

Company

Blueprint Medicines

Drug or Device Name

AYVAKIT™ (avapritinib)

Category

Pharmaceutical

Compound/Technical Name

Avapritinib

Trade Name

Ayvakit

Date of Approval

01/09/2020

Therapeutic Categories

PDGFRA exon 18 mutant gastrointestinal stromal tumors

Indications

On January 9, 2020, Ayvakit (avapritinib) was approved by the U.S. Food and Drug Administration (FDA) 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. The FDA has granted three breakthrough therapy designations to Ayvakit for the treatment of: 1) unresectable or metastatic GIST harboring the PDGFRA D842V mutation, 2) advanced systemic mastocytosis (SM), including the subtypes of aggressive SM, SM with an associated hematologic neoplasm and mast cell leukemia, and 3) moderate to severe indolent SM. On June 16, 2021, Ayvakit was FDA approved for the treatment of adults with advanced SM. In addition, we are currently enrolling a registration-directed clinical trial of Ayvakit in patients with indolent SM.

Background

Ayvakit, a selective and potent PDGFRA and KIT inhibitor, is one of nine approved or investigational precision therapies designed by scientists at Blueprint Medicines using the company's precision therapy platform. Since our founding just a decade ago, Blueprint Medicines has evolved into one of the world's leading precision therapy companies and, as a fully integrated enterprise, we are now delivering two approved medicines – including Ayvakit – directly to patients. PDGFRA and KIT are structurally related kinases implicated in multiple cancers. In patients with gastrointestinal stromal tumor (GIST), the activating PDGFRA D842V mutation occurs in approximately 5-6% of patients. Prior to Ayvakit, these patients had a poor prognosis with natural history data showing essentially no objective responses, median progression free survival (PFS) of only 3-5 months and median overall survival (OS) of approximately 15 months, despite best available therapy. Structurally, the D842V

mutation occurs in the activation loop, which shifts the kinase into the active conformation, thereby driving oncogenic signaling. Whereas Ayvakit is a type I inhibitor, previously approved GIST therapies are type II inhibitors that bind to the inactive conformation of the kinase and are thus ineffective against the PDGFRA D842V mutation. The KIT D816V mutation is homologous to the PDGFRA D842V mutation, also occurring in the activation loop. This mutation is the disease driver in nearly all patients with SM, a rare disease characterized by uncontrolled proliferation and activation of mast cells resulting in life-threatening organ infiltration and chronic, severe and often unpredictable symptoms. Imatinib lacks activity against KIT D816V and is approved in the U.S. for patients with advanced SM with no KIT D816V mutation or unknown KIT mutation status. The multikinase inhibitor midostaurin is approved for advanced SM; however, few patients achieve complete remission, and gastrointestinal and other adverse events are common and often lead to discontinuation.

Development

The development of Ayvakit was marked by strong signals of efficacy early in clinical development, which provided rapid proof of concept for both Ayvakit and our scientific platform early in the company's evolution. In the fourth quarter of 2015, we initiated the Phase 1 NAVIGATOR trial in patients with advanced GIST. By December, one of the first patients with PDGFRA D842V mutant GIST enrolled in the dose escalation portion of the trial showed a 40% reduction in tumor lesions at the first post-baseline scan. This early signal was highly encouraging for investigators who urgently needed a new treatment option for their patients, and fueled enthusiasm for continued development. As the trial continued, the first proof-of-concept data were presented at the 2016 EORTC-NCI-AACR Symposium. Important scientific presentations included a presentation during the New Drugs on the Horizon session at the 2017 AACR Annual Meeting and seminal publications in *Science Translational Medicine* and *Lancet Oncology*. Based on data from the NAVIGATOR trial, the FDA granted breakthrough therapy designation to Ayvakit for PDGFRA D842V mutant GIST in June 2017. In June 2019, we submitted a New Drug Application to the FDA, which resulted in approval of Ayvakit for PDGFRA exon 18 mutant GIST in January 2020, just over 4 years after the first trial patient received Ayvakit. Similarly, a strong signal of efficacy was observed early in the development of Ayvakit in SM. In March 2016, the first SM patient received Ayvakit in the Phase 1 EXPLORER trial. Important scientific presentations included a presentation at the Scientific Plenary Session at the 2018 ASH Annual Meeting. In 2018 and 2020, the FDA granted breakthrough therapy designations for advanced and indolent SM, respectively. In December 2020, we submitted an NDA to the FDA, which led to approval for advanced SM in June 2021.

Innovation

Prior failed efforts to target the PDGFRA D842V and KIT D816V activation loop mutations in GIST and SM largely focused on iterative medicinal chemistry efforts using the structure of imatinib – a type II KIT inhibitor first approved in 2001 – as a starting point. We took a different approach and designed a novel type I KIT inhibitor using our scientific platform, which includes a propriety compound library fully annotated against the kinome. Through this work, we designed a development candidate – first called BLU-285 – with high selectivity for KIT and PDGFRA and subnanomolar potency against the PDGFRA D842V and KIT D816V activation loop mutants. This profile translated into transformative clinical outcomes in clinical trial patients. In patients with PDGFRA D842V mutant GIST, who previously had no effective therapy, Ayvakit showed an 89% overall response rate (ORR) and the median duration of response (DOR) was not reached. In addition, preliminary overall survival (OS) data estimated 81% of patients were alive at 24 months. Ayvakit was generally well tolerated and the most common adverse events were nausea, fatigue, diarrhea, periorbital edema, anemia, decreased appetite, vomiting and

memory impairment. Following approvals in the U.S. and Europe, we are now working to bring Ayvakit to patients, including by working directly with the GIST clinical and patient communities to support broad use of actionable biomarker testing. In patients with advanced SM, Ayvakit showed a 57% ORR, with an additional 15% of patients demonstrating clinical improvement, an additional category of treatment response. In addition, 28% of patients had a complete remission (CR). The median DOR was 38.3 and median OS was not reached. Ayvakit was generally well tolerated and the most common adverse events were edema, diarrhea, nausea and fatigue/asthenia. By comparison, the multikinase inhibitor midostaurin previously showed an ORR of 17% in advanced SM with no CRs.

Pubmed

Evans E, et al. A precision therapy against cancers driven by KIT/PDGFR mutations. *Sci Transl Med*. 2017 Nov 1;9(414):eaao1690. doi: 10.1126/scitranslmed.aao1690. Link: <https://stm.sciencemag.org/content/9/414/eaao1690.short> Heinrich M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. *Lancet Oncol*. 2020 Jul;21(7):935-946. doi: 10.1016/S1470-2045(20)30269-2. Link: [https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(20\)30269-2/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30269-2/fulltext) Jones R, et al. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: Long-term efficacy and safety data from the NAVIGATOR phase I trial. *Eur J Cancer*. 2021 Mar;145:132-142. doi: 10.1016/j.ejca.2020.12.008. Epub 2021 Jan 16. Link: [https://www.ejancer.com/article/S0959-8049\(20\)31423-4/fulltext](https://www.ejancer.com/article/S0959-8049(20)31423-4/fulltext)

Attachments

- 1625252231ASH-2018-oral-presentation.pdf
- 1625252036BLU285_Science_Translational_Medicine-Nov2017.full.pdf
- 1625252170Avapritinib_GIST_Lancet_Oncology_2020.pdf
- 1625252216Blueprint-Medicines-ESMO-2020-Avapritinib-PDGFR-GIST-NAVIGATOR-Update-Presentation.pdf
- 1625107838AYVAKIT_prescribing_information.pdf

Submit