ROVER: A phase 1/2 study of avapritinib in pediatric patients with solid tumors dependent on KIT or PDGFRA signaling

TRLS-10

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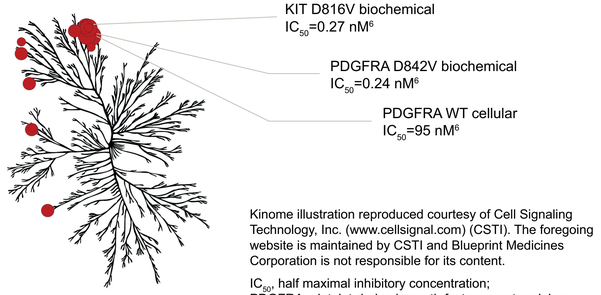
Background

- The prognosis is poor for pediatric patients with advanced relapsed/refractory (R/R) solid and central nervous system (CNS) tumors; response rates in these patients are only ~15% with targeted therapies[1]
- The most common pediatric tumors harboring *KIT* mutations are germ cell tumors and high-grade glioma (HGG), while the most common pediatric tumors with platelet-derived growth factor receptor alpha (*PDGFRA*) alterations are sarcoma and HGG[2–6]
  - Diffuse midline gliomas with H3K27-altered (DMG-H3K27a) are also dependent on PDGFRA signaling and may be vulnerable to PDGFRA inhibition in the absence of *PDGFRA* alterations[7]
- There are no KIT- or PDGFRA-targeted therapies currently approved for pediatric patients with R/R solid or CNS tumors, or DMG-H3K27a
- Avapritinib is a selective KIT and PDGFRA inhibitor that has demonstrated potent activity against KIT activation-loop (exon 17 and 18) and juxtamembrane (exon 11) mutants (all with biochemical IC_{50}<2 nM) and PDGFRA activation-loop (exon 18) mutants (D842V biochemical IC_{50} 0.24 nM; **Figure 1**); cellular IC_{50} of PDGFRA wild-type was 95 nM[8]
- Avapritinib has demonstrated CNS penetration preclinically with some preliminary evidence of clinical activity,[9,10] with potential for activity against CNS tumors
- Avapritinib is approved by the US Food and Drug Administration for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors harboring *PDGFRA* exon 18 mutations (including D842V), and for adult patients with indolent systemic mastocytosis (ISM) and advanced systemic mastocytosis (AdvSM); avapritinib is not recommended for patients with ISM or AdvSM with platelet counts <50x10^9/L. Avapritinib is also approved in Europe for adult patients with AdvSM after ≥1 prior systemic therapy[11,12]

Figure 1: Avapritinib has a highly selective kinome profile



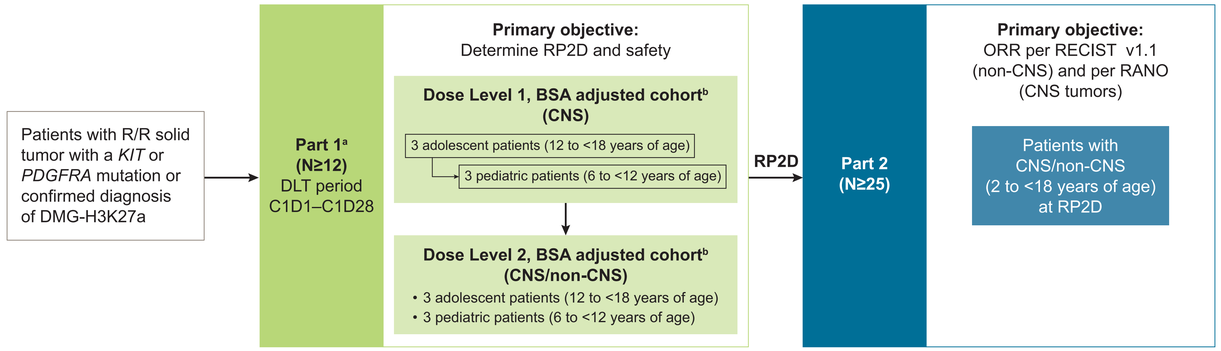
Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines Corporation is not responsible for its content.

IC_{50}, half maximal inhibitory concentration; PDGFRA, platelet-derived growth factor receptor alpha; WT, wild-type.

Study objective and design

- This phase 1/2, multicenter, open-label, single-arm study (NCT04773782) aims to evaluate the safety, pharmacokinetics (PK), and efficacy of avapritinib in pediatric patients with solid tumors dependent on KIT or PDGFRA signaling (**Figure 2**)
- Initially, 6 patients will receive avapritinib at Dose Level 1, normalized for body surface area. If no dose-limiting toxicity is observed, an additional 6 patients will be enrolled at Dose Level 2 normalized for body surface area

Figure 2: Study design



[a]Part 1 uses a 3+3 design. [b]Adolescent and pediatric groups may have different RP2D based on safety, efficacy and PK data.
BSA, body surface area; C, Cycle; CNS, central nervous system; D, Day; DLT, dose-limiting toxicities; DMG-H3K27a, diffuse midline gliomas with H3K27-altered; ORR, overall response rate; RANO, Response Assessment in Neuro-Oncology; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Table 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Part 1: 6 to <18 years of age and Part 2: 2 to <18 years of age • Confirmed diagnosis of CNS disease or R/R solid tumor with mutation in *KIT* or *PDGFRA*, or DMG-H3K27a,[a] which has progressed despite standard therapy and/or no alternative treatment option is available – Patients with R/R solid tumors with only *PDGFRA* and/or *KIT* amplifications may be included with approval from the Sponsor • All patients must have ≥1 measurable lesion as defined by RECIST v1.1 or RANO (for CNS tumors). If radiation therapy has been administered, ≥1 measurable lesion must not have been irradiated, or must have clearly progressed since being irradiated as per RANO and must be ≥12 weeks from radiation to any target lesion – In Part 2, up to 5 patients with newly diagnosed DMG-H3K27a where there is no standard therapy may enroll • Lansky (<16 years of age) or Karnofsky (≥16 years of age) score ≥50	• Inadequate end-organ function • Other systemic antineoplastic therapies[b,c] • Previous treatment with avapritinib • Ongoing treatment, or has received treatment within 28 days, with strong CYP3A inhibitors or inducers • Within 14 days before first dose of study treatment, platelet count <75×10^9/L (<100×10^9/L if a CNS tumor) with no platelet transfusion within 14 days prior to the measurement[d] • History of another primary malignancy that has been diagnosed or required treatment within the previous 3 years • History of thrombosis requiring treatment within the previous 6 months

[a]Per locally conducted testing. [b]Temozolomide within 4 weeks prior to the first dose of study drug, nitrosurea within 6 weeks prior to the first dose of study drug, or any other systemic antineoplastic therapy (including experimental therapy) within 5 half-lives or 28 days prior to the first dose of study drug, whichever is shorter. Focal external beam radiotherapy, including stereotactic radiosurgery, within 6 weeks prior to the first dose of avapritinib to either target or nontarget lesions. Systemic radiopharmaceuticals, including non-stereotactic radiosurgery, within 2 weeks of the first dose of avapritinib (within 6 weeks for patients with CNS tumors). Craniospinal irradiation within 6 weeks prior to the first dose of avapritinib. [c]All AEs related to other antineoplastic therapies must have resolved to Grade ≤1 (Grade ≤2 for peripheral neuropathy and/or ototoxicity) prior to the first dose of avapritinib. [d]In advanced SM, most intracranial bleeding was associated with Grade ≥3 thrombocytopenia. In patients with GIST, intracranial bleeding was not associated with thrombocytopenia.
CAR-T, chimeric antigen receptor T cell; CYP3A, cytochrome P 3A; GIST, gastrointestinal stromal tumors; SCT, stem cell transplant.

Table 2: Study endpoints

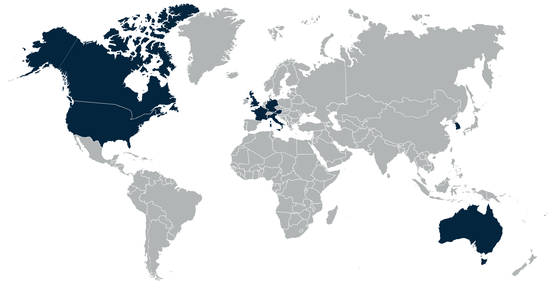
Primary endpoints	Secondary endpoints
• **Part 1** – Determination of RP2D based on DLTs – Safety and tolerability • **Part 2** – Objective response rate by RECIST v1.1 or RANO	• **Part 1** – Objective response rate by RECIST v1.1 or RANO • **Part 1 and Part 2** – Objective response rate by RAPNO[a] – Duration of response – Progression-free survival – Disease control rate at 24 weeks – Time to response – Avapritinib pharmacokinetics and pharmacodynamics – Safety and tolerability (Part 2) – Palatability assessments (Part 2)

[a]At institutions where RAPNO is performed.
RAPNO, Response Assessment in Pediatric Neuro-Oncology; RP2D, recommended phase 2 dose.

Enrollment and current status

- The target enrollment is at least 37 patients, with at least 12 patients in Part 1 and 25 patients in Part 2
  - The total number of patients enrolled in Part 1 is dependent on the dose identified as the RP2D
- Enrollment in this international, multicenter study began in February 2022 and is open at 26 sites in 9 countries, including centers in North America, Europe, and Asia/Pacific (**Figure 3**)
- The study is currently evaluating Dose Level 2

Figure 3: Study sites



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