

**Company**

Incyte Corp.

**Drug or Device Name**

Pemazyre® (pemigatinib)

**Category**

Pharmaceutical

**Compound/Technical Name**

pemigatinib

**Trade Name**

Pemazyre

**Date of Approval**

04/17/2020

**Therapeutic Categories**

Kinase inhibitor

**Indications**

Pemazyre is a kinase inhibitor indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

In August of 2022, Pemazyre received a second FDA approval for the treatment of adults with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement.

(1) Pemazyre FDA Approval: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-treatment-patients-cholangiocarcinoma-cancer-bile-ducts> \*See attached document for section content with references.

**Background**

Cholangiocarcinoma (CCA) is an aggressive cancer that forms in the bile duct.(6) Although rare, over the last three decades rates of CCA incidence and mortality have generally increased worldwide. (2,3,4,5) Symptoms of CCA include abdominal pain, nausea, weight loss, night sweats, fatigue, jaundice, general discomfort and weakness.(6,7) Patients with hepatobiliary cancers including CCA also exhibit high levels of depressiveness, anxiety and reduced quality of life.(8) Resection is the only potentially curative option for CCA, but few patients have resectable tumors at diagnosis.(6,7) Because early-stage disease is often asymptomatic, diagnosis typically occurs once the disease has already progressed to

an advanced stage.(6) For patients with unresectable tumors, prognosis is poor: for molecularly unselected patients with bile duct cancers, median overall survival following second-line chemotherapy is 6.2 months, and is associated with high rates of adverse events.(9,10) Approximately 10-15% of patients with intrahepatic CCA have tumors in which the fibroblast growth factor 2 (FGFR2) gene has undergone fusion or rearrangement with a gene encoding another protein.(11,12,13,14,16) Such fusions have been shown to be oncogenic drivers in some patients.(17) Pemigatinib is a small molecule inhibitor of FGFR 1, 2 and 3 kinases that blocks FGFR phosphorylation and signaling and decreases the viability of cells expressing FGFR gene alterations in preclinical models.(18) Prior to the approval of pemigatinib (Pemazyre®), patients with CCA had no targeted treatment options.(6) Now, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommends Pemazyre as a subsequent-line treatment option for unresectable or metastatic CCA with FGFR2 fusions or rearrangements following disease progression.(19) \*See attached document for section content with references

## Development

The active ingredient of Pemazyre was discovered through rational design and iterative lead optimization – thousands of molecules were synthesized and evaluated in a classic medicinal chemistry campaign taking several years. Through hypothesis-driven testing of its ability to inhibit FGFR phosphorylation and signaling and, in turn, to decrease the viability of cells expressing FGFR genetic alterations, early preclinical results demonstrated the potential of Pemazyre as a candidate for treatment of malignancies with FGFR alterations.(18) In animal models, Pemazyre suppressed the growth of tumors driven by dysregulated FGFR signaling, including tumors with FGFR2 fusions derived from patients with CCA.(18) Pre-clinical characterization of the pharmacokinetics and metabolism of Pemazyre, as well as a comprehensive toxicology program, provided evidence around dose-limiting toxicities, target organs, and exposures, which supported advancement into clinical studies.(1,20) Formulation studies enabled the preparation of Pemazyre as an immediate-release tablet that promotes rapid oral absorption.(1,18,20) The FDA approval of Pemazyre was based on the multicenter, open-label, single-arm, Phase 2 FIGHT-202 study, in which 36% of patients with CCA and FGFR2 fusions or rearrangements exhibited a clinical response to Pemazyre with a manageable safety profile.(21) The clinical development program also informed the understanding of potential drug-drug and drug-disease interactions and guidance for dose adjustments in those situations.(1) Characterization of doses and exposures associated with anti-tumor efficacy and on-target toxicity (hyperphosphatemia) was instrumental in setting the optimal dose range and protocols for adverse event management.(1) In parallel to its clinical development, and in recognition of its potential, the U.S. Food and Drug Administration (FDA) granted pemigatinib Breakthrough Therapy designation, Orphan Drug designation, Priority Review, and Accelerated Approval for the treatment of CCA. \*See attached document for section content with references.

## Innovation

Now that a targeted therapy like Pemazyre has been approved for CCA, clinicians have an important incentive to implement routine use of molecular testing during diagnosis.(1,22) Testing all patients with advanced/metastatic CCA is critical to identifying those with FGFR2 fusions or rearrangements who may benefit from FGFR inhibitor therapy; such testing is recommended by the NCCN Clinical Practice Guidelines in Oncology.(22) Pemazyre provides the first and only FDA-approved, individualized treatment option for these patients.(1,21) In addition to identifying patients with FGFR2 fusions or rearrangements who may benefit from Pemazyre treatment, an increased use of molecular testing in patients with CCA may also identify those who might benefit from other investigational interventions

in clinical trials. Pemazyre – the first and only FDA-approved treatment for adults with previously treated, unresectable locally advanced or metastatic CCA with a FGFR2 fusion or other rearrangement(1) – is also the first internally discovered product to be commercialized globally by Incyte.(21) To investigate the potential of Pemazyre beyond its current indication, multiple Phase 2 and 3 studies are ongoing through the FIGHT (Fibroblast Growth factor receptor in oncology and Hematology Trials) program, evaluating the use of Pemazyre in: first-line CCA with FGFR2 fusions/rearrangements; myeloid/lymphoid neoplasms with eosinophilia and FGFR1 gene rearrangement; and, other advanced malignancies with FGFR1/2/3 gene alterations.(23) The hope is that this research provides further insights into the science of FGFR and its role as a tumorigenic driver in an array of cancers to help pave the way for future therapeutic advances. \*See attached document for section content with references.

## Pubmed

1. Pemazyre™ (pemigatinib) Full Prescribing Information. U.S. Food and Drug Administration. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/213736s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213736s000lbl.pdf) 2. Florio AA, et al. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012. *Cancer* 2020;126:2666-2678. Available at: <https://pubmed.ncbi.nlm.nih.gov/32129902/> 3. Mukkamalla SKR, et al. Trends in incidence and factors affecting survival of patients with cholangiocarcinoma in the United States. *J Natl Compr Canc Netw* 2018;16:370-376. Available at: <https://pubmed.ncbi.nlm.nih.gov/29632056/> 4. Gad MM, et al. Epidemiology of cholangiocarcinoma; United States incidence and mortality trends. *Clin Res Hepatol Gastroenterol* 2020;44:885-893 Available at: <https://pubmed.ncbi.nlm.nih.gov/32359831/> 5. Bertuccio P, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. *J Hepatol* 2019;71:104-114. Available at: <https://pubmed.ncbi.nlm.nih.gov/30910538/> 6. Banales JM, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol.* 2020;17:557-588. Available at: <https://pubmed.ncbi.nlm.nih.gov/32606456/> 7. Forner A, et al. Clinical presentation, diagnosis and staging of cholangiocarcinoma. *Liver Int.* 2019;39 Suppl 1:98-107. Available at: <https://pubmed.ncbi.nlm.nih.gov/30831002/> 8. Graf J, Stengel A. Psychological Burden and Psycho-Oncological Interventions for Patients With Hepatobiliary Cancers-A Systematic Review. *Front Psychol.* 2021 May 5;12:662777. doi: 10.3389/fpsyg.2021.662777. PMID: 34025526; PMCID: PMC8131509. Available at: <https://pubmed.ncbi.nlm.nih.gov/34025526/> 9. Valle J, et al. *N Engl J Med.* 2010;362:1273-1281. Available at: <https://pubmed.ncbi.nlm.nih.gov/20375404/> 10. Lamarca A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol.* 2021 Mar 30. [Online ahead of print] Available at: <https://pubmed.ncbi.nlm.nih.gov/33798493/> 11. Farshidfar F, et al. *Cell Rep.* 2017;18(11):2780-2794. Available at: <https://pubmed.ncbi.nlm.nih.gov/28297679/> 12. Arai Y, et al. *Hepatology.* 2014;59:1427-1434. Available at: <https://pubmed.ncbi.nlm.nih.gov/24122810/> 13. Graham RP, et al. *Hum Pathol.* 2014;45(8):1630-1638. Available at: <https://pubmed.ncbi.nlm.nih.gov/24837095/> 14. Lowery MA, et al. *Clin Cancer Res.* 2018;24:4154-4161. Available at: <https://pubmed.ncbi.nlm.nih.gov/29848569/> 15. Javle M, et al. *Cancer.* 2016;122:3838-3847. Available at: <https://pubmed.ncbi.nlm.nih.gov/27622582/> 16. Goyal L, et al. *Cancer Discov.* 2017;7:252-263. Available at: <https://pubmed.ncbi.nlm.nih.gov/28034880/> 17. Rizvi S, Borad MJ. *J Gastrointest Oncol.* 2016;7:789-796. Available at: <https://pubmed.ncbi.nlm.nih.gov/27747092/> 18. Liu P, et al. INCB054828 (Pemigatinib), a Potent and Selective Inhibitor of Fibroblast Growth Factor Receptors 1, 2, and 3, Displays Activity Against Genetically Defined Tumor Models. *PLoS ONE* 2020;15(4): e0231877. <https://doi.org/10.1371/journal.pone.0231877> Available at: <https://pubmed.ncbi.nlm.nih.gov/32315352/> 19. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers V.4.2020. © National Comprehensive Cancer Network,

Inc. 2020. All rights reserved. Accessed June 19, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. 20. Merz V, et al. Pemigatinib, a potent inhibitor of FGFRs for the treatment of cholangiocarcinoma. *Future Oncol.* 2021;17:389-402. Available at: <https://pubmed.ncbi.nlm.nih.gov/33034201/> 21. Abou-Alfa GK, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol.* 2020 May;21(5):671-684. doi: 10.1016/S1470-2045(20)30109-1. Epub 2020 Mar 20. PMID: 32203698. Available at: <https://pubmed.ncbi.nlm.nih.gov/32203698/> 22. Mosele F, et al. *Ann Oncol.* 2020;31:1491-1505. Available at: <https://pubmed.ncbi.nlm.nih.gov/32853681/> 23. Weaver A, Bossaer, JB. *J Oncol Pharm Pract.* 2021;27:702-710. Available at: <https://pubmed.ncbi.nlm.nih.gov/33375902/> \*Please see attached document for section content with references.

#### Attachments

- 16456404191622129360Incyte\_PrixGalienUSA\_PemazyreNomination\_Final\_27May2021.docx
- 16456402571622129360Incyte\_PrixGalienUSA\_PemazyreNomination\_Final\_27May2021.docx
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