A phase 1/2, single-arm study to evaluate the safety, pharmacokinetics, and antitumor activity of avapritinib in pediatric patients with solid tumors dependent on KIT or PDGFRA signaling

EPCT-05

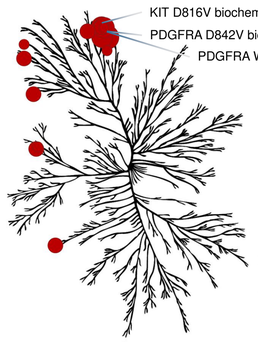
Susan Chi[1], Antony Hsieh[2], Megan Foley[2], Hongliang Shi[2], Preethi Swamy[2], Jill Rodstrom[2], Marc Rudoltz[3]

[1]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [2]Blueprint Medicines Corporation, Cambridge, Massachusetts, USA; [3]MSR Healthcare Consultants LLC, West Orange, New Jersey, USA

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[2–4]
  - In addition to tumors that harbor *KIT/PDGFRA* alterations, H3K27M gliomas and HGG are dependent on PDGFRA signaling and may be vulnerable to PDGFRA inhibition in the absence of PDGFRA alterations[5]
- There are no KIT- or PDGFRA-targeted therapies currently approved for pediatric patients with R/R solid or CNS tumors, or H3K27M gliomas
- 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[6]
- Avapritinib demonstrated CNS penetration clinically and preclinically,[7] with potential for activity against CNS tumors
- Avapritinib is approved by the US FDA for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring *PDGFRA* exon 18 mutations (including D842V)[8]
  - In the EU, avapritinib is approved for the treatment of adult patients with unresectable or metastatic GIST harboring a *PDGFRA* D842V mutation[9]

Figure 1: Avapritinib has a highly selective kinome profile

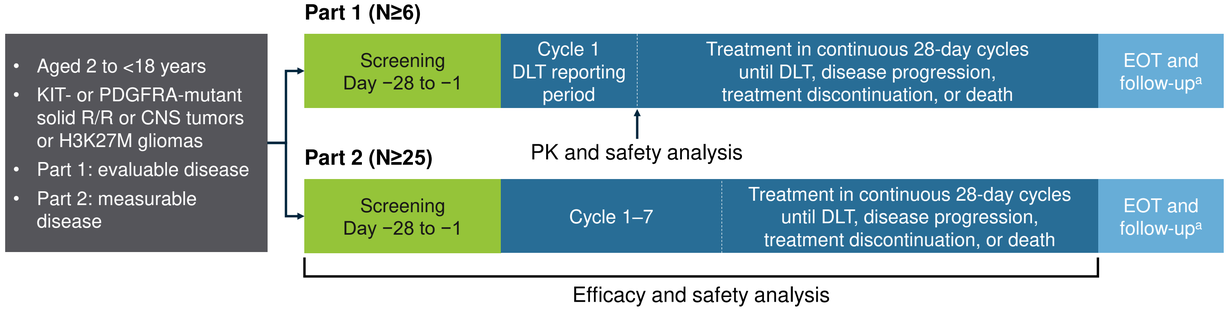


Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines Corporation is not responsible for its content.
IC_{50}, half maximal inhibitory concentration; WT, wild-type.

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: Study design



[a]EOT occurs 14 days after last dose; safety follow-up occurs ≥30 days from last dose; patients will be offered survival follow up from last dose of study drug every 3 months until death, withdrawal of consent, or loss to follow-up. DLT, dose-limiting toxicity; EOT, end of treatment; QD, daily.

- Patients will receive avapritinib 300 mg QD normalized by body surface area and adjusted according to physiologically-based PK modelling in children
- If the first dose given is not identified as the recommended phase 2 dose (RP2D), a subsequent dose will be selected and an additional 6 patients treated at each dose level
- The maximum avapritinib dose given will be 300 mg QD

Table 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Aged 2 to <18 years of age • Confirmed diagnosis of R/R solid or CNS tumor with mutation in *KIT* or *PDGFRA,* or H3K27M glioma, which has progressed despite standard therapy and no alternative treatment option is available • In part 1, patients should have evaluable disease • In part 2, patients should have ≥1 measurable lesion defined by RECIST v1.1 or RANO/RAPNO for CNS tumors • A Lansky (≤16 years of age) or Karnofsky (>16 years of age) score ≥50 – If the patient is unable to walk due to paralysis but mobile in a wheelchair, the patient is considered ambulatory for the purpose of assessing ambulatory status	• Inadequate end-organ function • Systemic antineoplastic therapies within the previous 28 days • Previous treatment with avapritinib • Received autologous SCT following myeloablative therapy or CAR-T therapy within 3 months prior to the first dose of avapritinib, or allogeneic SCT at any time • Ongoing treatment, or has received treatment within 2 weeks, with strong CYP3A inhibitors, inducers, or EIAEDs • History of primary malignancy that has been diagnosed or required treatment within the previous 3 years • History of thrombosis requiring treatment within the previous 6 months

CAR-T, chimeric antigen receptor T cell; CYP3A, cytochrome P 3A; EIAED, enzyme-inducing anti-epileptic drug; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SCT, stem cell transplant.

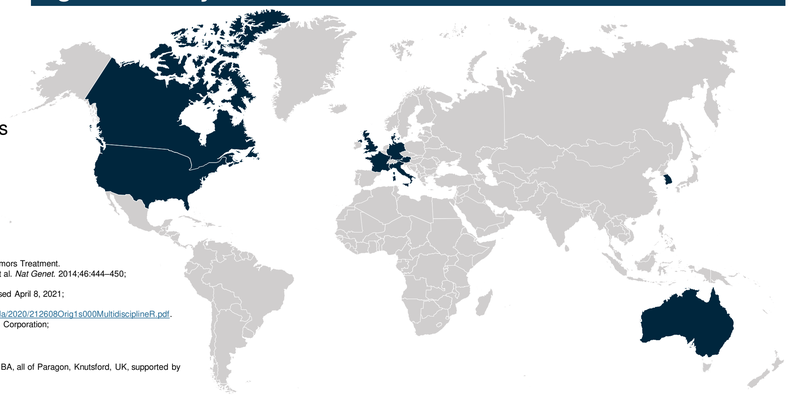
Table 2: Study endpoints

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/RAPNO)	• **Part 1** – Objective response rate • **Part 1 and part 2** – Duration of response – Progression-free survival – Disease control rate – Avapritinib pharmacokinetics – Safety and tolerability

Enrollment and current status

- The target enrollment is at least 31 patients, with at least 6 patients in part 1 and 25 patients in part 2
  - The total number of patients to be enrolled in part 1 is dependent on the dose identified as the RP2D
- Enrollment in this international, multicenter study is planned from August 2021 at 25 sites in 10 countries including centers in North America, Europe, and Asia/Pacific (**Figure 3**)

Figure 3: Study sites



References

1. Cohen JW et al. *Oncologist.* 2020;25:532–540; 2. National Cancer Institute. Childhood Extracranial Germ Cell Tumors Treatment. https://www.cancer.gov/types/extracranial-germ-cell/hp/germ-cell-treatment-pdq. Accessed April 8, 2021; 3. Wu G et al. *Nat Genet.* 2014;46:444–450; 4. National Cancer Institute. SEER Cancer Statistics Review 1975–2009. https://seer.cancer.gov/archive/csr/1975_2009_pops09/results_merged/sect_29_childhood_cancer_iccc.pdf. Accessed April 8, 2021; 5. Filbin MG et al. *Science.* 2018;360:331–335; 6. Evans EK et al. *Sci Transl Med.* 2017;9:eaao1690; 7. US FDA. Multi-disciplinary review and Evaluation Avapritinib. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212608Orig1s000MultidisciplineR.pdf. Accessed April 8, 2021; 8. AYVAKIT™ (avapritinib). Highlights of Prescribing Information. 2020. Blueprint Medicines Corporation; 9. AYVAKYT (avapritinib). Summary of Product Characteristics. 2020. Blueprint Medicines Corporation.

Acknowledgments

Medical writing support was provided by Natasha Tracey, PhD, and editorial support was provided by Travis Taylor, BA, all of Paragon, Knutsford, UK, supported by Blueprint Medicines Corporation, Cambridge, MA, according to Good Publication Practice guidelines.

Disclosures

This research was funded by Blueprint Medicines Corporation. Blueprint Medicines reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content. SC has acted as a consultant for Blueprint Medicines Corporation and Epizyme. AH, MF, HS, PS, and JR are employees and shareholders of Blueprint Medicines Corporation. MR has acted as a paid consultant for Blueprint Medicines Corporation, ImmunoMet Therapeutics, NextCure, Inc., Novellus Ltd, EpiVax, Inc., Premier Research and Ikena Oncology, and is a shareholder of BroadSpot Imaging Corporation, Cerus Corporation, ENB Therapeutics, Inc., FEMSelect, Healionics, ImmunoMet Therapeutics, Kronos Bio, Kura Oncology, Mycovia Pharmaceuticals, Inc., and Novartis.