional hazards model, with results presented with 95% confidence intervals. The significance level for these analyses would also be set at 0.05. For response analysis, the best overall response would be presented in a contingency table with frequencies and percentages. Objective response rates (CR/PR) would be reported with exact binomial two-sided 95% confidence intervals. Neurocognitive Function (NCF) and Health-Related Quality of Life (HRQoL) would be analyzed using descriptive statistics for values and changes from baseline. A linear mixed model would be used for primary NCF analysis, and the Reliable Change Index (RCI) would define cognitive failure. The association between NCF and HRQoL over time would be analyzed, with a significance level of 0.05 and 95% confidence intervals estimated for relevant comparisons. No formal comparison of safety endpoints was conducted, and no p-values or confidence intervals were calculated for safety analyses.	

Summary of Results	Summary of Results Due to low patient enrolment and the study chair's decision to discontinue the study, the planned results could not be delivered, and no statistical analysis was performed. However, study metrics were generated, including the total number of registered and enrolled patients, identification of screening failures, follow-up curves, eligibility criteria, and demographic, clinical, and pathologic characteristics at randomization. Data on stratification, baseline laboratory, treatment allocation, extent of treatment exposure, reasons for treatment discontinuation, disease status (including progressions and deaths), and quality-of-life completion rates were also presented. Summary of Accrual A total of 20 patients were registered over 10.5 months by 15 institutions, with an average registration rate of 1.3 patients per month. Ten patients were randomized within 8.5 months by 9 institutions, achieving an average randomization rate of 1.2 patients per month. All randomized patients were part of the SHH-activated subgroup, with no patients randomized in the WNT group or group Summary of Follow-up The median follow-up duration was 20.8 months in the control arm and 22.7 months in the experimental arm. Summary of Treatment Exposure One patient in the control arm mistakenly received Sonidegib, and their data were pooled with the experimental arm (n=6). In the control arm, 75% of patients started Lomustine treatment, with a median maintenance treatment duration of 37.3 weeks and a median relative dose intensity (RDI) of 90.3%. In the experimental arm, all patients started Lomustine treatment, with a median treatment duration of 37.4 weeks and a median RDI of 90.0%.
Safety Results	Summary of Safety In the control arm (n=4), severe (grade ≥3) adverse events included a 100% incidence of decreased white blood cell count and a 75% incidence of decreased neutrophil count. In the experimental arm (n=6), severe adverse events included a 66.7% incidence of both decreased neutrophil count and decreased white blood cell count. Sonidegib-related adverse events were observed, including anemia, gastrointestinal disorders, and musculoskeletal disorders. Serious adverse reactions associated with Sonidegib included severe nausea and dehydration. Cisplatin and Lomustine were also associated with serious adverse reactions, such as nausea and acute kidney injury. In the experimental arm, acute kidney injury and nausea were reasonably related to Sonidegib, while other AESI, including neurological and auditory events, showed no causal relationship to treatment.

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Efficacy Results	Summary of Efficacy All randomized patients were non-progressive and alive (n=10).	
Conclusions	The 1634 protocol trial aimed to evaluate the efficacy and safety of a personalized risk-adapted therapy, including sonidegib, for post-pubertal patients with medulloblastoma, focusing on progression-free survival (PFS) as the primary endpoint. Despite the trial's potential to improve outcomes and reduce radiotherapy-related toxicity, it faced significant challenges, including low patient enrollment, which led to the premature termination of recruitment. Consequently, the planned efficacy analyses could not be performed, but the trial still provided valuable insights into treatment delivery and safety, with follow-up data collected for at least five months post-treatment. The trial's design incorporated measures to minimize bias, such as randomization and stratification, and emphasized the importance of safety monitoring, particularly for dose-limiting toxicities associated with sonidegib. Although the trial did not achieve its intended sample size, it highlighted the feasibility of using a dose-attenuated chemotherapy regimen to manage toxicity and the potential of sonidegib as a targeted therapy for SHH-driven tumors.	
Date of Report	Final Study Report: 14/11/2025; Short Report: 18/11/2025	