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FDA Approval Summary: Pemigatinib for Previously Treated, Unresectable Locally Advanced or Metastatic Cholangiocarcinoma with FGFR2 Fusion or Other Rearrangement

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Abstract

On April 17, 2020, the Food and Drug Administration granted accelerated approval to pemigatinib (PEMAZYRE, Incyte Corporation) 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. Approval was based on FIGHT-202 (NCT02924376), a multicenter open-label single-arm trial. Efficacy was based on 107 patients with locally advanced unresectable or metastatic cholangiocarcinoma whose disease had progressed on or after at least one prior therapy and had an FGFR2 gene fusion or rearrangement. Patients received pemigatinib, 13.5 mg orally, once daily for 14 consecutive days, followed by 7 days off therapy. Safety was based on a total of 466 patients, 146 of whom had cholangiocarcinoma and received the recommended dose). Efficacy endpoints were overall response rate (ORR) and duration of response (DOR) determined by an independent review committee using RECIST 1.1. ORR was 36% (95% CI: 27%, 45%). Median DOR was 9.1 months. The most common adverse reactions were hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin. Ocular

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toxicity and hyperphosphatemia are important risks of pemigatinib. The recommended dose is 13.5 mg orally once daily for 14 consecutive days followed by 7 days off therapy in 21-day cycles. FDA also approved the FoundationOne® CDX (Foundation Medicine, Inc.) as a companion diagnostic for patient selection.

Introduction

Cholangiocarcinoma (CCA) is a rare cancer arising from epithelial cells of bile ducts. CCA is grouped into anatomic subtypes—intrahepatic (iCCA), perihilar, or extrahepatic based on location of origin in the biliary tract. CCA accounts for approximately 3% of all gastrointestinal cancers worldwide and represents 3% of overall cancer-related mortality in the United States. (1, 2). Surgery is the preferred treatment option, but a mere 35% of patients are eligible for resection at the time of diagnosis (3). Median overall survival in patients with advanced CCA who are treated with standard of care chemotherapy is less than one year (4).

Treatment with gemcitabine and cisplatin represents the standard of care in the first-line advanced or metastatic setting, with limited treatment options thereafter. . Entrectinib and larotrectinib are approved for patients whose tumors harbor NTRK gene fusions, while pembrolizumab is approved for patients who are microsatellite-high/mismatch repair deficient (pembrolizumab) who are tumor mutational burden high (5, 6).

Fibroblast growth factor/fibroblast growth factor receptor (FGFR) fusions are a reported genetic modification in iCCA identified as an early driver of oncogenic events in iCCA (7). FGFR2 fusions are present in an estimated 13-14% of patients with iCCA (8, 9). Pemigatinib is a selective, potent, oral competitive inhibitor of FGFR1, FGFR2, and FGFR3 (10, 11).

Herein, we provide a summary of the FDA’s review of the marketing application that led to the accelerated approval of pemigatinib for the treatment of previously treated unresectable locally advanced or metastatic CCA.

Nonclinical Pharmacology and Toxicology

Pemigatinib is a kinase inhibitor that has activity against FGFR1, FGFR2, and FGFR3 at concentrations (0.39-1.2 nM) that were achieved at the 13.5 mg dose level used in clinical trials conducted to support the approval of the drug (free Cmax of approximately 22 nM based on ~91% protein binding). Treatment with pemigatinib inhibited in vitro and in vivo FGFR phosphorylation in FGFR2-amplified human gastric cancer cells and inhibited in vitro FGFR phosphorylation in Ba/F3 cells stably expressing TEL-FGFR1 or TEL-FGFR3 fusion proteins and in FGFR2-amplified cells spiked with human whole blood. Pemigatinib also reduced the phosphorylation of FGFR1 and the downstream signaling proteins ERK1/2 and STAT5 in cells expressing the constitutively active FGFR1OP2-FGFR1 fusion protein. Consistent with these findings, incubation with pemigatinib inhibited the in vitro viability of cancer cell lines with FGFR1 or FGFR2 amplification, FGFR1, FGFR2, or FGFR3 fusions and FGFR3 translocations at clinically relevant concentrations.

Clinical Pharmacology

The geometric mean steady-state pemigatinib AUC0-24h was 2620 nM·h (54% CV) and Cmax was 236 nM (56% CV) for 13.5 mg orally once daily. Steady state was achieved within 4 days following repeated once daily dosing.

Administration of pemigatinib with a high-fat and high-calorie meal (approximately 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500-600 calories from fat) had no clinically meaningful effect on pemigatinib pharmacokinetics.

Pemigatinib is predominantly metabolized by CYP3A4 in vitro.

Pemigatinib is a CYP3A4 substrate, and moderate and strong CYP3A4 inducers should be avoided during pemigatinib therapy; if a moderate or strong CYP3A4 inhibitor is administered concomitantly with pemigatinib, the pemigatinib dose should be reduced.

Clinical Trial Design

Incyte submitted the results of the FIGHT-202 trial (NCT02924376) along with a safety database comprising patients who were exposed to pemigatinib in various studies, to support the request for approval; the results of the FIGHT-202 trial have been published (12).

FIGHT-202 is a multi-center, international, open-label, non-randomized, single-arm, multi-cohort trial evaluating the safety and efficacy of pemigatinib in adult patients with surgically unresectable or advanced/metastatic cholangiocarcinoma. FIGHT-202 accrued patients from 67 sites across the United States, Europe, and Asia. Patients were assigned to one of three cohorts based on tumor FGFR status. Cohort A, which was the basis for approval of the indication, enrolled patients with FGFR2 rearrangements or fusions. Tumor FGFR status was centrally confirmed with the Foundation Medicine Clinical Trial Assay (CTA). Qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene leaving the FGFR2 kinase domain intact.

Patients received pemigatinib in 21-day cycles at a dosage of 13.5 mg orally once daily for 14 consecutive days, followed by 7 days off therapy and administered until disease progression or unacceptable toxicity. Major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR) as determined by an independent review committee (IRC) according to RECIST v1.1. Secondary endpoints were duration of response (DOR), progression-free survival, and overall survival; evaluation of patient reported outcomes was exploratory.

Results

Table 1 summarizes demographic and baseline disease characteristics. Cohort A enrolled 107 patients with FGFR2 fusions (N=92) or rearrangements (N=15). The median age was 56 years (range: 26 to 77 years), 61% were female, 74% were White, and 95% had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of less than 2 (ECOG 0: 42%; ECOG 1: 53%). Ninety-eight percent of patients had iCCA. A total of 92

(86%) patients had in-frame fusions and 15 patients (14%) had other FGFR2 rearrangements that could not be confidently predicted to be in-frame fusions, including 5 patients with rearrangements without an identifiable partner gene.

Among the patients with in-frame FGFR2 gene fusions, the most common FGFR2 fusion identified was FGFR2-BICC1 (34%). Fourteen percent of patients had other FGFR2 rearrangements that could not be confidently predicted to be in-frame fusions, including rearrangements without an identifiable partner gene. All patients had received at least 1 prior line of systemic therapy (27% with had 2 prior lines; 12% with 3 or more prior lines). Ninety-six percent of patients had received prior platinum-based therapy including 76% with prior gemcitabine/cisplatin.

Efficacy Results

In the first 107 patients with FGFR2 gene fusion/rearrangement-positive cholangiocarcinoma who received at least one dose of pemigatinib, the estimated ORR was 35.5% (95% confidence interval [CI]: 26.5%, 45.3%), including 3 complete responses (2.8%) and 35 partial responses (32.7%) [Table 2]. Eleven responses (29%) were ongoing at the time of data cut-off. Among the 38 patients with confirmed tumor responses, median DOR was 9.1 months (95% CI 6.0,13.5); 24 of the 38 (63%) responders had a DOR lasting at least 6 months and 7 (18%) responders had DOR lasting at least 12 months.

Safety Results

Safety was evaluated in 146 patients enrolled on Cohort A of FIGHT-202 who received at least one dose of pemigatinib and is further supported by data from an additional 320 patients treated with pemigatinib as a single agent in 5 other single-arm, open-label clinical trials (NCT02393248, NCT03235570, NCT02872714, NCT02924376, NCT03011372). Safety was assessed in 3 distinct populations: 1) in patients with cancer irrespective of tumor FGF/FGFR status, who received a minimum of one cycle (21 days) of pemigatinib as a single agent (either on an intermittent or continuous daily dosing schedule), n=466; 2) in patients with cholangiocarcinoma who received pemigatinib as a single agent, irrespective of FGF/FGFR status, n=161, and; 3) in patients with cholangiocarcinoma enrolled in FIGHT-202 Cohort A (FGFR rearrangement), who received at least one dose of pemigatinib, n=146. All patients had unresectable or metastatic solid tumors and no satisfactory alternative treatment options.

Among 146 patients with cholangiocarcinoma enrolled in FIGHT-202 Cohort A, the median duration of treatment was 181 days (range: 7 to 730 days). Nearly all (99%) of patients experienced at least one adverse event (AE), and Grade 3 or 4 adverse drug reactions (ADR) occurred in 64% of patients [Table 3]. Serious adverse reactions including fatal events. Fatal adverse reactions occurred in 4.1% of patients.

The most common adverse reactions (incidence ≥20%) were hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin (Table 3).

Ocular toxicity and hyperphosphatemia are significant risks of pemigatinib and are included in the Warnings and Precautions section in the product labeling. Retinal pigment epithelial detachment (RPED) was reported in 6% of the 466 patients who received pemigatinib across clinical trials. Grade 3-4 RPED was reported in 0.6% of patients. The median time to first onset of RPED was 62 days. RPED led to dose interruption of pemigatinib in 1.7% of patients, and dose reduction and permanent discontinuation in 0.4% and in 0.4% of patients, respectively. RPED resolved or improved to Grade 1 severity in 87.5% of patients who required dosage modification due to this adverse reaction.

Grading of hyperphosphatemia was based on CTCAE 5.0. Among 466 patients who received pemigatinib, hyperphosphatemia as a laboratory abnormality was reported in 92% of patients. The median time to onset of hyperphosphatemia was 8 days (range 1-169). Phosphate lowering therapy was administered in 29% of patients.

In the FIGHT-202 study, the incidence of hyperphosphatemia as a laboratory abnormality was 94% and no patients were discontinued from pemigatinib for hyperphosphatemia, and hyperphosphatemia was successfully managed with dietary changes and institution of phosphate binders, with drug interruption and dosage reduction when necessary. There were no patients on Study −202 with serum phosphate >7mg/dL for >10 days and no patients on any study had serum phosphate > 10 mg/dL for >7 days.

Discussion / Regulatory Insights

The approval of pemigatinib marked the first approval for the treatment of advanced cholangiocarcinoma and was the second FDA approval for an FGFR-targeted therapy (13). Data from the FIGHT 202 trial demonstrated a treatment effect on ORR considered to be of sufficient magnitude and durability to represent evidence of effectiveness. Because the trial evaluated ORR and the treatment is for a serious and life-threatening disease, the FDA granted accelerated approval with continued approval contingent upon verification of clinical benefit; Incyte agreed to a postmarketing requirement to conduct a randomized clinical trial demonstrating improvement of progression-free survival or overall survival in patients with unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 gene fusion or rearrangement. FIGHT-302 (NCT03656536) is an ongoing open-label, randomized controlled trial which evaluates the efficacy and safety of pemigatinib compared to gemcitabine and cisplatin in patients with unresectable, metastatic CCA harboring a an FGFR2 rearrangement.

The major review issues were the evaluation of the most serious risks of pemigatinib which were ocular toxicity and hyperphosphatemia.

While Incyte did not record serious retinal detachment in animal studies, there are literature reports supporting a role for basic fibroblast growth factor and FGFR/MAPK signaling in protecting/maintaining retinal pigment epithelial cells (14). FGF and/or FGFR play a key role in lens, corneal, and retina development and adult function (15). All four FGFR genes are expressed in the lens; FGFR1 and FGFR2 are also expressed in the retina and cornea. Ophthalmologic findings in the 28-day monkey study included moderate lens opacities and

slight attenuation of retinal vessels at pemigatinib dose levels ≥0.33 mg/kg and 1 mg/kg, respectively.

To monitor for potential retinal-related visual disturbances during treatment with pemigatinib, eye examinations were required at screening, during treatment every 3 cycles (± 14 days), at the end of treatment, and as clinically indicated. Comprehensive eye examinations included visual acuity tests, slit-lamp examination, and fundoscopy with digital imaging. Additional ophthalmologic assessments e.g., optical coherence tomography (OCT) were to be performed if clinically relevant retinal findings were observed on ophthalmologic examinations, and in patients with reported visual adverse events (AEs) or change in visual acuity if the events or changes were suspected to be of retinal origin.

Communication of the risk of RPED was also a noteworthy review issue. During labeling negotiations, Incyte agreed to use the composite term for RPED to communicate the incidence of ocular toxicity more accurately (preferred terms: chorioretinopathy, detachment of retinal pigment epithelium, maculopathy, retinopathy, retinal detachment or disorder, retinal thickening, serous retinal detachment, subretinal fluid). Evidence of RPED is typically not detected by visual acuity examination, slit-lamp examination or fundoscopy until the serous detachment involves the fovea and can be detected earlier by visual field testing or OCT. Although OCT evaluation was conducted in patients with signs or symptoms related to visual toxicity in the pemigatinib clinical trials, the incidence of asymptomatic RPED is not well characterized because routine periodic OCT monitoring was not conducted in clinical trials. Routine OCT testing was not performed in patients lacking visual symptoms. The USPI includes instructions for periodic OCT assessment in patients treated with pemigatinib. FDA also recommended that Incyte amend ongoing trials to include OCT assessment at baseline and periodically in all patients (in addition to as needed based on symptoms) to further characterize this risk, and, that this monitoring also occur in all future trials.

No patients discontinued pemigatinib due to ocular toxicity in FIGHT-202 and most ocular toxicity was reversible with discontinuation of pemigatinib. Therefore, the risk of ocular toxicity is described in the Warnings and Precautions section of product labeling for pemigatinib and dosage modification instructions for ocular toxicity are included in the Dosage and Administration section.

Hyperphosphatemia is an on-target effect of FGFR inhibition and was expected with pemigatinib administration. Hyperphosphatemia generally does not cause symptoms unless there is precipitation of calcium-phosphate crystals leading to hypocalcemia; soft tissue mineralization, tetany, seizure activity, QT interval prolongation, and arrhythmias may result from effects on calcium, extra skeletal deposition of calcium phosphate crystals, and electrical hyperexcitability The assessment of hyperphosphatemia included analyses of adverse events as well as elevated phosphate levels recorded as a laboratory abnormality. Severe (Grades ≥ 3) hypophosphatemia was mainly a laboratory finding and was generally not associated with clinically significant signs or symptoms. No patients enrolled in FIGHT-202 were discontinued from pemigatinib for hyperphosphatemia, and hyperphosphatemia was successfully managed with dietary changes and institution of

phosphate binders, with drug interruption and dosage reduction when necessary. Incyte was also asked to submit autopsy reports, if applicable, to assess for ectopic mineralization due to imbalances in calcium/phosphate metabolism. Only 3 autopsy reports were available, and the review of these autopsy reports did not yield any instances of ectopic mineralization.

Due to the prevalence of hyperphosphatemia with pemigatinib and the need for early identification and intervention to avoid potential clinical sequelae, hyperphosphatemia is described in the Warnings and Precautions section of product labeling, and management guidelines are included in the dosage modification table.

Post marketing requirements to determine the pharmacokinetics of pemigatinib in patients with severe renal insufficiency and hepatic impairment were completed in 2021. Updates to labeling to reflect recommended dosage of pemigatinib for patients with severe renal impairment (eGFR estimated by MDRD 15 to 29 mL/min/1.73 m2) or hepatic impairment (hepatic impairment (total bilirubin > 3 × ULN with any AST) be 9 mg orally once daily for 14 consecutive days followed by 7 days off therapy, in 21-day cycles have occurred.

Concurrently with the drug approval, FDA approved the Foundation Medicine companion diagnostic assay (Foundation Medicine CDx) supplemental Premarket Approval (sPMA) application to select patients with cholangiocarcinoma harboring FGFR2 gene fusions and select rearrangements, for treatment with pemigatinib. FDA's risk and benefit analysis is shown in Table 4.

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Table 1:

Demographic Characteristics of Patients in FIGHT-202

Demographic Characteristics (N=107)	**n (%)**
Sex	
Male	42 (39)
Female	65 (61)
Age	
Mean years (SD)	55 (12)
Median (years)	56
Min, max (years)	26, 77
Age Group	
< 65 years	82 (77)
≥ 65 years	25 (23)
Race	
White	79 (74)
Black or African American	7 (7)
Asian	11 (10)
Other	4 (3.7)
Missing	6 (6)
Ethnicity	
Hispanic or Latino	2 (2)
Not Hispanic or Latino	87 (81)
Region	
United States	64 (60)
Other	43 (40)
ECOG Score	
0	45 (42)
1-2	62 (58)

Table 2:

ORR per RECIST 1.1 as assessed by IRC

Efficacy Parameter	N = 107
ORR (95% CI)	36% (27, 45)
Complete response n=3	2.8%
Partial response n=35	33%
Median DoR (months) (95% CI)[a]	9.1 (6.0, 14.5)
Patients with DoR ≥ 6 months, n (%)	24 (63%)
Patients with DoR ≥ 12 months, n (%)	7 (18%)

[a]The 95% confidence interval (CI) was calculated using the Brookmeyer and Crowley's method.

Note: Data are by RECIST v1.1 per IRC, and all responses were confirmed.

Table 3:

Adverse Reactions (≥ 15% Incidence) in Patients Receiving Pemigatinib in FIGHT-202

	Pemigatinib N=146	
Adverse Reaction	**All Grades[a] (%)**	**Grades ≥ 3[*] (%)**
Metabolism and nutrition disorders		
Hyperphosphatemia[b]	60	0
Decreased appetite	33	1.4
Hypophosphatemia[c]	23	12
Dehydration	15	3.4
Skin and subcutaneous tissue disorders		
Alopecia	49	0
Nail toxicity[d]	43	2.1
Dry skin	20	0.7
Palmar-plantar erythrodysesthesia syndrome	15	4.1
Gastrointestinal disorders		
Diarrhea	47	2.7
Nausea	40	2.1
Constipation	35	0.7
Stomatitis	35	5
Dry mouth	34	0
Vomiting	27	1.4
Abdominal pain	23	4.8
General disorders		
Fatigue	42	4.8
Edema peripheral	18	0.7
Nervous system disorders		
Dysgeusia	40	0
Headache	16	0
Eye disorders		
Dry eye[e]	35	0.7
Musculoskeletal and connective tissue disorders		
Arthralgia	25	6
Back pain	20	2.7
Pain in extremity	19	2.1
Infections and infestations		
Urinary tract infection	16	2.7
Investigations		
Weight loss	16	2.1

Source: US package insert (11).

*Only Grades 3 – 4 were identified.

[a]Graded per NCI CTCAE 4.03

[b]Includes hyperphosphatemia and blood phosphorous increased; graded based on clinical severity and medical interventions taken according to the "investigations-other, specify" category in NCI CTCAE v4.03.

[c]Includes hypophosphatemia and blood phosphorous decreased

[d]Includes nail toxicity, nail disorder, nail discoloration, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia.

[e]Includes dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis.

Table 4:

FDA Benefit: Risk Analysis

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Each year, an estimated 8,000 people in the United States are diagnosed with bile duct cancer and the 5-year survival for intrahepatic bile duct cancer is 9%. FGFR2 fusions are present in an estimated 13-14% of patients with iCCA. Patients with FGFR rearrangements appear to have a longer median overall survival compared to those with iCCA lacking a FGFR rearrangement.	Cholangiocarcinoma is a serious and life-threatening illness and there is no satisfactory available therapy for the treatment of cholangiocarcinoma with a FGFR2 gene fusion or other rearrangement that has received at least one prior line of treatment.
Current Treatment Options	Current treatment options for patients with CCA are limited, and at the time of pemigatinib approval, there were no approved treatments for the treatment of patients with CCA in the second-line setting, irrespective of whether the tumor harbors an FGFR2 gene fusion or rearrangement.	There is an unmet medical need for new effective treatments for patients with cholangiocarcinoma with a FGFR2 gene fusion or other rearrangement who have received at least one prior line of treatment.
Benefit	FIGHT-202 demonstrated a clinically meaningful and durable ORR in patients with previously treated, locally advanced or metastatic cholangiocarcinoma with a FGFR2 gene fusion or other rearrangement. The estimated ORR was 36% (95% confidence interval [CI]: 27%, 45%). At the time of the analysis, the median DOR was 9.1 months; 24 of the 38 (63%) responders had a DOR lasting at least 6 months and 7 (18%) responders had a DOR of at least 12 months.	The magnitude and duration of responses observed in patients with cholangiocarcinoma with a FGFR2 gene fusion who received prior treatment was large, and reasonably likely to predict clinical benefit. The submitted evidence meets the statutory evidentiary standard for accelerated approval. Incyte has agreed to a postmarketing requirement to submit data from a randomized trial to verify and confirm the clinical benefit of pemigatinib in patients with FGFR2 fusion/rearrangement-positive cholangiocarcinoma.
Risk and Risk Management	The most common adverse reactions occurring with an incidence ≥ 20% were hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin. Ocular toxicity and hyperphosphatemia are important risks of pemigatinib.	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. Most of the adverse reactions to pemigatinib were manageable with supportive care and dose modification as needed. The significant and potentially serious adverse reactions of hyperphosphatemia and ocular toxicity are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in product labeling.