CONNECT 1903: A Pilot and Study of Larotrectinib for Treatment of Children with Newly Diagnosed HGG with *NTRK* Fusion (NCT04655404)

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BACKGROUND & METHODS

Recurrent fusions in neurotrophic tropomyosin-receptor kinase genes *NTRK* 1-3 are found in variety of cancers, including pediatric HGG: DIPG (~4%) and non-brainstem HGG (~10%). For non-brainstem HGG seen in children <3 years of age, approximately 40% harbor *NTRK* alterations. *NTRK* fusions provide a promising target for gliomas and to that end, Larotrectinib, a globally approved, highly potent, small molecule inhibitor of TRKA/BC, has previously been investigated and has shown tolerability and efficacy in children with recurrent solid tumors. Compassionate use in a case of infantile GBM has shown proof-of-concept with blood-brain penetrance and efficacy. Further evidence in two earlier clinical trials has also been previously demonstrated in children with recurrent *TRK*-fusion primary intracranial tumors (NCT02637687, NCT02576431).

This international trial conducted through the CONNECT consortium, supported in part by Bayer, investigates larotrectinib monotherapy; its feasibility and tolerability in combination with standard systemic chemotherapy (Baby POG or HIT-SKK) or radiation therapy whereby treatment plan determination is response-based. A phase 0 surgical cohort will be explored whereby patients who are planned to undergo a definitive resection will receive pre-surgery larotrectinib, and target inhibition, intratumoral and plasma pharmacokinetics will be explored. Radiographic responses will also be quantitated.

This trial is currently open to accrual at CONNECT sites across North America, Australia and Germany. Seven patients have enrolled to date. Additional sites in UK and Netherlands are pending activation. A total of 15 patients are anticipated to be enrolled and evaluable.

OBJECTIVES

Primary Objectives

- To assess the disease control rate (Complete Response [CR], Continued Complete Response [CCR], Partial Response [PR] and Stable Disease [SD]) of larotrectinib after 2 cycles of larotrectinib monotherapy.
- To assess the feasibility and safety of larotrectinib when given in combination with chemotherapy, and the safety when given post-focal radiation therapy.
- To characterize the plasma and tumor pharmacokinetics (PK) and pharmacodynamics (PD) of larotrectinib in children who undergo a second definitive resection (surgical cohort only).

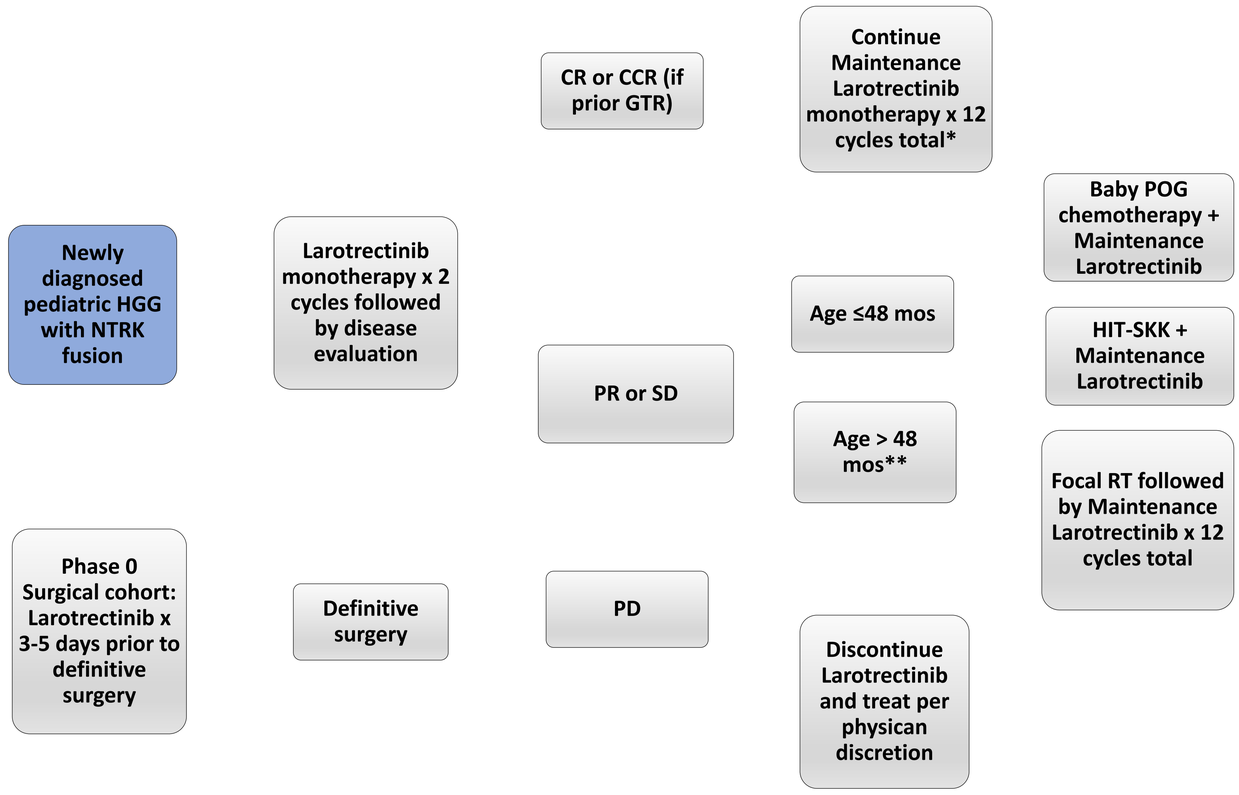
Secondary Objectives

- To assess the objective response rate (ORR) (Complete Response [CR] and Partial Response [PR]) of larotrectinib after 2 cycles of larotrectinib monotherapy.
- To assess overall (OS) and progression-free survivals (PFS) at 1, 3 and 5 years and compared to historical data from BABYPOG and HIT-SKK.

Exploratory Objectives

- To assess the CSF pharmacokinetics (PK) of larotrectinib when/if LP is performed or if CSF is obtained at surgery or CSF diversion.
- To biologically characterize tumors and to assess biomarker of response or resistance by tumor methylation profiling, whole genome sequencing (WGS) or whole exome sequencing (WES) (tumor and blood), and RNA-Seq (tumor).
- To explore the ability of Larotrectinib to inhibit NTRK-mediated signaling in tumor
- To explore volumetric measurements of tumor including necrotic and cystic components (if present) and correlate with 2-dimensional measurements and response criteria.

TREATMENT SCHEMA



*Continuation of treatment beyond 12 cycles, and up to max 26 cycles, may be considered for patients on Larotrectinib monotherapy if they are receiving clinical benefit from the study, at the discretion of the treating physician.
**Patients who are ≥ 36 months of age or with DIPG who are >18 months of age, may be considered for focal RT, at the discretion of the local investigator.

KEY ELIGIBILITY CRITERIA

- Patients with newly-diagnosed high-grade (HGG), including diffuse intrinsic pontine gliomas (DIPG), whose tumors harbor an NTRK fusion alteration by FISH, PCR, or next generation sequencing are eligible.
- Patients must have had histologically verified high-grade glioma such as anaplastic astrocytoma, glioblastoma, or H3 K27-mutant diffuse midline glioma verified at a CONNECT site.
- Patients with disseminated DIPG or HGG are eligible only if the patient is to receive chemotherapy only, i.e. no craniospinal RT is intended to be given.
- Patients with leptomeningeal disease only, with no definitive identifiable primary tumor, and documented NTRK fusion, may be considered.
- Surgical cohort only: Patients with newly diagnosed HGG with NTRK fusions who have undergone prior biopsy and for whom further resection is indicated for a more definitive surgery at an enrolling site will be eligible to enroll onto the surgical study. DIPG patients are not eligible for the surgical cohort.
- Age: ≤ 21 years of age
- Performance status: ≥ 50% by Karnofsky/Lansky
- Patients must not have received prior anti-cancer chemo- or radiotherapy
- Adequate organ function
- Prior corticosteroid usage is allowed
- No uncontrolled intercurrent infectious illness, prior malabsorption syndrome or condition affection oral absorption
- No strong cytochrome P450 4A4 inhibitor or inducer
- No prior solid organ transplantation is allowed

TREATMENT PLAN

- Larotrectinib: 100 mg/m2 BID (max dose 100mg/dose) with dose levels for reduction.
- A cycle length of larotrectinib is 28 days.
- Two dose level reduction are allowed.

Dose Level	Dose
-2	50 mg/m^2/dose BID (50 mg/dose max dose BID
-1	70 mg/m^2/dose BID (75 mg/dose max dose BID)
1*	100 mg/m^2/dose BID (100 mg/dose max dose BID)

- Standard-of-care chemotherapy regimens, BabyPOG and HIT-SKK, and raidation therapy as per institutional guidelines.

BIOLOGIC CORRELATES

- NTRK fusion assessment
- Pharmacokinetics (surgical cohort)
  - Plasma, tumor and CSF
- Genomics and Pharmacodynamics
  - Tumor (surgical cohort and archival sample)
  - Whole genome, RNA and ChIP sequenving
  - DNA methylations profiling
  - Germline testing
- Radiologic
  - MRI correlations with response

ACKNOWLEDGEMENTS

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RESTRICTED