Incyte Announces FDA Approval of Pemazyre® (pemigatinib) as the First and Only Targeted Treatment for Myeloid/Lymphoid Neoplasms (MLNs) with FGFR1 Rearrangement

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– This marks the second indication for Pemazyre, which received accelerated FDA approval in 2020 for adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement

– Pemazyre is the only FGFR inhibitor with multiple indications

WILMINGTON, Del.--(BUSINESS WIRE)--Aug. 26, 2022-- Incyte (Nasdaq:INCY) today announced that the U.S. Food and Drug Administration (FDA) has approved Pemazyre® (pemigatinib), a selective fibroblast growth factor receptor (FGFR) inhibitor, for the treatment of adults with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement. MLNs with FGFR1 rearrangement are extremely rare and aggressive blood cancers that may impact less than 1 in 100,000 people in the United States[1].

“The approval of Pemazyre represents an important treatment advancement for people living with MLNs with FGFR1 rearrangement who currently have limited treatment options,” said Hervé Hoppenot, Chief Executive Officer, Incyte. “These are complex hematologic malignancies with a range of presentations, and this approval highlights Incyte’s continued leadership and commitment to advancing care for patients with rare blood cancers.”

A patient with an MLN with FGFR1 rearrangement may present with bone marrow involvement with a chronic myeloid malignancy (such as myeloproliferative neoplasm [MPN], myelodysplastic syndrome/MPN) or a blast phase malignancy (such as B- or T-cell acute lymphoblastic leukemia/lymphoma, acute myeloid leukemia or mixed phenotype acute leukemia). Bone marrow involvement may or may not be accompanied by extramedullary disease (EMD); some patients may present with EMD only. MLNs with FGFR1 rearrangement are caused by chromosomal translocations involving the FGFR1 gene, with various partner genes resulting in constitutive activation of the FGFR1 receptor tyrosine kinase, impacting cell differentiation, proliferation and survival[2]. Patients often relapse because existing first-line therapies sometimes fail to induce durable clinical and cytogenetic responses.

The FDA approval was based on data from the Phase 2 FIGHT-203 study, a multicenter open-label, single-arm trial that evaluated the safety and efficacy of Pemazyre in 28 patients with relapsed or refractory MLNs with FGFR1 rearrangement. Patients could have relapsed after allogeneic hematopoietic stem cell transplantation (allo-HSCT) or after a disease modifying therapy or were not a candidate for allo-HSCT or other disease modifying therapies.

- Study participants included patients with documented MLNs with an 8p11 translocation on conventional cytogenetics and/or an FGFR1 rearrangement on break-apart FISH testing. (An FDA-approved test for detection of FGFR1 rearrangement in patients with relapsed or refractory MLNs is not available.)
- In patients with chronic phase in the marrow with or without EMD (N = 18), the complete response (CR) rate was 78% (14/18; 95% CI 52, 94). The median time to response of CR was 104 days (range, 44 to 435 days). The median duration of CR was not reached (range, 1+ to 988+ days).
- In patients with blast phase in the marrow with or without EMD (N = 4), two patients achieved a CR (duration: 1+ and 94 days).
- In patients with EMD only (N = 3), one patient achieved a CR (duration: 64+ days).
- For all patients (N = 28 including three patients without evidence of morphologic disease) the complete cytogenetic response rate was 79% (22/28; 95% CI: 59, 92).

The most common (≥ 20%) adverse reactions were hyperphosphatemia (74%), nail toxicity (62%), alopecia (59%), stomatitis (53%), diarrhea (50%), dry eye (50%), fatigue (44%), rash (35%), abdominal pain (35%), anemia (35%), constipation (32%), dry mouth (32%), epistaxis (29%), retinal pigment epithelial detachment (26%), extremity pain (26%), decreased appetite (24%), dry skin (24%), dyspepsia (24%), back pain (24%), nausea (21%), blurred vision (21%), peripheral edema (21%) and dizziness (21%).

“In patients with relapsed or refractory MLNs with FGFR1 rearrangement treated with Pemazyre in FIGHT-203, the high rate of complete response and complete cytogenetic response in patients with chronic phase disease and the high rate of complete cytogenetic response in patients with blast phase disease is clinically meaningful, especially in light of the lack of these specific responses with existing first-line treatments,” said Dr. Srdan Verstovsek, M.D., Ph.D., Professor, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, and principal investigator for the FIGHT-203 study.

The supplemental New Drug Application (sNDA) for Pemazyre for the treatment of adults with relapsed or refractory MLNs with FGFR1 rearrangement was reviewed by the FDA under Priority Review. The FDA grants Priority Review to medicines that may offer a major advance in treatment where none currently exists. The designation shortens the review period to six months compared to 10 months for Standard Review.

Incyte established its leadership in rare blood cancers more than 10 years ago with the development of the first JAK inhibitor approved by the FDA for the treatment of certain patients with myelofibrosis and polycythemia vera. Incyte continues to research additional pathways to address rare blood cancers through its LIMBER (Leadership In MPNs Beyond Ruxolitinib) clinical development program, designed to evaluate multiple therapies and investigational strategies to improve and expand treatments for patients living with MPNs and other related hematologic malignancies and conditions.

Incyte is committed to supporting patients and removing barriers to access medicines. Eligible patients in the U.S. who are prescribed Pemazyre have access to IncyteCARES (Connecting to Access, Reimbursement, Education and Support), a comprehensive program offering personalized patient

support, including financial assistance and ongoing education and additional resources. More information about IncyteCARES is available by visiting www.incytecares.com or calling 1-855-452-5234.

About FIGHT-203
FIGHT-203 is a Phase 2, multicenter trial that enrolled patients 18 years and older with myeloid/lymphoid neoplasms (MLNs) with a fibroblast growth factor receptor 1 (FGFR1) rearrangement. Sponsored by Incyte, the study evaluated the safety and efficacy of pemigatinib for the treatment of adults with MLNs with FGFR1 rearrangement. Patients received pemigatinib 13.5 mg once daily in 21-day cycles, either on a continuous schedule (the approved recommended starting dosage for use in patients with MLNs with FGFR1 rearrangement) or as an intermittent schedule (14 days on, 7 days off, an unapproved dosage regimen in MLN with FGFR1 rearrangement). Pemigatinib was administered until disease progression or unacceptable toxicity or until patients were able to receive allo-HSCT. For more information about the study, please visit https://clinicaltrials.gov/ct2/show/NCT03011372.

About Pemazyre® (pemigatinib)
Pemazyre, a fibroblast growth factor receptor (FGFR) inhibitor, is the first targeted treatment approved for use in the United States for treatment of adults with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement.

Pemazyre is also indicated for the treatment of adults with relapsed or refractory previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a 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 (DOR). Continued approval may be contingent on verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

Ocular Toxicity
Retinal Pigment Epithelial Detachment (RPED): PEMAZYRE can cause RPED, which may cause symptoms such as blurred vision, visual floaters, or photopsia. Clinical trials of PEMAZYRE did not conduct routine monitoring including optical coherence tomography (OCT) to detect asymptomatic RPED; therefore, the incidence of asymptomatic RPED with PEMAZYRE is unknown.

Among 635 patients who received a starting dose of PEMAZYRE 13.5 mg across clinical trials, RPED occurred in 11% of patients, including Grade 3-4 RPED in 1.3%. The median time to first onset of RPED was 56 days. RPED led to dose interruption of PEMAZYRE in 3.1% of patients, and dose reduction and permanent discontinuation in 1.3% and in 0.2% of patients, respectively. RPED resolved or improved to Grade 1 levels in 76% of patients who required dosage modification of PEMAZYRE for RPED.

Perform a comprehensive ophthalmological examination including OCT prior to initiation of PEMAZYRE and every 2 months for the first 6 months and every 3 months thereafter during treatment. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of PEMAZYRE. Modify the dose or permanently discontinue PEMAZYRE as recommended in the prescribing information for PEMAZYRE.

Dry Eye: Among 635 patients who received a starting dose of PEMAZYRE 13.5 mg across clinical trials, dry eye occurred in 31% of patients, including Grade 3-4 in 1.6% of patients. Treat patients with ocular demulcents as needed.

Hyperphosphatemia and Soft Tissue Mineralization
PEMAZYRE can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcification, calcinosis, and non-uremic calciphylaxis. Increases in phosphate levels are a pharmacodynamic effect of PEMAZYRE. Among 635 patients who received a starting dose of PEMAZYRE 13.5 mg across clinical trials, hyperphosphatemia was reported in 93% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 8 days (range 1-169). Phosphate lowering therapy was required in 33% of patients receiving PEMAZYRE.

Monitor for hyperphosphatemia and initiate a low phosphate diet when serum phosphate level is >5.5 mg/dL. For serum phosphate levels >7 mg/dL, initiate phosphate lowering therapy and withhold, reduce the dose, or permanently discontinue PEMAZYRE based on duration and severity of hyperphosphatemia as recommended in the prescribing information.

Embryo-Fetal Toxicity
Based on findings in an animal study and its mechanism of action, PEMAZYRE can cause fetal harm when administered to a pregnant woman. Oral administration of pemigatinib to pregnant rats during the period of organogenesis caused fetal malformations, fetal growth retardation, and embryo-fetal death at maternal exposures lower than the human exposure based on area under the curve (AUC) at the clinical dose of 13.5 mg.

Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the last dose.

Adverse Reactions: Cholangiocarcinoma
Serious adverse reactions occurred in 45% of patients receiving PEMAZYRE (n=146). Serious adverse reactions in ≥2% of patients who received PEMAZYRE included abdominal pain, pyrexia, cholangitis, pleural effusion, acute kidney injury, cholangitis infective, failure to thrive, hypercalcemia, hyponatremia, small intestinal obstruction, and urinary tract infection. Fatal adverse reactions occurred in 4.1% of patients, including failure to thrive, bile duct obstruction, cholangitis, sepsis, and pleural effusion.

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received PEMAZYRE. Adverse reactions requiring permanent discontinuation in ≥1% of patients included intestinal obstruction and acute kidney injury.

Dosage interruptions due to an adverse reaction occurred in 43% of patients who received PEMAZYRE. Adverse reactions requiring dosage interruption in ≥1% of patients included stomatitis, palmar-plantar erythrodysesthesia syndrome, arthralgia, fatigue, abdominal pain, AST increased, asthenia, pyrexia, ALT increased, cholangitis, small intestinal obstruction, alkaline phosphatase increased, diarrhea, hyperbilirubinemia, electrocardiogram QT prolonged, decreased appetite, dehydration, hypercalcemia, hyperphosphatemia, hypophosphatemia, back pain, pain in extremity, syncope, acute kidney injury, onychomadesis, and hypotension.

Dose reductions due to an adverse reaction occurred in 14% of patients who received PEMAZYRE. Adverse reactions requiring dosage reductions in ≥1% of patients who received PEMAZYRE included stomatitis, arthralgia, palmar-plantar erythrodysesthesia syndrome, asthenia, and onychomadesis.

Clinically relevant adverse reactions occurring in ≤10% of patients included fractures (2.1%). In all patients treated with pemigatinib, 0.5% experienced pathologic fractures (which included patients with and without cholangiocarcinoma [N = 635]). Soft tissue mineralization, including cutaneous calcification, calcinosis, and non-uremic calciphylaxis associated with hyperphosphatemia were observed with PEMAZYRE treatment.

Within the first 21-day cycle of PEMAZYRE dosing, serum creatinine increased (mean increase of 0.2 mg/dL) and reached steady state by Day 8, and then decreased during the 7 days off therapy. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

In cholangiocarcinoma (n=146) the most common adverse reactions (incidence ≥20%) were hyperphosphatemia (60%), alopecia (49%), diarrhea (47%), nail toxicity (43%), fatigue (42%), dysgeusia (40%), nausea (40%), constipation (35%), stomatitis (35%), dry eye (35%), dry mouth (34%), decreased appetite (33%), vomiting (27%), arthralgia (25%), abdominal pain (23%), hypophosphatemia (23%), back pain (20%), and dry skin (20%).

Adverse Reactions: Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement

Serious adverse reactions occurred in 53% of patients receiving PEMAZYRE at all dosages (n=34). Serious adverse reactions in > 5% of patients included acute kidney injury. Fatal adverse reactions occurred in 9% of patients who received PEMAZYRE, including acute kidney injury, multiple organ dysfunction syndrome, and malignant neoplasm progression, occurring in one patient each.

Permanent discontinuation due to an adverse reaction occurred in 12% of patients who received PEMAZYRE at all dosages. Adverse reactions requiring permanent discontinuation included cardiac failure, multiple organ dysfunction syndrome, blood alkaline phosphatase increase, and calciphylaxis. In patients who started treatment on the recommended dosage (n = 20), adverse reactions requiring dosage interruption of PEMAZYRE occurred in 80% of patients. Adverse reactions which required dosage interruption in > 2 patients treated at the recommended dosage included nail toxicities (20%) and hyperphosphatemia (15%).

Dose reductions of PEMAZYRE due to an adverse reaction occurred in 80% of patients who started treatment on the recommended dosage. Adverse reactions requiring dose reductions occurring in > 2 patients were nail toxicities (20%), hyperphosphatemia (20%), and alopecia (15%).

The most common (≥ 20%) adverse reactions were hyperphosphatemia (74%), nail toxicity (62%), alopecia (59%), stomatitis (53%), diarrhea (50%), dry eye (50%), fatigue (44%), rash (35%), abdominal pain (35%), anemia (35%), constipation (32%), dry mouth (32%), epistaxis (29%), retinal pigment epithelial detachment (26%), extremity pain (26%), decreased appetite (24%), dry skin (24%), dyspepsia (24%), back pain (24%), nausea (21%), blurred vision (21%), peripheral edema (21%), and dizziness (21%).

Drug Interactions

Avoid concomitant use of strong and moderate CYP3A inhibitors with PEMAZYRE. Reduce the dose of PEMAZYRE if concomitant use with a strong or moderate CYP3A inhibitor cannot be avoided. Avoid concomitant use of strong and moderate CYP3A inducers with PEMAZYRE.

Special Populations
Advise lactating women not to breastfeed during treatment with PEMAZYRE and for 1 week after the last dose.

Reduce the recommended dose of PEMAZYRE for patients with severe renal impairment as described in the prescribing information.

Reduce the recommended dose of PEMAZYRE for patients with severe hepatic impairment as described in the prescribing information.

Please see Full Prescribing Information for PEMAZYRE.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

You may also report side effects to Incyte Medical Information at 1-855-463-3463.

About Incyte
Incyte is a Wilmington, Delaware-based, global biopharmaceutical company focused on finding solutions for serious unmet medical needs through the discovery, development and commercialization of proprietary therapeutics. For additional information on Incyte, please visit Incyte.com and follow @Incyte.

Forward-Looking Statements
Except for the historical information set forth herein, the matters set forth in this press release, including statements regarding whether or when Pemazyre might provide a successful treatment option for patients with MLN with FGFR1 rearrangement, the Company's ongoing clinical development program for pemigatinib, the FIGHT-203 clinical trial program, the LIMBER program and Incyte's research in and approach to rare blood cancers and their treatment, contain predictions, estimates and other forward-looking statements.

These forward-looking statements are based on the Company's current expectations and subject to risks and uncertainties that may cause actual results to differ materially, including unanticipated developments in and risks related to: unanticipated delays; further research and development and the results of clinical trials possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development; the ability to enroll sufficient numbers of subjects in clinical trials and the ability to enroll subjects in accordance with planned schedules; the effects of the COVID-19 pandemic and measures to address the pandemic on the Company's clinical trials supply chain and other third-party providers and development and discovery operations; determinations made by the FDA or other regulatory authorities; the Company's dependence on its relationships with its collaboration partners; the efficacy or safety of the Company's products and the products of the Company's collaboration partners; the acceptance of the Company's products and the products of the Company's collaboration partners in the marketplace; market competition; sales, marketing, manufacturing and distribution requirements; and other risks detailed from time to time in the Company's reports filed with the Securities and Exchange Commission, including its annual report and its quarterly report on Form 10-Q for the quarter ended June 30, 2022. The Company disclaims any intent or obligation to update these forward-looking statements.

[1]Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2017;92:1243-1259.

[2]Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. *Blood*. 2017;129(6):704–714.

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