

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

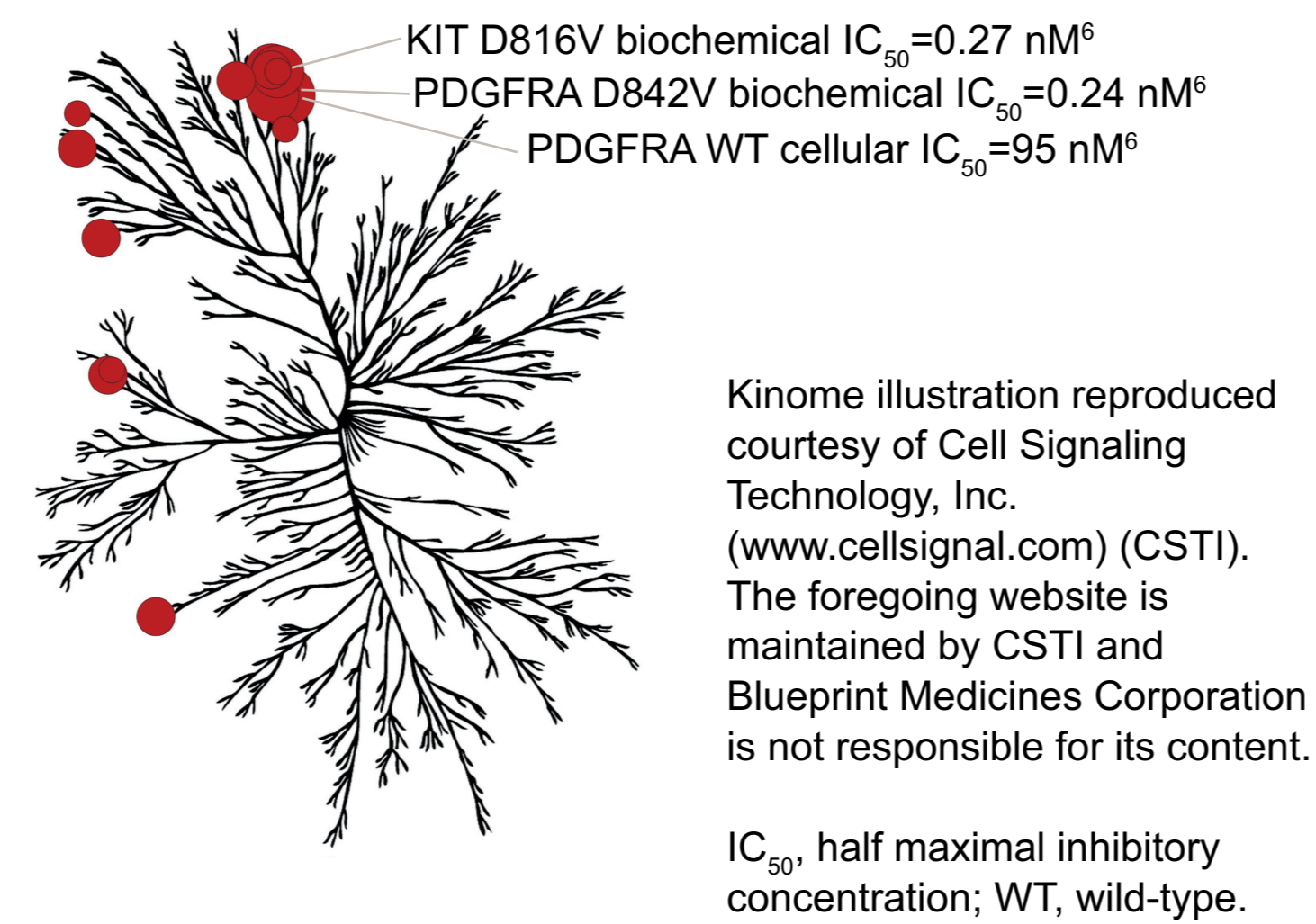
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Background

- 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 therapies¹
- 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 HGG²⁻⁶
 - 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* alterations⁷
- 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 nM⁸
- Avapritinib has demonstrated CNS penetration clinically and preclinically,⁹ with potential for activity against CNS tumors
- Avapritinib is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring *PDGFRA* exon 18 mutations (including D842V), and adult patients with advanced systemic mastocytosis (SM), including aggressive SM, SM with an associated hematologic neoplasm, and mast cell leukemia; avapritinib is not recommended for patients with advanced SM with platelet counts $< 50 \times 10^9/L$ ¹⁰
 - In the European Union, avapritinib is approved for the treatment of adult patients with unresectable or metastatic GIST harboring a *PDGFRA* D842V mutation¹¹
 - In China, avapritinib is approved for the treatment of adult patients with unresectable or metastatic GIST harboring *PDGFRA* exon 18 mutations (including D842V)¹²

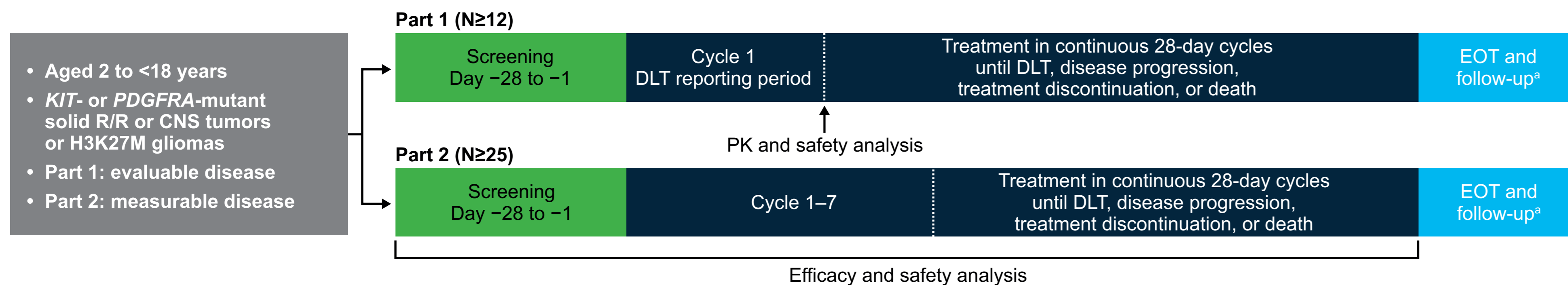
Figure 1: Avapritinib has a highly selective kinome profile



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



*EOT occurs 14 days after last dose; safety follow-up occurs ≥30 days after 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.

- Initially, 6 patients will receive avapritinib at 80% equivalent of the adult dose (300 mg) daily (QD), normalized by body surface area. Adjustments may be made according to physiologically-based PK modelling in children. If no dose-limiting toxicity is observed, an additional 6 patients will be enrolled at a 100% equivalent of the adult dose (300 mg)
- The maximum avapritinib dose given will be 300 mg QD

Table 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> Aged 2 to <18 years of age Confirmed diagnosis of R/R solid or CNS tumor with mutation in <i>KIT</i> or <i>PDGFRA</i>^a, 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 <ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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 28 days, 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

^aPer locally conducted mutational testing. 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

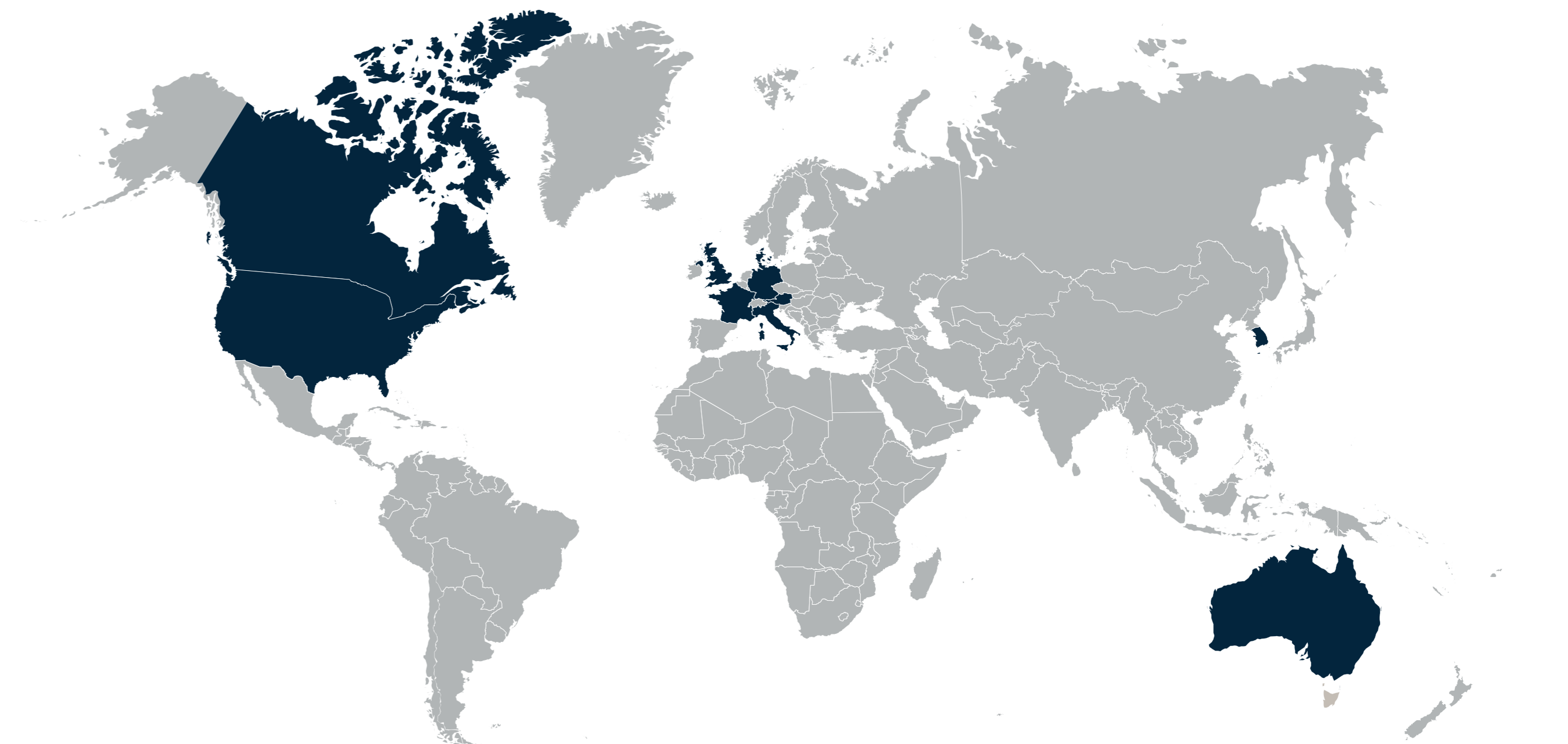
Primary endpoints	Secondary endpoints
<ul style="list-style-type: none"> Part 1 <ul style="list-style-type: none"> Determination of RP2D based on DLTs Safety and tolerability Part 2 <ul style="list-style-type: none"> Objective response rate (by RECIST v1.1 or RANO/RAPNO) 	<ul style="list-style-type: none"> Part 1 <ul style="list-style-type: none"> Objective response rate Part 1 and Part 2 <ul style="list-style-type: none"> Duration of response Progression-free survival Disease control rate Avapritinib pharmacokinetics Safety and tolerability

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 to be enrolled in part 1 is dependent on the dose identified as the RP2D
- Enrollment in this international, multicenter study is planned from December 2021 at 26 sites in 10 countries, including centers in North America, Europe, and Asia/Pacific (**Figure 3**)

Figure 3: Study sites



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