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 HGG2,3. 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 alterations1.

There are no KIT- or PDGFRA-targeted therapies currently approved for pediatric patients with R/R solid 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 IC50 < 2 nM) and PDGFRA activation-loop (exon 18) mutants (DMIV2 biochemical IC50 = 0.24 nM, Figure 1); cellular IC50 of PDGFRA- WT cell line was 65 nM.

Avapritinib has demonstrated CNS penetration clinically and preclinically4, with 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 systemic mastocytosis (SM) including aggressive SM, SM with an associated hematologic neoplasm, and mast cell leukaemia; avapritinib is not recommended for patients with advanced SM with platelet counts <50 X 10^9/L.

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.

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 1: Avapritinib has a highly selective kinase profile

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Figure 2: Study design

Table 1: Key eligibility criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>1. Age 2 to 18 years</td>
<td>1. Inadequate end-organ function</td>
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<td>2. 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 therapy option is available.</td>
<td>2. Previous treatment with avapritinib</td>
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<td>3. In part 1, patients should have evaluable disease</td>
<td>3. Received autotousic SCT following myelosuppressive therapy or CAR-T therapy within 3 months prior to the first dose of avapritinib, or allogenic SCT at any time</td>
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<td>4. In part 2, patients should have ≥ 1 measurable lesion defined by RECIST v1.1 or RANO/RAPNO for CNS tumors</td>
<td>4. Ongoing treatment, or has received treatment within 28 days, with strong CYP3A inhibitors, inducers, or EIAEDs</td>
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<td>5. A Lansky (10 years of age) or Karnofsky (≥ 15 years of age) score ≥50</td>
<td>5. History of primary malignancy that has been diagnosed or required treatment within the previous 3 years</td>
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<td>6. The patient is considered ambulatory for the purpose of assessing ambulatory status</td>
<td>6. History of thrombosis requiring treatment within the previous 6 months</td>
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Figure 3: Study sites

References

1. Cohen JW et al. Systemic antineoplastic therapies within the previous 28 days |
2. Mackay A et al. Previous treatment with avapritinib |
3. philR RP2D, recommended phase 2 dose |
4. Part 1 and Part 2 | 4. Ongoing treatment, or has received treatment within 28 days, with strong CYP3A inhibitors, inducers, or EIAEDs |
5. National Cancer Institute. SEER Cancer Statistics | 5. History of primary malignancy that has been diagnosed or required treatment within the previous 3 years |
6. Childhood Extracranial Germ Cell Tumors Treatment | 6. History of thrombosis requiring treatment within the previous 6 months |
7. Filbin MG et al. Enzyme-inducing anti-epileptic drug; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pancreatic Neuroendocrine | 7. CNS tumors |
8. CTNI-24

Enrollment and current status

The target enrollment is at least 27 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)

Table 2: Study endpoints

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<thead>
<tr>
<th>Primary endpoints</th>
<th>Secondary endpoints</th>
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<tr>
<td>Part 1</td>
<td>Part 1 and Part 2</td>
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<tr>
<td>1. Objective response rate</td>
<td>1.Duration of response</td>
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<tr>
<td>2. Safety and tolerability</td>
<td>2. Progression-free survival</td>
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<tr>
<td>3. Objective response rate (by RECIST v1.1 or RANO/RAPNO)</td>
<td>3. Disease control rate</td>
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Figure 3: Study sites

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