**Prix Galien USA Best Pharmaceutical Agent 2021: Pemazyre**

**Entry Information**

**Category:** Best Pharmaceutical Agent

**Drug/device name:** Pemazyre

**Compound/tech. 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.[[1]](#endnote-1)

[Pemazyre FDA Approval](https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-treatment-patients-cholangiocarcinoma-cancer-bile-ducts)

**Background information and need for drug/device**

**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]](#endnote-2),[[3]](#endnote-3),[[4]](#endnote-4),[[5]](#endnote-5)

Symptoms of CCA include abdominal pain, nausea, weight loss, night sweats, fatigue, jaundice, general discomfort and weakness.[[6]](#endnote-6),[[7]](#endnote-7) Patients with hepatobiliary cancers including CCA also exhibit high levels of depressiveness, anxiety and reduced quality of life.[[8]](#endnote-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]](#endnote-9),[[10]](#endnote-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]](#endnote-11),[[12]](#endnote-12),[[13]](#endnote-13),[[14]](#endnote-14),[[15]](#endnote-15),[[16]](#endnote-16) Such fusions have been shown to be oncogenic drivers in some patients.[[17]](#endnote-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]](#endnote-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]](#endnote-19)

**History of the development of the drug/device**

**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]](#endnote-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]](#endnote-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.

**Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition**

**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]](#endnote-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.19 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 rearrangement1 – 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 (**FI**broblast **G**rowth factor receptor in oncology and **H**ematology **T**rials) 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]](#endnote-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.

**Pubmed references/links**

Referenced via endnotes below

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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. [↑](#endnote-ref-19)
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