Study of Efficacy and Safety of Ribociclib (LEE011) in Combination With Topotecan and Temozolomide (TOTEM) in Pediatric Patients With Relapsed or Refractory Neuroblastoma and Other Solid Tumors

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Phase I/II Multicenter Study to Assess Efficacy and Safety of Ribociclib (LEE011) in Combination With Topotecan and Temozolomide (TOTEM) in Pediatric Patients With Relapsed or Refractory Neuroblastoma and Other Solid Tumors
ClinicalTrials.gov Identifier:
NCT05429502
Novartis Reference Number:CLEE011Q12101
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All compounds are either investigational or being studied for (a) new use(s). Efficacy and safety have not been established. There is no guarantee that they will become commercially available for the use(s) under investigation.

Study Description

This is a Phase I/II study to assess the efficacy and safety of ribociclib in combination with topotecan and temozolomide (TOTEM) in pediatric patients with relapsed or refractory (r/r) neuroblastoma (NB), and other solid tumors, including medulloblastoma (MB), high-grade glioma (HGG), malignant rhabdoid tumors (MRT), and rhabdomyosarcoma (RMS). The study consists of Phase I -part A (dose finding) and Phase I - part B (multiple expansion cohorts). Phase II may begin after evaluation of Phase I data (safety, tolerability, efficacy, pharmacokinetics and biomarker data), with consideration of other emerging data that may impact on the treatment landscape, before initiating Phase II in patients with relapsed or refractory NB and/or other tumors studied in Phase I.

* Phase I-Part A (dose finding): a dose finding to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of ribociclib in combination with TOTEM.
* Phase I- Part B (multiple expansion cohorts): it will be initiated to confirm RP2D identified from Phase I-part A. Multiple expansion cohorts have been planned to assess the preliminary antitumor activity and safety of ribociclib in combination with TOTEM in participants with r/r NB (cohort 1), MB (cohort 2), HGG (cohort 3), MRT (cohort 4), and RMS (cohort 5)
* Phase II- Double-blind, randomized, placebo controlled in r/r NB: It is a two-arm randomized, double blinded, placebo controlled, parallel group trial in participants with r/r NB.

Condition
Neuroblastoma
Phase
Phase1, Phase2
Overall Status

Recruiting
Number of Participants
231
Start Date
Dec 27, 2022
Completion Date
Jan 28, 2028
Gender
All
Age(s)
12 Years - 21 Years (Child, Adult)

Interventions

Drug

Ribociclib

Ribociclib administered at the RP2D defined from Phase I-Part A.
Drug

Temozolomide

Starting out dose of temozolomide for first two cohorts for Phase 1-Part A: 150mg/m2/day. Starting out dose for subsequent cohorts in Phase 1-Part A will initiate at 100mg/m2/day and will be determined for Phase 1-Part B depending on safety outcome and for phase II.
Drug

Topotecan

Starting out dose of topotecan administered at standard dose given to neuroblastoma patients (0.75 mg/m2/day).

Eligibility Criteria

Inclusion Criteria:

1. Participants and/or guardian have the ability to understand and the willingness to sign a written informed consent document.
2. Age ≥ 12 months and ≤ 21 years at the time of signing consent form Note: The first dose level of Phase I - part A (dose finding) will enroll participants ≥ 12 years - 21 years old, and may expand to younger participants (≥ 12 months to \< 12 years) as determined by the data.
3. Histologically or cytologically confirmed solid tumors listed below that have progressed despite standard therapy or for which no effective standard therapy exists.

1. Neuroblastoma (for Phase I and Phase II): Histologically proven neuroblastoma as per International Neuroblastoma Staging System (INSS); Relapsed or refractory disease; Measurable disease per International Neuroblastoma Response criteria (INRC); Bone marrow only disease not eligible; Available MYCN status before screening

2. Medulloblastoma (for Phase I) regardless of genetic status (i.e. Groups 3 or 4 WNT-activated or non-WNT, SHH-activated or non-SHH)
3. High-grade glioma (for Phase I): including HGG NOS, WHO Grade III or Grade IV; Glioblastoma, IDH-wildtype or IDH-mutant; Anaplastic astrocytoma, IDH-mutant; Anaplastic oligodendroglioma, IDH-mutant; Anaplastic pleomorphic xanthoastrocytoma; Diffuse midline gliomas, H3 K27-altered; Diffuse hemispheric glioma, H3 G34-mutant; Diffuse pediatric-type HGG, H3-wildtype and IDH-wildtype.
4. Malignant rhabdoid tumor (for Phase I) includes diagnoses of atypical teratoid/rhabdoid tumor (AT/RT), and rhabdoid tumor of the kidney (RTK), and other soft tissues as defined by 2 of the 3 following criteria; either (1)+(2) or (1)+(3): (1) Morphology and immunophenotypic panel consistent with rhabdoid tumor; (2) Loss of SMARCB1 confirmed by immunohistochemistry; (3) Molecular confirmation of tumor-specific bi-allelic SMARCB1 loss/mutation is encouraged in cases where SMARCB1 immunohistochemistry is equivocal, and required if SMARCB1 immunohistochemistry is not available
5. Rhabdomyosarcoma (for Phase I) independent of fusion status and subtype
4. Participants with CNS disease who are on corticosteroids should take stable doses for at least 7 days prior to first dose of ribociclib with no plans for escalation.
5. Performance status:

1. ≤ 16 years: Lansky Play score ≥ 50%
2. \>16 years: Karnofsky performance status ≥ 50% or ECOG \< 3
6. Life expectancy of ≥ 12 weeks at the time of enrollment
7. Adequate bone marrow function (bone marrow may be involved with tumor) and organ function
8. Adequate hepatic, renal, cardiac function
9. Females who are sexually active must agree to use highly effective contraception during and for 6 months after treatment. Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose of study medication. Pregnant or lactating females are not eligible for the study.
10. Sexually active males (including those that have had a vasectomy), who do not agree to abstinence, must be willing to use a condom during intercourse while on study treatment and for 6 months after stopping treatment.

Exclusion Criteria:

1. Known hypersensitivity to any of the excipients of ribociclib or topotecan or temozolomide.
2. Not recovered from clinical and laboratory acute toxicities related to prior anti-cancer therapies
3. Concurrent severe and/or uncontrolled concurrent medical conditions (serious infections or significant cardiac, pulmonary, hepatic, psychiatric, GI disease, or other organ dysfunction) that in the investigator's judgement could compromise their ability to tolerate or absorb protocol therapy or would interfere with the study procedures or results
4. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality
5. History of QTc prolongation; taking medications with a known risk to prolong the QT interval hat cannot be discontinued or replaced by safe alternative medication
6. Currently taking medications that are mainly metabolized by CYP3A4/5 with a narrow therapeutic index, strong inducers or inhibitors of CYP3A4/5, herbal preparations/medications and dietary supplements
7. Vaccinated with live, attenuated vaccines within 4 weeks
8. Participated in a prior investigational study within 30 days
9. Received prior treatment with a CDK4/6 inhibitor
10. Received last dose of anticancer therapy (including experimental) within 4 weeks
11. Previous myeloablative therapy with autologous hematopoietic stem cell rescue within 8 weeks
12. Allogeneic stem cell transplant within 3 months

13. Has last fraction of radiation within 4 weeks
14. Major surgery within 2 weeks
15. Pregnant or nursing (breast feeding) female participant or female participant who plans to become pregnant or breast-feed during the trial.

Other protocol-defined inclusion/exclusion criteria may apply

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Novartis Investigative Site

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