AYVAKIT™ (avapritinib) is a kinase inhibitor approved by the U.S. Food and Drug Administration for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

AVAPRITINIB IN ADVANCED PDGFRA D842V-MUTANT GASTROINTESTINAL STROMAL TUMOR (NAVIGATOR): A MULTICENTER, OPEN-LABEL, PHASE 1 TRIAL

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Click here for the publication, which is provided courtesy of Blueprint Medicines, the manufacturer of AYVAKIT. This publication contains information not included in the approved label for AYVAKIT. Blueprint Medicines does not recommend or endorse the use of AYVAKIT outside the FDA-approved product labeling.

Unmet need in patients with PDGFRA D842V GIST

- More than 85% of GISTs attributed to KIT or PDGFRA mutations
- PDGFRA D842V is a primary driver mutation in 5-6% of GIST cases
  - D842V mutation confers drug resistance by shifting the kinase to the active conformation
- Prior to AYVAKIT, patients with unresectable or metastatic D842V-mutant GIST had a poor prognosis:
  - Median progression-free survival (PFS) of 3-5 months
  - Overall survival (OS) of approximately 15 months

Avapritinib was designed to potently and selectively target the active conformation of KIT and PDGFRA

STUDY METHODOLOGY

- The NAVIGATOR (NCT02508532) study was a two-part, open-label, dose-escalation (part 1)/expansion (part 2) Phase 1 study
- Primary endpoints in part 1: maximum tolerated dose (MTD), recommended phase 2 dose (PR2D), evaluation of safety
- Primary endpoints in part 2: overall response rate (ORR) and overall safety profile of avapritinib
- Secondary endpoints in part 2: duration of response (DOR) and PFS (these are only 2 of the 4 secondary endpoints in this study)

SELECT SAFETY INFORMATION

The most common adverse reactions (≥20%) were edema, nausea, fatigue/asthenia, anemia, cognitive impairment, vomiting, diarrhea, decreased appetite, abdominal pain, increased lacrimation, constipation, rash and dizziness.

Please see Important Safety Information on back cover and the full Prescribing Information for AYVAKIT.

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NAVIGATOR description

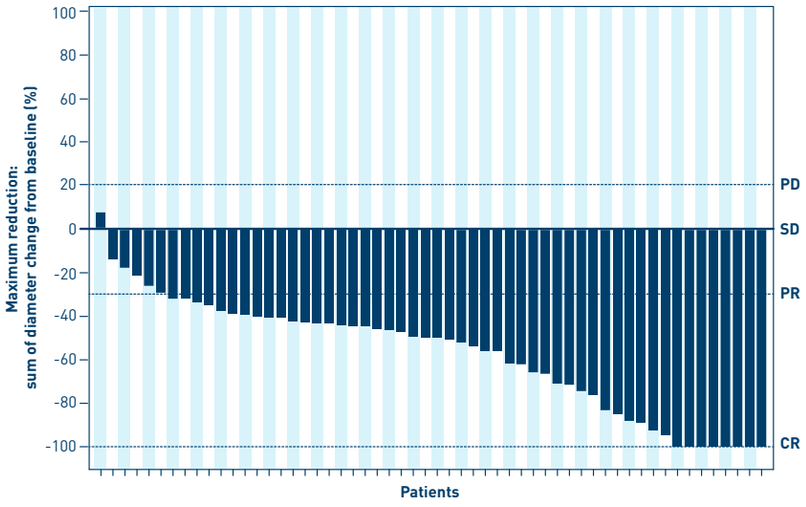
At data cutoff in this publication, a total of 82 patients were included in the safety population and 56 patients in the D842V group.

- In part 1 (dose escalation) of the study, an initial 46 patients with unresectable GIST were enrolled, of which 20 patients had a PDGFRA D842V mutation. Oral avapritinib was administered once daily with a starting dose of 30 mg-600 mg.
- In part 2 (dose expansion) of the study, an additional 36 patients with PDGFRA D842V-mutant GIST regardless of previous therapy were enrolled with starting doses of 300 or 400 mg oral avapritinib once daily.
- Although only a subset of patients was reported in the enclosed publication, the NAVIGATOR study included a broad range of patients who had unresectable or metastatic GIST with 1 or more measurable target lesion per modified Response Evaluation Criteria in Solid Tumors version 1.1.

Results in patients with the PDGFRA D842V mutation

ORR (primary endpoint) was achieved in 88% (49/56) (95% CI: 76%, 95%) of patients with D842V mutation treated with avapritinib in part 1 and 2, including 5 patients (9%) who achieved a complete response (CR) and 44 patients (79%) who achieved partial response (PR).

Maximal percentage change in sum of target lesion diameters from baseline in patients with PDGFRA D842V-mutant GIST (n=56)*



88% ORR
(95% CI: 76%, 95%)

MEDIAN DOR NOT REACHED

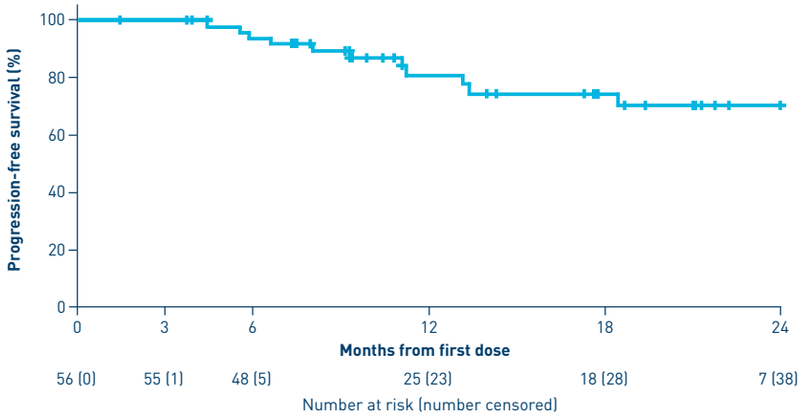
12-MONTH DOR
70%
(95% CI: 54%, 87%)

*Maximum tolerated dose (MTD) was 400 mg and recommended phase 2 dose (RP2D) was 300 mg.

Stable disease was seen in 7 patients (13%).

PD=progressive disease; SD=stable disease.
Horizontal lines denoting CR, PR, SD, and PD refer only to response in target lesions.

Progression-free survival



12-MONTH PFS
81%
(95% CI 69%, 93%)

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Safety

- Table lists treatment-related adverse events occurring in ≥10% of all patients
- There were no treatment-related grade 5 adverse events

Adverse events related to study drug*[a] (all doses) (N=82)

Adverse event	Grade (%)			Adverse event	Grade (%)		
	Gr 1-2	Gr 3	Gr 4		Gr 1-2	Gr 3	Gr 4
Any related adverse event	43%	51%	6%	Eyelid edema	13%	0%	0%
Nausea	61%	1%	0%	Leukopenia	12%	1%	0%
Fatigue	49%	6%	0%	Headache	12%	0%	0%
Diarrhea	39%	5%	0%	Hyperbilirubinemia	9%	4%	0%
Periorbital edema	43%	1%	0%	Dry mouth	11%	0%	0%
Anemia	26%	17%	0%	Pleural effusion	7%	4%	0%
Decreased appetite	32%	1%	0%	Cognitive disorder	7%	2%	0%
Vomiting	30%	1%	0%	Dry skin	10%	0%	0%
Memory impairment	30%	0%	0%	Hypomagnesemia	9%	1%	0%
Hair color changes	29%	0%	0%	Rash	10%	0%	0%
Increased lacrimation	29%	0%	0%	Decreased weight	10%	0%	0%
Peripheral edema	29%	0%	0%	Decreased neutrophil count	2%	5%	1%
Increased bilirubin	21%	2%	0%	Vertigo	5%	2%	0%
Face edema	23%	0%	0%	Lymphopenia	2%	2%	0%
Dysgeusia	20%	0%	0%	Hypocalcemia	1%	2%	0%
Hypophosphatemia	12%	6%	1%	Mental impairment	1%	1%	1%
Neutropenia	11%	7%	0%	Peripheral neuropathy	2%	1%	0%
Dizziness	17%	0%	0%	Delirium	0%	2%	0%
Dyspepsia	16%	0%	0%	Psychotic disorder	0%	2%	0%
Alopecia	15%	0%	0%				

*As determined by investigator.
[a]National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

The above table has been adapted from Table 2. For full breakdown of adverse events by Grade, see Table 2 in the reference.

With the RP2D dose of 300 mg, the most common grade 1-2 events were nausea (22/32; 69%), diarrhea (13/32, 41%), decreased appetite (12/32, 38%), and fatigue (12/32, 38%).

Cognitive effects occurred in 33/82 (40%) patients. Cognitive effects were primarily Grade 1 (19, 23%), and resulted in treatment discontinuation in only two patients (2%). At least one dose reduction or treatment interruption was required in 69/82 (84%) patients.

Intracranial bleeding occurred in 2/82 (2%) patients.

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Limitations

- NAVIGATOR is an open-label, single-arm, phase 1 study. Due to the rarity of D842V-mutant GIST tumors, safety features were not comprehensively characterized with a control group.
- The secondary endpoints of DOR, PFS, and OS were not sufficiently mature at the time of the analysis to further interpret the outcomes.
- PDGFRA D842V resistance mechanisms remain unknown due to the small number of patients who had disease progression at data cutoff.

INDICATION

AYVAKIT is a kinase inhibitor indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

IMPORTANT SAFETY INFORMATION

There are no contraindications for AYVAKIT.

Intracranial hemorrhage (e.g., subdural hematoma, intracranial hemorrhage, and cerebral hemorrhage) occurred in 1% of 267 patients (0.7% Grade 3 or 4) with GIST and overall in 3% of 335 patients (1.2% Grade 3 or 4) who received AYVAKIT. Overall, 0.9% of patients receiving AYVAKIT required permanent discontinuation for an intracranial hemorrhage. Withhold AYVAKIT and then resume at a reduced dose upon resolution, or permanently discontinue AYVAKIT based on severity.

In 335 patients receiving AYVAKIT, CNS adverse reactions occurred overall in 58% of patients including cognitive impairment (41%; 3.6% Grade 3 or 4), dizziness (20%; 0.6% Grade 3 or 4), sleep disorders (15%; 0.3% Grade 3 or 4), mood disorders (13%; 1.5% Grade 3 or 4), speech disorders (6%; none Grade 3 or 4), and hallucinations (2.1%; none Grade 3 or 4). Overall, 3.9% of patients required permanent discontinuation of AYVAKIT for a CNS adverse reaction. Depending on severity, withhold AYVAKIT and then resume at the same dose or at a reduced dose upon improvement, or permanently discontinue AYVAKIT.

AYVAKIT can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential and pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use an effective method of contraception during treatment with AYVAKIT and for 6 weeks after the final dose of AYVAKIT. Advise women not to breastfeed during treatment with AYVAKIT and for two weeks after the final dose. Advise females and males of reproductive potential that AYVAKIT may impair fertility.

In 204 patients with unresectable or metastatic GIST, the most common adverse reactions (≥ 20%) were edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash and dizziness.

To report suspected adverse reactions, contact Blueprint Medicines Corporation at 1-888-258-7768 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Avoid coadministration of AYVAKIT with strong and moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce dose of AYVAKIT. Avoid coadministration of AYVAKIT with strong and moderate CYP3A inducers.

Please see the full Prescribing Information for AYVAKIT.

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