SYNOPSIS – HRNBL2

EudraCT number	2019-001068-31		Version	V1.1	19/07/2019	
Title	"HR-NBL2: High-risk neuroblastoma study 2.0 of SIOP-Europe-Neuroblastoma/SIOPEN" Randomized, international and multicentric phase 3 study that evaluates and compares 2 treatment strategies in 3 therapeutic phases (induction, high-dose chemotherapy and radiotherapy) for patients with high-risk neuroblastoma.					
Abbreviated title	HR-NBL2		Phase	3		
Sponsor	Gustave Roussy 114 rue Edouard Vaillant 94805 Villejuif Cedex France					
Coordonnating Investigator	Dominique VALTEAU COUANET, MD, PhD Gustave Roussy					
Number of centers	Total	TBD	France	28 centers for inclusion	International	TBD
Indication	Patients with High Risk Neuroblastoma					
Background	In this protocol the term high-risk neuroblastoma refers to children with either: ▪ Stage M disease over the age of 12 months, any *MYCN* status ▪ L2, M or Ms neuroblastoma with *MYCN* amplification, any age High-risk neuroblastoma represents the largest neuroblastoma subgroup. The prognosis of these patients has been progressively improved over the years through an intensified induction regimen, surgery of the primary tumor, high-dose chemotherapy (HDC) followed by autologous stem cell rescue (ASCR), radiotherapy and immunotherapy. As a result of this strategy, the current 3-year event-free survival (EFS) is now around 40% from date of randomization and 55% for those patients who complete all the different parts of the treatment. However, a further improvement in patient outcome is warranted.					
Primary Objective	**R-I:** Comparison of the EFS rate of 2 induction regimens, GPOH and RAPID COJEC, in patients with high-risk neuroblastoma. **R-HDC:** Comparison of the EFS rate of single HDC with busulphan and melphalan (Bu-Mel) versus tandem HDC with Thiotepa followed by Bu-Mel in patients with high-risk neuroblastoma. **R-RTx:** Comparison of the EFS rate of 21.6 Gy radiotherapy to the preoperative tumor bed versus 21.6 Gy radiotherapy and a sequential boost up to 36 Gy to the residual tumor in patients with macroscopic					

	residual disease after HDC and surgery.
Secondary Objectives	1) To describe the EFS and overall survival (OS) from date of randomization of the whole cohort, 2) To describe the effect of RAPID COJEC and GPOH induction regimens on metastatic disease during and after the end of induction, 3) To assess the correlation of the response of metastatic disease during and after induction with survival (EFS and OS), 4) To describe the effect of HDC with Bu-Mel versus Thiotepa + Bu-Mel on progression-free survival (PFS) and OS, 5) To describe and compare the toxicity associated with RAPID COJEC and GPOH induction therapy, 6) To describe and compare the acute and long term toxicities of both HDC arms, 7) To describe the long term toxicities of dinutuximab beta, 8) To investigate the relationship between the quality of surgical resection of the primary tumor, local control and survival, 9) To investigate the impact of the radiotherapy dose on local relapse rate. 10) To collect data on selected circulating biomarkers, biological and genomic features (see Laboratory manual) to determine and compare the effect of these on response to treatment, EFS, incidence of relapse/progression and OS.
Exploratory Objectives	1) To conduct sub-group analyses to study the impact of R-I, R-HDC and R-RTx in subpopulations such as patients with L2-*MYCN* amplified neuroblastoma or patients according to age groups (infants, young children, older children and adolescents), 2) To validate prospectively the new international criteria for response assessment in neuroblastoma, 3) To validate prospectively the new international mIBG scoring methodology, 4) To evaluate the impact of mIBG-positive residual bone disease before HDC, after HDC and at the end of treatment on the risk of bone recurrence, 5) To prospectively study the relative prognostic value of planar vs SPECT-SPECT/CT(fusion) methodology of MIBG imaging, 6) To describe quality of standards of care: time from start of symptoms to histological diagnosis, time from diagnosis till initiation of treatment, proportion of dose reductions or interrupted chemotherapy cycles, time to start radiotherapy, among others.
Methodology	This is an international multicenter, open-label, randomized phase III trial including three sequential randomizations to assess efficacy of induction and consolidation chemotherapies and radiotherapy for patients with high-risk neuroblastoma. The first randomization **(R-I)** will compare the efficacy of two induction chemotherapies (RAPID COJEC and GPOH regimens) in a phase III setting. The primary endpoint will be the 3-year EFS from date of randomization . The R-I randomization will be stratified on age, stage, *MYCN* status and countries. The second randomization **(R-HDC)** will compare the efficacy of single

	HDC with Bu-Mel versus tandem HDC with Thiotepa followed by Bu-Mel. The primary endpoint is 3-year EFS calculated from the date of the R-HDC randomization. The R-HDC randomization will be stratified on the age, stage, *MYCN* status, induction chemotherapy regimen, response to induction phase and countries. The impact of local treatment in this phase III setting will be assessed, according to the presence or not of a macroscopic residual disease after surgery and HDC. In case of macroscopic residual disease, 21.6 Gy radiotherapy to the preoperative tumor bed will be randomized **(R-RTx)** versus the same treatment plus a sequential boost of additional 14.4 Gy to the residual tumor. The primary endpoint of R-RTx is 3-year EFS from the date of the R-RTx randomization. The R-RTx randomization will be stratified on age, stage, *MYCN* status, induction chemotherapy regimen, HDC regimen and countries. In case of no macroscopic residual disease, 21.6 Gy radiotherapy will be delivered to the preoperative tumor bed.
Inclusion Criteria **R-I randomization (RAPID COJEC/GPOH)**	At diagnosis (or up to 21 days after one cycle of chemotherapy for patients with localized neuroblastoma with *MYCN* amplification). R-I eligibility criteria: - Established diagnosis of neuroblastoma according to the SIOPEN-modified International Neuroblastoma Risk Group (INRG) criteria, High-risk neuroblastoma defined as: • Stage M neuroblastoma above 365 days of age at diagnosis (no upper age limit) and Ms neuroblastoma 12-18 months old, any *MYCN* status* <u>or</u> • L2, M or Ms neuroblastoma with *MYCN* amplification, any age * *In Germany, patients aged less than 18 months with stage M and without MYCN amplification will not be enrolled in HR-NBL2 trial.* - No previous chemotherapy (except one cycle of Etoposide-Carboplatin or**,** in Germany and Nertherlands, one course of the current protocol for low/intermediate risk neuroblastoma). - Females of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to initiation of treatment. Sexually active patients must agree to use acceptable and appropriate contraception while on study drug and for one year after stopping the study drug. Acceptable contraception is defined in CTFG Guidelines “Recommendations related to contraception and pregnancy testing in clinical trials” (Appendix 11). Female patients who are lactating must agree to stop breast-feeding. - Written informed consent to enter the R-I randomization from patient or parents/legal representative, patient, and age-appropriate assent. - Patient affiliated to a social security regimen or beneficiary of the same according to local requrements. - Patients should be able and willing to comply with study visits and procedures as per protocol.

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Non inclusion Criteria	<u>Non-inclusion criteria specific to the R-I randomization (RAPID COJEC/GPOH) :</u> 1) Urinary outflow obstruction 2) severe arrhythmia, heart failure, previous cardiac infarct, acute inflammatory heart disease 3) severe peripheral neuropathy 4) demyelinating form of Charcot-Marie-Tooth syndrome 5) hearing impairment 6) Concurrent prophylactic use of phenytoin 7) cardiorespiratory disease that contraindicates hyperhydration <u>Non-inclusion criteria common to all randomizations (R-I, R-HDC and R-RTx) :</u> 1) Any negative answer concerning the inclusion criteria of R-I or R-HDC or R-RTx will render the patient ineligible for the corresponding therapy phase randomization. However, these patients may remain on study and be considered to receive standard treatment of the respective therapy phase, and may be potentially eligible for subsequent randomizations. 2) Liver function: Alanine aminotransferase (ALT) > 3.0 x ULN and blood bilirubin > 1.5 x ULN (toxicity ≥ grade 2). In case of toxicity ≥ grade 2, call national principal investigator study coordinator to discuss the feasibility. 3) Renal function: Creatinine clearance and/or GFR < 60 ml/min/1.73m² (toxicity ≥ grade 2). If GFR < 60ml/min/1.73m², call national principal investigator to discuss.the feasibility.

	4) Dyspnea at rest and/or pulse oximetry <95% in air. 5) Any uncontrolled intercurrent illness or infection that in the investigator opinion would impair study participation. 6) Patient under guardianship or deprived of his liberty by a judicial or administrative decision or incapable of giving his consent. 7) Participating in another clinical study with an IMP while on study treatment. 8) Concomittant use with yellow fever vaccine and with live virus or bacterial vaccines. 9) Patient allergic to peanut or soya. 10) Chronic inflammatory bowel disease and/or bowel obstruction. 11) Pregnant or breastfeeding women. 12) Known hypersensitivity to the active substance or to any of the excipients of study drugs known 13) Concomitant use with St John's Wort (Hypericum Perforatum).
Treatment	Patients will receive ▪ Induction chemotherapy - Randomization between RAPID COJEC and GPOH chemotherapy ▪ Surgery of the primary tumor ▪ Consolidation chemotherapy - Randomization between single HD Bu-Mel and tandem HDC consisting in Thiotepa (900mg/m^2) and Bu-Mel, followed by ASCR ▪ External radiotherapy of the primary tumor - Randomization of the dose of radiotherapy (21.6 Gy vs 21.6 Gy + 14.4 Gy boost) in patients with macroscopic residual tumor; - 21.6 Gy radiotherapy to the pre-operative tumor bed in patients with no macroscopic residual tumor ▪ Maintenance treatment with immunotherapy and isotretinoin. The duration of the whole treatment for each participant will be of around 1 year. In this trial, the Investigational Products (IMPs) are : - Cisplatin - Carboplatin - Cyclophosphamide - Dacarbazine - Doxorubicin - Etoposide - Ifosfamide - Thiotepa - Busulfan (in the Thiotepa-BuMel arm) - Melphalan (in the Thiotepa-BuMel arm) - Vincristine - Vindesine All the IMPs will be taken from pharmacy hospital stocks.
Primary evaluation criterion	**R-I:** 3-year EFS from date of R-I randomization **R-HDC:** 3-year EFS from date of R-HDC randomization **R-RTx:** 3-year EFS from date of RTx randomization
Secondary evaluation criteria	For the whole population of high-risk neuroblastoma: ▪ 3- and 5-year EFS, PFS and OS calculated from date of randomization

	For each treatment phase: ▪ 5-year EFS, 3- and 5-year PFS and OS calculated from date of randomization ▪ Cumulative incidence of relapse/progression ▪ Cumulative incidence of treatment related mortality and of disease related mortality ▪ Overall response as per the new INRG response criteria [Park JR, JCO 2017] (including primary tumor after induction), skeletal response on MIBG, bone marrow response, local control ▪ Therapy-related toxicity
Exploratory endpoints	▪ Rate of patients that discontinued therapy Response rates, survival rates and the cumulative incidence of relapse/progressions will be analyzed according to: - Clinical factors: age, stage, metastatic response at the end of induction chemotherapy. - Serological factors at diagnosis: LDH, ferritin. - Biological factors: *MYCN*, ALK and TERT and circulating biomarker status.
Sample size determination	**R-I:** induction regimens RAPID COJEC vs GPOH Assuming a baseline 3-year EFS of 40%, with a sample size of 686 patients (343 in each arm) and a two-sided alpha=5% this trial will have 90% power to demonstrate an improvement of 12% in 3-year EFS, within a recruitment period of 3 years and a minimum follow up of 1.5 years. **R-HDC:** consolidation regimen Bu-Mel vs Thiotepa + Bu-Mel The 3-year EFS in the Bu-Mel arm (with immunotherapy) is estimated to be 55%. This study aims to show an improvement of 12% for the Thiotepa + Bu-Mel arm (3-year EFS of 67%). With a recruitment of 448 patients (224 in each arm) over a period of 3 years and a minimum follow-up of 2 years, the power to show a 12% difference is 80% (two-sided logrank test and α=5%). **R-RTx:** 21.6 Gy radiotherapy vs 21.6 Gy + 14.4 Gy boost in patients with macroscopic residual disease The 3-year EFS of patients with 21.6 Gy radiotherapy is estimated to be 38%. This study aims to show an improvement of 15% for the arm with 21.6 Gy + 14.4 Gy boost (3-year EFS of 53%). With a recruitment of 226 patients (113 in each arm) over a period of 4 years and a minimum follow-up of 4 years, the power to show a 15% difference is 80% (two-sided logrank test and α=5%).
Number of patients	Total : 800

Duration of the trial	Inclusion	6 years
	Treatment	Around 1 year
	Follow-up	5 years
	Duration of the study	12 years
	Long term Follow-up	Overall Survival