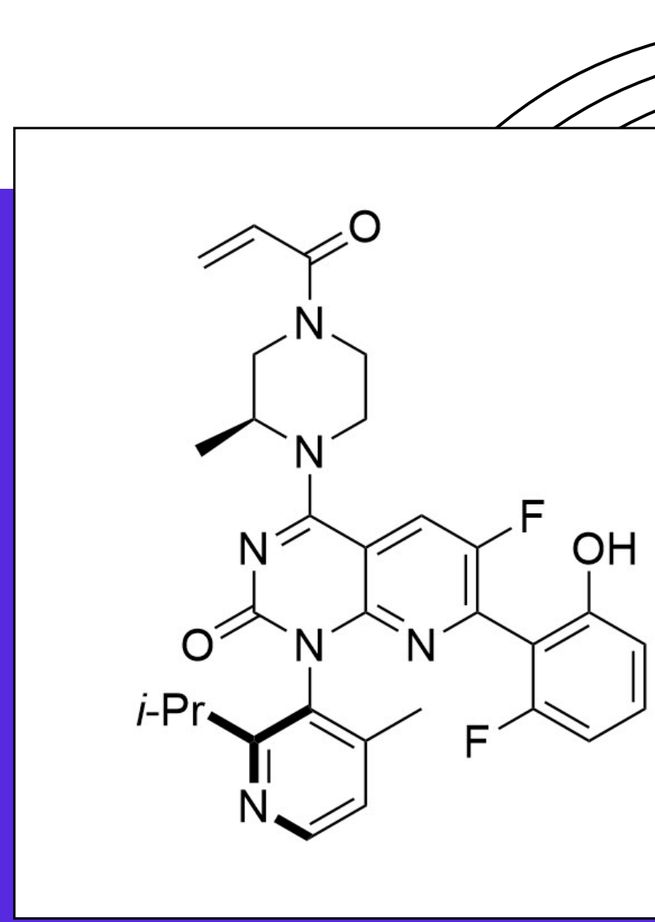
2021 Small Molecule Drug Approvals - Oncology Deep Dive



drug hunter

01 umbralisib (PI3Kδ and CK1ε inhibitor)

02 tivozanib (pan-VEGFR kinase inhibitor)

03 mephalan flufenamide (nitrogen mustard prodrug)

04 mobocertinib (EGFR exon 20 insertion kinase inhibitor)

05 sotorasib ($KRAS^{G12C}$ inhibitor)

06 trilaciclib (CDK4/6 kinase inhibitor)

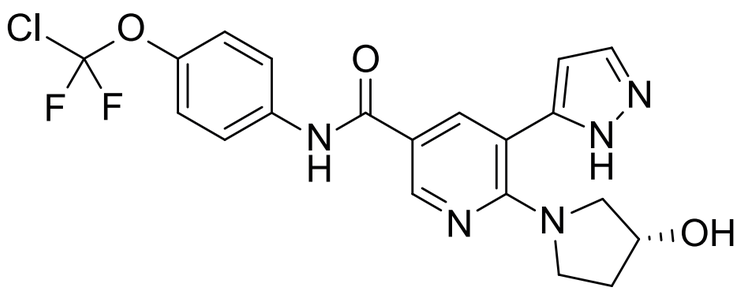
07 infigratinib (FGFR1/2/3 inhibitor)

08 tepotinib (MET kinase inhibitor)

09 asciminib (allosteric BCR-ABL1 kinase inhibitor)

asciminib

allosteric BCR-ABL1 kinase inhibitor



ABL/BCR-ABL1 kinase inhibitor
myeloid leukemia
oral: up to 200 mg BID

Asciminib is an oral, ABL/BCR-ABL1 allosteric kinase inhibitor approved for adults with Philadelphia chromosome-positive chronic myeloid leukemia (CML) who were previously treated with at least two tyrosine kinase inhibitors. It was derived from one of the compounds identified through a phenotypic, differential cytotoxicity screen, confirming with NMR and XRD. Asciminib binds to native ABL1 and BCR-ABL1 tumor kinase in a unique and non-competitive manner. It is the sixth BCR-ABL inhibitor (imatinib, dasatinib, nilotinib, ponatinib, bosutinib), but the first allosteric inhibitor.

Chimeric BCR-ABL1 fusions are the cause of 95% of CML cases and are generated by failed DNA damage repair resulting in a shortened chromosome 22, or Philadelphia chromosome. The chimeric protein is constitutively active as it is missing the myristoylation autoregulatory element and drives uncontrolled hematopoietic stem cell proliferation. But because BCR-ABL1 retains the myristate binding site, kinase activity can still be inhibited through asciminib binding to the allosteric myristate site without affecting other kinases. This was shown using an activity screen of 335 protein kinases in which the presence of asciminib did not have any substantial effect on off-target kinase activities. These results suggest that asciminib treatment may produce fewer side-effects than classical kinase inhibitors. In addition, because a large portion of resistant tumors are due to mutations in the ATP-binding pocket, of which T315I is the most difficult to treat, asciminib is potentially better at treating cancers that are resistant to competitive kinase inhibitors.

In a Phase III active-controlled trial, significantly more patients on asciminib (25%) were found to reach a major molecular response and complete cytogenetic response compared to treatment with the current first-line TKI for CML, bosutinib (13%), making it a potential best-in-class drug. A Phase I study is currently investigating the safety of asciminib in combination with other kinase inhibitors in CML patients with the T315I mutation. An 80 mg dose is usually given and those with T315I mutation are given 200 mg.

The molecule was patented by Novartis AG (US8829195B2).

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