Pemazyre® (pemigatinib)

Prescribing Information and Data Review in Cholangiocarcinoma

MSL-PEM-US-0012 03/26

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Notice

- Some information contained in this presentation may not be included in the approved Prescribing Information for PEMAZYRE (pemigatinib). This presentation is not intended to offer recommendations for any administration, indication, dosage, or other use for PEMAZYRE in a manner inconsistent with the approved Prescribing Information

Indication and Usage

- PEMAZYRE is 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)
  - Relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with *FGFR1* rearrangement

- **Please see the Full Prescribing Information, including Warnings & Precautions and Patient Information for PEMAZYRE**

- **FOR MEDICAL INFORMATION PURPOSES ONLY. NOT FOR PROMOTIONAL USE. DO NOT COPY, DISTRIBUTE OR OTHERWISE REPRODUCE**

FDA, Food and Drug Administration.
PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023.

Table of Contents

SECTION 1 FIGHT-202 Data Analyses

SECTION 2 Dosing in CCA

SECTION 3 Warnings, Precautions, Dose Modifications, and Specific Populations

Click the section tab of interest to be taken to the corresponding portion of the deck

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FIGHT-202 Data Analyses

- Introduction and Primary Analysis
- Final Analysis

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Introduction and Primary Analysis

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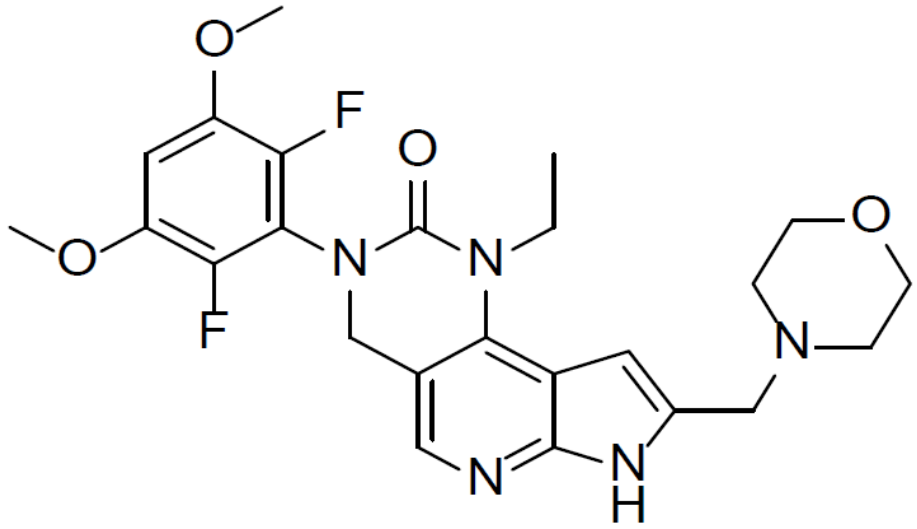
Pemigatinib is a Small Molecule Inhibitor of FGFR1, 2, and 3

- Pemigatinib is a small molecule kinase inhibitor that targets FGFR1, 2 and 3 with IC_{50} values of less than 2 nM
- Pemigatinib inhibited FGFR1-3 phosphorylation and signaling and decreased cell viability in cancer cell lines with activating *FGFR* amplifications and fusions
- Pemigatinib exhibited anti-tumor activity in mouse xenograft models of human tumors with *FGFR1*, *FGFR2*, or *FGFR3* alterations

Pemigatinib



Learn More: Pemigatinib pharmacodynamics and pharmacokinetics

IC_{50}, half maximal inhibitory concentration.

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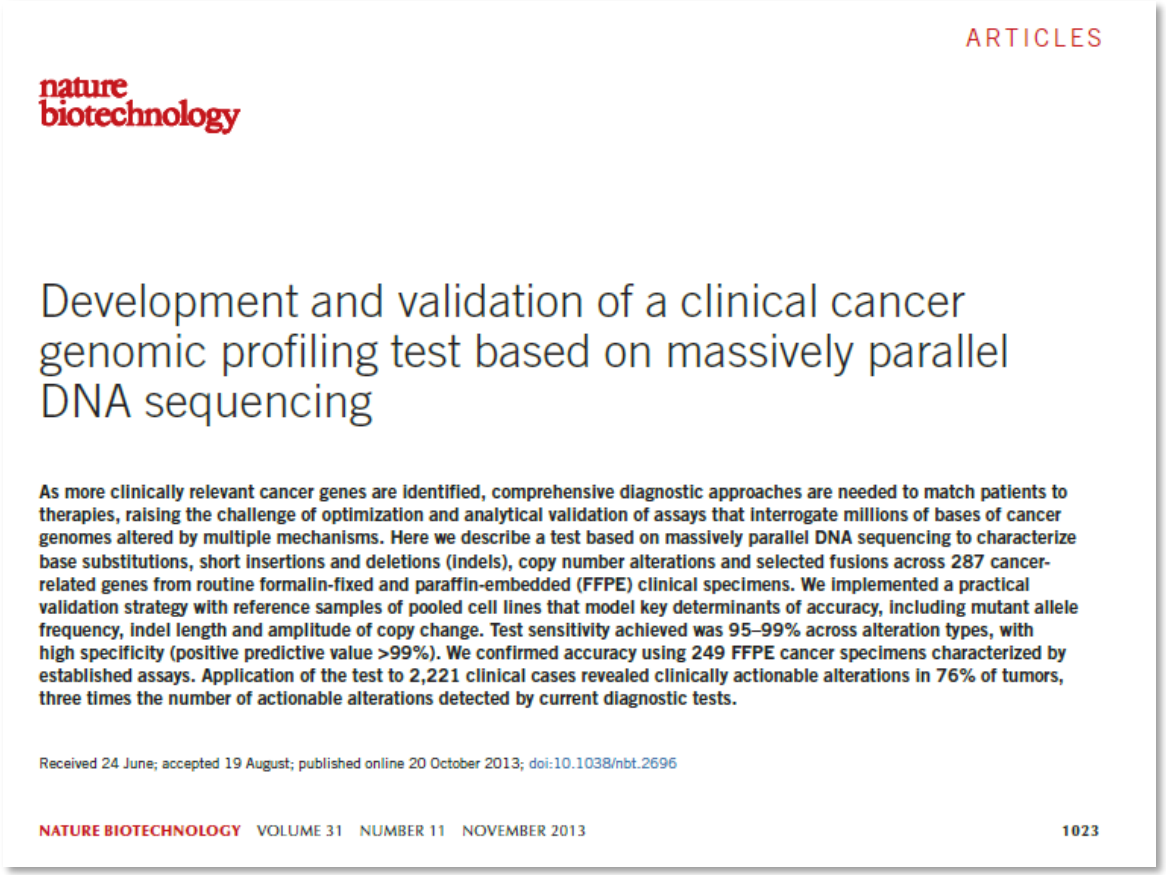
Treatment with Pemigatinib is Based on the Presence of a FGFR2 Fusion or Rearrangement as Detected by an FDA-Approved Test[1]

- FoundationOne® CDx is the approved companion diagnostic for pemigatinib[1]
- FoundationOne® CDx detects substitutions, insertions/deletions, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures, including MSI and tumor mutational burden[2,3]
  - FDA-approved, NGS-based broad companion diagnostic for comprehensive genomic profiling of solid tumors
  - Clinically validated to detect *FGFR2* fusions and other rearrangements
  - Gene-partner agnostic
  - Typical turnaround time is <2 weeks from receipt of specimen
  - Large clinical data validation sets



ARTICLES

nature biotechnology

Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing

As more clinically relevant cancer genes are identified, comprehensive diagnostic approaches are needed to match patients to therapies, raising the challenge of optimization and analytical validation of assays that interrogate millions of bases of cancer genomes altered by multiple mechanisms. Here we describe a test based on massively parallel DNA sequencing to characterize base substitutions, short insertions and deletions (indels), copy number alterations and selected fusions across 287 cancer-related genes from routine formalin-fixed and paraffin-embedded (FFPE) clinical specimens. We implemented a practical validation strategy with reference samples of pooled cell lines that model key determinants of accuracy, including mutant allele frequency, indel length and amplitude of copy change. Test sensitivity achieved was 95–99% across alteration types, with high specificity (positive predictive value >99%). We confirmed accuracy using 249 FFPE cancer specimens characterized by established assays. Application of the test to 2,221 clinical cases revealed clinically actionable alterations in 76% of tumors, three times the number of actionable alterations detected by current diagnostic tests.

Received 24 June; accepted 19 August; published online 20 October 2013; doi:10.1038/nbt.2696

From: Frampton GM, et al. *Nat Biotechnol*. 2013;31:1023-1031.

FoundationOne® CDx is a registered trademark of Foundation Medicine, Inc.
FDA, US Food and Drug Administration; MSI, microsatellite instability.
1. PEMAZYRE® (pemigatinib). Prescribing information. Incyte Corporation; June 2023. 2. FoundationOne® CDx. Overview. Accessed September 2024. https://www.foundationmedicine.com/test/foundationone-cdx. 3. FoundationOne® CDx. Technical Information. Accessed September 2024. https://assets.ctfassets.net/vhribv12lmne/6Rt6csmCPuaguuqmgi2iY8/2fe839f0e9075cf4a047bf241374e6af/F1CDx.Label.Technical_Info_Final_July_2019.pdf.

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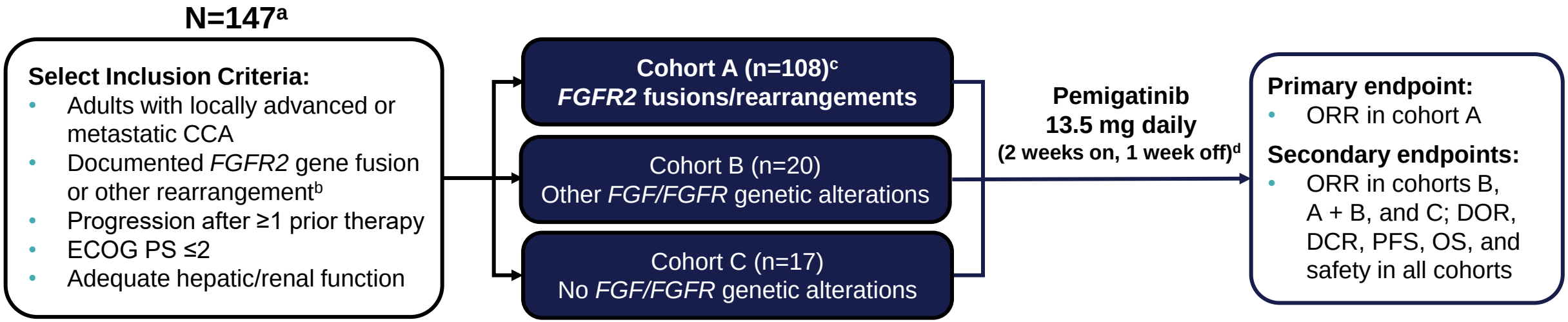
FIGHT-202: Study Design and Methods[1,2]

Study Design: Phase 2, multicenter, open-label, single-arm study (NCT02924376) evaluating the efficacy and safety of pemigatinib in patients with previously treated unresectable locally advanced or metastatic CCA



The study was not designed to make statistical comparisons between cohorts; no formal hypothesis testing or inferential analyses were conducted

[a] The total includes 2 patients for whom FGF/FGFR status could not be centrally determined; the 2 patients were not assigned to a cohort and were evaluated for safety but not for efficacy. [b] Patients prescreened for FGF/FGFR status, documented either centrally (FoundationOne®, Foundation Medicine), based on local assessment, or an existing Foundation Medicine report. Retrospective central confirmation of locally documented FGF/FGFR status was required.[3] [c] Only Cohort A (n = 107) comprised the efficacy population for the accelerated approval of pemigatinib in patients with CCA harboring an FGFR fusion or rearrangement.[4] [d] Administered until disease progression or unacceptable toxicity.
ECOG PS, Eastern Cooperative Oncology Group performance status; DOR, duration of response; IRC, independent review committee; QD, once daily.

1. ClinicalTrials.gov. Accessed July 2024. https://clinicaltrials.gov/study/NCT02924376. 2. Vogel A, et al. *ESMO Open*. 2024;9:103488.
3. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684. 4. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023.

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Demographics and Clinical Characteristics

Demographics	Cohort A (n=107)
Age, median (range), years	56 (26–77)
Sex, n (%)	
Men	42 (39)
Women	65 (61)
Race	
White	74%
ECOG PS, n (%)	
0	45 (42)
1	57 (53)
2	5 (5)

95%

Clinical Characteristics	Cohort A (n=107)
CCA location, n (%)	
Intrahepatic	105 (98)
FGFR status, n (%)	
In-frame fusions	92 (86)
Rearrangement	15 (14)
Prior platinum-based chemotherapy	103 (96)
Prior gemcitabine/cisplatin	81 (76)
Number of prior regimens, n (%)[a]	
1	65 (61)
2	29 (27)
≥3	13 (12)

[a] Maximum number of 5 therapies in cohort A.

1. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023. 2. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684.

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Efficacy Results

Efficacy Parameter[a]	Cohort A (n=107)
Overall response rate, % (95% CI)	**36 (27-45)**
CR	2.8
PR	33
Median duration of response, mo (95% CI)[b,c]	**9.1 (6.0-14.5)**
Patients with DOR ≥6 months, n (%)	24 (63)
Patients with DOR ≥12 months, n (%)	7 (18)

Median duration of treatment was 181 days (range 7-730 days)[c]

Median time to response was 2.7 months (range 0.7-6.9 months)

[a] Assessed and confirmed by independent central review per RECIST v1.1. [b] The 95% CI was calculated using the Brookmeyer and Crowley's method. [c] Data is as of 4-month safety update (August), not primary data cutoff.
CI, confidence interval; CR, complete response; PR, partial response; RECIST, response evaluation criteria in solid tumors.
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Adverse Reactions Reported in ≥15% of Patients

Adverse Reaction, %	N=146[a] All Grades[b]	N=146[a] Grades ≥3
Metabolism and nutrition disorders		
Hyperphosphatemia[c]	60	0
Decreased appetite	33	1.4
Hypophosphatemia[d]	23	12
Dehydration	15	3.4
Skin and subcutaneous tissue disorders		
Alopecia		
Nail toxicity[e]	49	0
Dry skin	43	2.1
Palmar-plantar erythrodysesthesia syndrome	20	0.7
	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

Adverse Reaction, %	N=146[a] All Grades[b]	N=146[a] Grades ≥3
General disorders		
Fatigue	42	4.8
Peripheral edema	18	0.7
Nervous system disorders		
Dysgeusia	40	0
Headache	16	0
Eye disorders[f]		
Dry eye	35	0.7
Musculoskeletal/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

[a] Safety analysis includes patients enrolled in cohorts A, B, and C along with 1 patient who did not have confirmed *FGF/FGFR* status by central laboratory and was not assigned to any cohort. [b] Graded per NCI CTCAE 4.03. [c] 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. [d] Includes hypophosphatemia and blood phosphorous decreased. [e] Includes nail toxicity, nail disorder, nail discoloration, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia. [f] Includes dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis.

CTCAE, common terminology criteria for adverse events; NCI, National Cancer Institute.

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Adverse Reactions Overview

- **The most common adverse reactions (≥20% all grades) were:**
  - Hyperphosphatemia
  - Alopecia
  - Diarrhea
  - Nail toxicity
  - Fatigue
  - Dysgeusia
  - Nausea
  - Constipation
  - Stomatitis
  - Dry eye
  - Dry mouth
  - Decreased appetite
  - Vomiting
  - Arthralgia
  - Abdominal pain
  - Hypophosphatemia
  - Back pain
  - Dry skin

- **The most common grade 3/4 adverse reactions (≥5%) were:**
  - Hypophosphatemia
  - Arthralgia
  - Stomatitis

- **Clinically relevant adverse reactions occurring in ≤10% of patients included fractures (2.1%)**
  - In all patients treated with pemigatinib, 1.3% experienced pathologic fractures, which included patients with and without CCA (N=466)
  - Soft tissue mineralization, including cutaneous calcification, calcinosis, and non-uremic calciphylaxis associated with hyperphosphatemia were observed with pemigatinib treatment

Safety analysis includes patients enrolled in cohorts A, B, and C along with 1 patient who did not have confirmed *FGF/FGFR* status by central laboratory and was not assigned to any cohort.

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Select Laboratory Abnormalities Reported in ≥10% (Any Grade) Worsening From Baseline in Patients

Laboratory Abnormality, %	N=146[a] All Grades[b]	Grades 3-4
Hematology		
Decreased hemoglobin	43	6
Decreased lymphocytes	36	8
Decreased platelets	28	3.4
Increased leukocytes	27	0.7
Decreased leukocytes	18	1.4
Chemistry		
Increased phosphate[c]	94	0
Decreased phosphate	68	38
Increased alanine aminotransferase	43	4.1
Increased aspartate aminotransferase	43	6
Increased calcium	43	4.1
Increased alkaline phosphatase	41	11
Increased creatinine[d]	41	1.4
Decreased sodium	39	12
Increased glucose	36	0.7
Decreased albumin	34	0
Increased urate	30	10
Increased bilirubin	26	6
Decreased potassium	26	5
Decreased calcium	17	2.7
Increased potassium	12	2.1
Decreased glucose	11	1.4

Increased Creatinine:

- Within the first 21-day cycle, serum creatinine increased 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

[a] The denominator used to calculate the rate varied from 142-146 based on the number of patients with a baseline value and at least one post-treatment value. [b] Graded per NCI CTCAE 4.03. [c] Based on CTCAE 5.0 grading. [d] Graded based on comparison to upper limit of normal.

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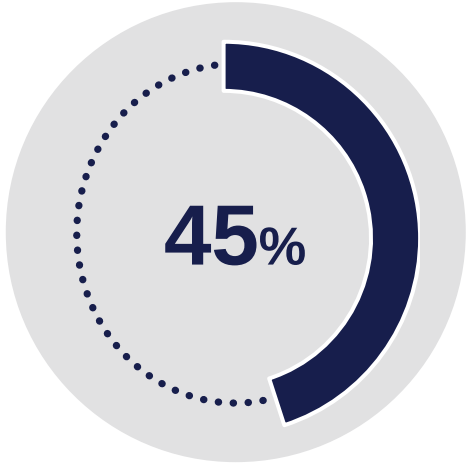
Serious or Fatal Adverse Reactions in Patients Who Received Pemigatinib

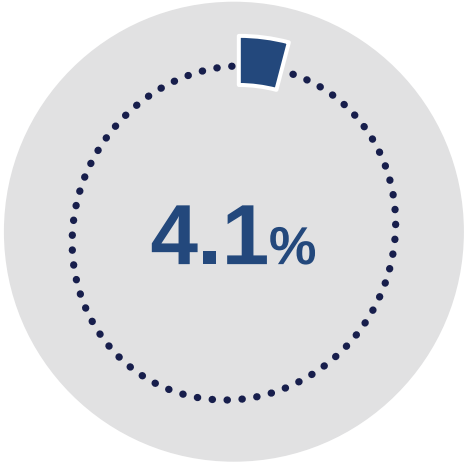
Serious Adverse Reactions



45% of patients receiving pemigatinib had serious ARs

- Serious ARs occurring in ≥2% of patients) included:
  - Abdominal pain
  - Pyrexia
  - Cholangitis
  - Pleural effusion
  - Acute kidney injury
  - Cholangitis infective
  - Failure to thrive
  - Hypercalcemia
  - Hyponatremia
  - Small intestinal obstruction
  - Urinary tract infection

Fatal Adverse Reactions



4.1% of patients receiving pemigatinib had fatal ARs

- Fatal ARs occurring in 4.1% of patients included:
  - Failure to thrive
  - Bile duct obstruction
  - Cholangitis
  - Sepsis
  - Pleural effusion

ARs, adverse reactions.

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Dose Modifications and Discontinuations Due to Adverse Reactions

Dose Interruptions: 43%

- 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: 14%

- Adverse reactions requiring dosage reductions in ≥1% of patients included stomatitis, arthralgia, palmar-plantar erythrodysesthesia syndrome, asthenia, and onychomadesis

Discontinuations: 9%

- Adverse reactions requiring permanent discontinuation in ≥1% of patients included intestinal obstruction and acute kidney injury

Values based on all 146 patients enrolled in fight-202.

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fight-202 Data Summary

Design

- In the fight-202 study, pemigatinib was assessed in patients with previously treated, unresectable, locally advanced or metastatic CCA with documented *FGFR2* fusions and other rearrangements

Efficacy

- The ORR was 36% (95% CI, 27-45)
- 33% of patients had a PR and 2.8% of patients had a CR
- Median DOR was 9.1 months (95% CI, 6.0-14.5 months)

Safety

- The median duration of treatment was 181 days (range: 7-730 days)
- The most common ARs (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
- The most common grade 3 ARs (incidence ≥5%) were hypophosphatemia, arthralgia, and stomatitis
- Treatment discontinuation due to ARs occurred in 9% of patients

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Final Analysis

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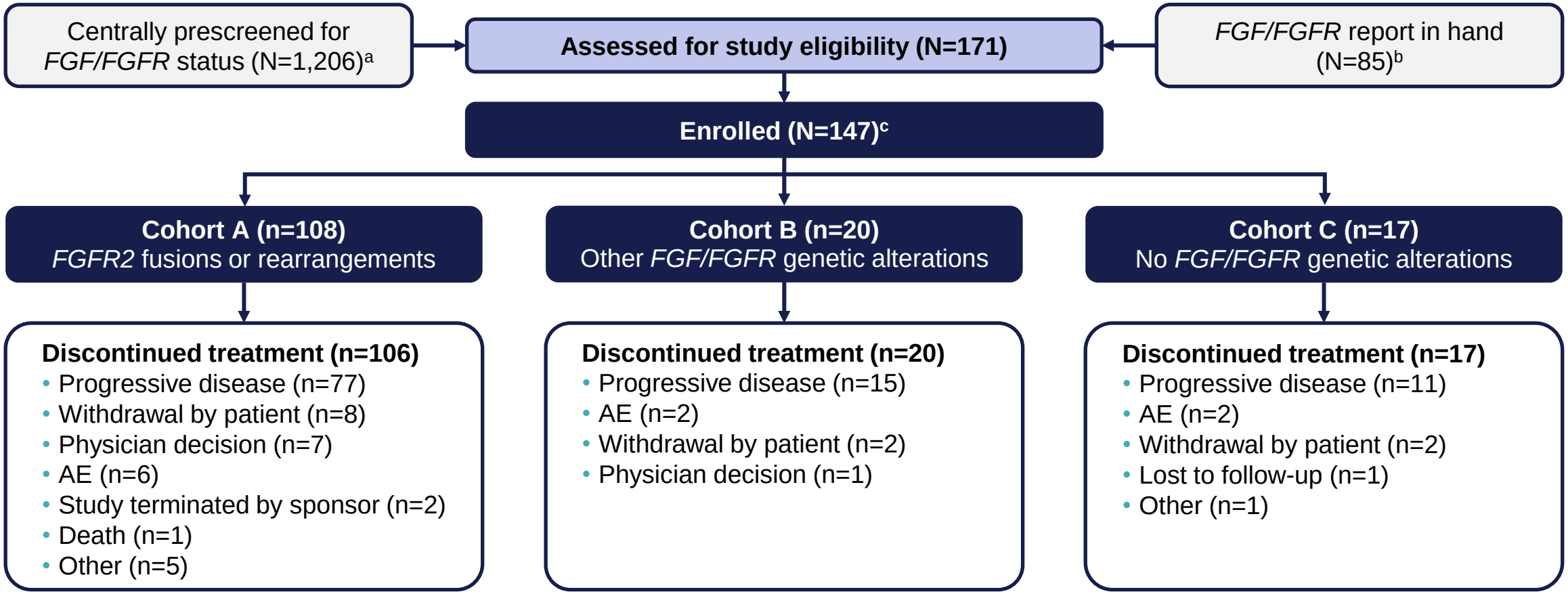
Patient Disposition[1]



Enrollment between January 17, 2017-July 8, 2021.[1,2]

[a] FoundationOne®, Foundation Medicine. [b] Most patients with report in-hand had undergone FoundationOne® testing for *FGF/FGFR* status. [c] The total includes 2 patients for whom *FGF/FGFR* status could not be centrally determined; the 2 patients were not assigned to a cohort and were evaluated for safety but not for efficacy.

1. Vogel A, et al. *ESMO Open*. 2024;9:103488. 2. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684.

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Baseline Demographics and Clinical Characteristics

fight-202

Characteristics	Cohort A (n=108) *FGFR2* fusions or rearrangements	Cohort B (n=20) Other *FGF/FGFR* genetic alterations	Cohort C (n=17) No *FGF/FGFR* genetic alterations	Total (N=147)[a]
Age, median (range), y	55.5 (26-77)	63.0 (45-78)	65.0 (49-78)	59.0 (26-78)
Women, %	61	55	41	58
White, %	73	45	82	71
Time since initial diagnosis, median (range), y	1.3 (0.2-11.1)	0.7 (0.2-2.5)	1.0 (0.3-4.3)	1.1 (0.2-11.1)
ECOG PS, n (%)				
0	43	35	35	41
1	53	50	47	52
2	5	15	18	8
Intrahepatic CCA, %	99	65	59	90
Metastatic disease, %	82	100	94	86
≥2 prior systemic therapies, %	40	40	35	39

Results of final analysis (January 17, 2017-July 8, 2021).[1,2]

[a] The total includes 2 patients for whom *FGF/FGFR* status could not be centrally determined; the 2 patients were not assigned to a cohort and were evaluated for safety but not for efficacy.

1. Vogel A, et al. *ESMO Open*. 2024;9:103488. 2. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684.

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Exposure, Duration of Follow-Up, and Overall Responses[1]

Characteristics	Cohort A (n=108) *FGFR2* fusions or rearrangements	Cohort B (n=20) Other *FGF/FGFR* genetic alterations	Cohort C (n=17) No *FGF/FGFR* genetic alterations
Median (range) duration of exposure, months	7.2 (0.2-51.1)	1.4 (0.2-12.9)	1.2 (0.2-4.7)
Median duration of follow-up, (range), months	42.9 (19.9-52.2)	47.5 (43.7-51.1)	51.9 (49.5-53.7)
ORR (95% CI), [a] %	37 (27.9-46.9)	0 (0-16.8)	0 (0-19.5)
Best OR,[a] n (%)			
CR	3 (2.8)	0	0
PR	37 (34.3)	0	0
SD	49 (45.4)	8 (40.0)	3 (17.6)
PD	16 (14.8)	7 (35.0)	11 (64.7)
NE	3 (2.8)	5 (25.0)	3 (17.6)
DCR (CR+PR+SD), n (%)	89 (82.4)	8 (40.0)	3 (17.6)
DOR, median (95% CI), mo	9.1 (6.0-14.5)	–	–

Results of final analysis (January 17, 2017-July 8, 2021).[1,2]
Note: The absence of an active comparator group due to the single-arm design of the fight-202 study is an important limitation.
[a] Assessed and confirmed by independent central review.
NE, not evaluable; OR, objective response; PD, progressive disease.
1. Vogel A, et al. *ESMO Open*. 2024;9:103488. 2. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684.

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Treatment-Related TEAEs Occurring in ≥30% of Patients in Cohort A[1]

fight-202

Event	Cohort A (n=108) *FGFR2* fusions or rearrangements		Cohort B (n=20) Other *FGF/FGFR* genetic alterations		Cohort C (n=17) No *FGF/FGFR* genetic alterations		Total (N=147)[a]	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any TEAE, %	94.4	37.0	85.0	30.0	82.4	5.9	91.8	32.7
Hyperphosphatemia	50.9	0	55.0	0	70.6	0	53.7	0
Alopecia	56.5	0	15.0	0	11.8	0	46.3	0
Diarrhea	40.7	3.7	25.0	0	23.5	5.9	36.1	3.4
Stomatitis	39.8	8.3	20.0	0	17.6	0	34.7	6.1
Dysgeusia	38.9	0	15.0	0	17.6	0	34.0	0
Fatigue	35.2	1.9	20.0	0	35.3	0	32.7	1.4
Dry mouth	35.2	0	10.0	0	5.9	0	29.3	0
Dry eye	30.6	0	0	0	0	0	23.1	0.7

Results of final analysis (January 17, 2017-July 8, 2021).[1,2]

[a] The total includes 2 patients for whom *FGF/FGFR* status could not be centrally determined; the 2 patients were not assigned to a cohort and were evaluated for safety but not for efficacy.

TEAE, treatment-emergent adverse event.

1. Vogel A, et al. *ESMO Open*. 2024;9:103488. 2. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684.

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Summary

- FIGHT-202 was a phase 2 open-label, single-arm study evaluating the efficacy and safety of pemigatinib in patients with previously treated locally advanced/metastatic or unresectable CCA

- Final results obtained between January 17, 2017, and July 8, 2021, showed that among patients with *FGFR2* fusions or rearrangements (n=108), pemigatinib treatment resulted in:
  - An ORR of 37% and a CR rate of 3%
  - A median DOR of 9.1months
  - A median PFS of 7.0 months and median OS of 17.5 months

- The most common treatment-related TEAEs in all patients were hyperphosphatemia (53.7%), alopecia (46.3%), and diarrhea (36.1%)
  - All hyperphosphatemia events were of low severity

Vogel A, et al. *ESMO Open*. 2024;9:103488.

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Dosing in CCA

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Pemigatinib Recommended Dosing and Administration in CCA

- Select patients for the treatment of unresectable locally advanced or metastatic CCA based on the presence of an *FGFR2* fusion or rearrangement as detected by an FDA approved test
  - Information on FDA approved test(s) for the detection of an *FGFR2* fusion or rearrangement is available at http://www.fda.gov/CcompanionDiagnostics
- The recommended dose of pemigatinib is 13.5 mg taken orally once daily for 14 days followed by 7 days off therapy, in 21-day cycles. Treatment should continue until disease progression or unacceptable toxicity occurs

Administration

- Take with or without food at approximately the same time each day

Formulation

- Swallow tablets whole. Do not crush, chew, split, or dissolve tablets

Missed Dose

- If the patient misses a dose ≥4 hours or if vomiting occurs, resume dosing with the next scheduled dose

Available tablet strengths include: 4.5 mg, 9 mg, and 13.5 mg

PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023.

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General Dose Modification Guidelines

Recommended Dose Reductions in CCA for Adverse Reactions

First Dose Reduction

- Pemigatinib 9 mg once daily for 14 days, followed by 7 days off therapy

Second Dose Reduction

- Pemigatinib 4.5 mg once daily for 14 days, followed by 7 days off therapy

Discontinue Treatment

- Discontinue if unable to tolerate pemigatinib 4.5 mg once daily

Consult the USPI for details related to dosing modification

USPI, US prescribing information.

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Warnings, Precautions, Dose Modifications, and Use in Specific Populations

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Warnings and Precautions: Ocular Toxicities

RPED

- Pemigatinib can cause RPED, which may cause symptoms such as blurred vision, visual floaters, or photopsia
- Clinical trials of pemigatinib did not conduct routine monitoring including OCT to detect asymptomatic RPED; therefore, the incidence of asymptomatic RPED with pemigatinib is unknown
- Among 635 patients who received a starting dose of pemigatinib 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 pemigatinib 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 pemigatinib for RPED

Dry Eye

- Among 635 patients who received a starting dose of pemigatinib 13.5 mg across clinical trials, dry eye occurred in 31% of patients, including Grade 3-4 in 1.6% of patients
- Patients should be treated with ocular demulcents as needed

OCT, optical coherence tomography; RPED, retinal pigment epithelial detachment.

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Monitoring and Dose Modifications for RPED

Monitoring for RPED

- Perform a comprehensive ophthalmological examination, including OCT:
  - Prior to initiation of pemigatinib
  - Every 2 months for the first 6 months
  - 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 pemigatinib

Pemigatinib Dose Modification for RPED

- If asymptomatic and stable on serial examination, continue pemigatinib
- If symptomatic or worsening on serial examination, withhold pemigatinib
  - If asymptomatic and improved on subsequent examination, resume pemigatinib at a lower dose
  - If symptoms persist or examination does not improve, consider permanent discontinuation of pemigatinib, based on clinical status

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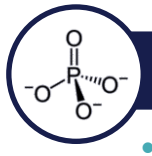
Warnings and Precautions: Hyperphosphatemia and Soft Tissue Mineralization



Hyperphosphatemia

- Pemigatinib can cause hyperphosphatemia leading to:
  - Soft tissue mineralization
  - Cutaneous calcification
  - Calcinosis
  - Non-uremic calciphylaxis
- Increases in phosphate levels are a pharmacodynamic effect of pemigatinib
- Among 635 patients who received a starting dose of pemigatinib 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 pemigatinib
- Monitor for hyperphosphatemia and initiate a low phosphate diet when serum phosphate level is >5.5 mg/dL

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Monitoring and Dose Modifications for Hyperphosphatemia

Pemigatinib Dose Modifications for Hyperphosphatemia

Serum Phosphate Level	Management Strategy
>5.5 mg/dL	• Monitor serum phosphate levels, and initiate a low phosphate diet
>7 mg/dL to ≤10 mg/dL	• Initiate phosphate lowering therapy and monitor serum phosphate weekly • Withhold pemigatinib if levels are not <7 mg/dL within 2 weeks of starting phosphate lowering therapy • Resume pemigatinib at the same dose when phosphate levels are <7 mg/dL for first occurrence; resume at a lower dose level for subsequent recurrences
>10 mg/dL	• Initiate phosphate lowering therapy and monitor serum phosphate weekly • Withhold pemigatinib if levels are not ≤10 mg/dL within 1 week after starting phosphate lowering therapy • Resume pemigatinib at the next lower dose level when phosphate levels are <7 mg/dL • Permanently discontinue pemigatinib for recurrence of serum phosphate >10 mg/dL following 2 dose reductions

Severity as defined by NCI CTCAE version 4.03.

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Dose Modifications for Other Adverse Reactions

Pemigatinib Dose Modifications for Other Adverse Reactions

Grade 3	• Withhold pemigatinib until resolves to Grade 1 or baseline • Resume pemigatinib at next lower dose if resolves within 2 weeks • Permanently discontinue pemigatinib if does not resolve within 2 weeks • Permanently discontinue pemigatinib for recurrent Grade 3 after 2 dose reductions
Grade 4	• Permanently discontinue pemigatinib

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Dose Modifications for Concomitant Use With CYP3A Inhibitors and Inducers

Pemigatinib Dose Modifications for Concomitant Use With CYP3A Inhibitors and Inducers

Strong and Moderate CYP3A Inhibitors	• Avoid concomitant use with pemigatinib • If concomitant use cannot be avoided – Reduce pemigatinib dose from 13.5 mg to 9 mg – Reduce pemigatinib dose from 9 to 4.5 mg • If concomitant use of a strong or moderate CYP3A inhibitor is discontinued – Increase the pemigatinib dose (after 3 plasma half-lives of the CYP3A inhibitor) to the dose that was used before starting the strong or moderate inhibitor
Strong and Moderate CYP3A Inducers	• Avoid concomitant use of strong and moderate CYP3A inducers with pemigatinib

- Concomitant use of pemigatinib with a strong or moderate CYP3A inducer decreases pemigatinib plasma concentrations, which may reduce the efficacy of pemigatinib
- Concomitant use of a strong or moderate CYP3A inhibitor with pemigatinib increases pemigatinib plasma concentrations, which may increase the incidence and severity of adverse reactions

CYP3A, cytochrome P4503A.

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Dose Modifications for Severe Renal or Hepatic Impairment

Pemigatinib Dose Modification for Severe Renal and Hepatic Impairment

Severe Renal Impairment	• The recommended dosage of pemigatinib for patients with severe renal impairment (eGFR estimated by MDRD 15 mL/min/1.73 m^2 to 29 mL/min/1.73 m^2) is 9 mg with the schedule (intermittent or continuous) designated for the indication
Severe Hepatic Impairment	• The recommended dosage of pemigatinib for patients with severe hepatic impairment (total bilirubin >3 x ULN with any AST) is 9 mg with the schedule (intermittent or continuous) designated for the indication

eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; ULN, upper limit of normal.

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Warnings and Precautions: Embryo-Fetal Toxicity

Embryo-Fetal Toxicity

- Based on findings in an animal study and its mechanism of action, pemigatinib 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 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 pemigatinib and for 1 week after the last dose
  - Advise males with female partners of reproductive potential to use effective contraception during treatment with pemigatinib and for 1 week after the last dose

AUC, area under the curve.

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Use in Specific Populations

Lactation

- Advise women not to breast feed during treatment and for 1 week after the final dose

Pediatric Use

- Safety and efficacy has not been established in pediatric patients

Geriatric Use

- In fight-202, 32% patients were ≥65 and 8% ≥75 years
- No overall differences seen in safety or effectiveness versus younger patients

Renal Impairment

- Reduce the recommended dose of pemigatinib for patients with severe renal impairment
- No dose adjustment for mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73m^2)
- No dose adjustment is recommended for patients with end-stage renal disease (eGFR <15 mL/min/1.73 m^2) who are receiving intermittent hemodialysis

Hepatic Impairment

- Reduce the recommended dose of pemigatinib for patients with severe hepatic impairment
- No dose adjustment for mild or moderate hepatic impairment

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Appendix

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Frequency of *FGFR* Aberrations Across Tumor Types

BACK

Disease Group	N	*FGFR 1* REARRANGEMENTS	*FGFR 1* MUTATIONS	*FGFR 2* REARRANGEMENTS	*FGFR 2* MUTATIONS	*FGFR 3* REARRANGEMENTS	*FGFR 3* MUTATIONS	ANY *FGFR* MUTATIONS	ANY *FGFR* REARRANGEMENTS	ANY MUTATIONS OR REARRANGEMENTS
Bladder	4338	0.04%	0.09%	0.14%	0.64%	3.39%	14.68%	15.42%	3.57%	**18.99%**
Cholangiocarcinoma	4826	0.04%	0.02%	9.15%	1.76%	0.25%	0.17%	1.95%	9.45%	**11.40%**
Endometrial	7055	0.04%	0.39%	0.18%	7.74%	0.30%	0.18%	8.31%	0.52%	**8.83%**
Glioma	10072	0.58%	2.33%	0.16%	0.26%	2.06%	0.28%	2.87%	2.79%	**5.66%**
Unknown primary	13989	0.06%	0.07%	1.68%	1.06%	0.47%	1.13%	2.26%	2.21%	**4.47%**
Cervix	2008	0.05%	0.10%	0.35%	0.95%	1.34%	1.54%	2.59%	1.74%	**4.33%**
Kidney	4687	0.02%	0.09%	0.10%	0.17%	0.64%	3.12%	3.37%	0.77%	**4.14%**
Head and neck	4210	0.07%	0.09%	0.10%	0.38%	0.57%	1.83%	2.30%	0.74%	**3.04%**
Melanoma	7097	0.05%	0.20%	0.00%	1.62%	0.03%	0.41%	2.23%	0.08%	**2.31%**
Plasma cell neoplasm	2530	0.04%	0.00%	0.00%	0.08%	0.20%	1.89%	1.98%	0.24%	**2.22%**
Stomach	4343	0.00%	0.04%	0.74%	1.03%	0.14%	0.20%	1.29%	0.87%	**2.16%**
Biliary	2677	0.04%	0.07%	1.23%	0.52%	0.22%	0.04%	0.64%	1.49%	**2.13%**
Breast	25569	0.10%	0.32%	0.41%	0.69%	0.14%	0.18%	1.19%	0.65%	**1.84%**
Ovary	14028	0.05%	0.14%	0.23%	0.86%	0.07%	0.13%	1.13%	0.35%	**1.48%**
Pancreas	14260	0.06%	0.09%	0.89%	0.21%	0.08%	0.09%	0.40%	1.03%	**1.43%**
Esophagus	6451	0.05%	0.06%	0.43%	0.39%	0.23%	0.17%	0.62%	0.71%	**1.33%**
NSCLC	50152	0.03%	0.08%	0.11%	0.30%	0.22%	0.40%	0.78%	0.35%	**1.13%**
Soft tissue sarcoma	6290	0.25%	0.32%	0.15%	0.13%	0.02%	0.14%	0.59%	0.41%	**1.00%**
CRC	30323	0.06%	0.13%	0.06%	0.34%	0.03%	0.22%	0.68%	0.14%	**0.82%**
Small cell	3189	0.00%	0.12%	0.06%	0.34%	0.00%	0.25%	0.72%	0.06%	**0.78%**
Prostate	7938	0.09%	0.12%	0.07%	0.24%	0.10%	0.09%	0.44%	0.25%	**0.69%**
Thyroid	2077	0.10%	0.00%	0.19%	0.05%	0.00%	0.10%	0.14%	0.29%	**0.43%**
Acute leukemia	3956	0.25%	0.08%	0.03%	0.08%	0.00%	0.00%	0.15%	0.28%	**0.43%**
Leiomyosarcoma	2524	0.12%	0.04%	0.04%	0.12%	0.04%	0.00%	0.16%	0.20%	**0.36%**
MDS	2491	0.04%	0.00%	0.00%	0.08%	0.00%	0.00%	0.08%	0.04%	**0.12%**

Figures indicate % of patients in each disease group with the respective *FGFR* alteration(s).
CRC, colorectal cancer; NSCLC, non-small cell lung cancer; MDS, myelodysplastic syndromes.
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Pharmacodynamics and Pharmacokinetics of Pemigatinib

BACK

Pharmacodynamics	
Impact on QTc interval	No impact
Increase in serum phosphate	Exposure dependent

Pharmacokinetics	
Time to achieve steady state	Within 4 days
Half-life	15.4 hours
Time to peak plasma concentration	1.13 hours
Excretion	82.4% in feces, 12.6% in urine
Effect of food	No effect on PK
Metabolism	CYP3A4 *in vitro*
Severe renal impairment	Mean pemigatinib AUC ↑ by 59%
Severe hepatic impairment	Mean pemigatinib AUC ↑ by 136%
Use with strong CYP3A inhibitor	Itraconazole ↑ pemigatinib C_{max} by 17% and AUC by 88% after a single dose of 4.5 mg
Use with moderate CYP3A inhibitor	Predicted to ↑ pemigatinib exposure by 50-80%
Use with strong CYP3A inducer	Rifampin ↓ pemigatinib C_{max} by 62% and AUC by 85% following a single dose of 13.5 mg
Use with moderate CYP3A inducer	Predicted to ↓ pemigatinib exposure by >50%

PK, pharmacokinetics; QTc, corrected QT interval.

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