Pemigatinib Adverse Events and Management Strategies

MSL-PEM-US-0021 03/25

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**

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Pemigatinib in Cholangiocarcinoma

Study Design[1,2]

fight-202

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

N=147[a]

Select Inclusion Criteria:
- Adults with locally advanced or metastatic CCA
- Documented *FGFR2* gene fusion or other rearrangement[b]
- Progression after ≥1 prior therapy
- ECOG PS ≤2
- Adequate hepatic/renal function

Cohort A (n=108)[c]
***FGFR2* fusions/rearrangements**

Cohort B (n=20)
Other *FGF/FGFR* genetic alterations

Cohort C (n=17)
No *FGF/FGFR* genetic alterations

Pemigatinib 13.5 mg daily (2 weeks on, 1 week off)[d]

Primary endpoint:
- ORR in cohort A

Secondary endpoints:
- ORR in cohorts B, A + B, and C; DOR, DCR, PFS, OS, and safety in all cohorts

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 Sep 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. PEMAZYR. Package insert. Incyte; June 2023.

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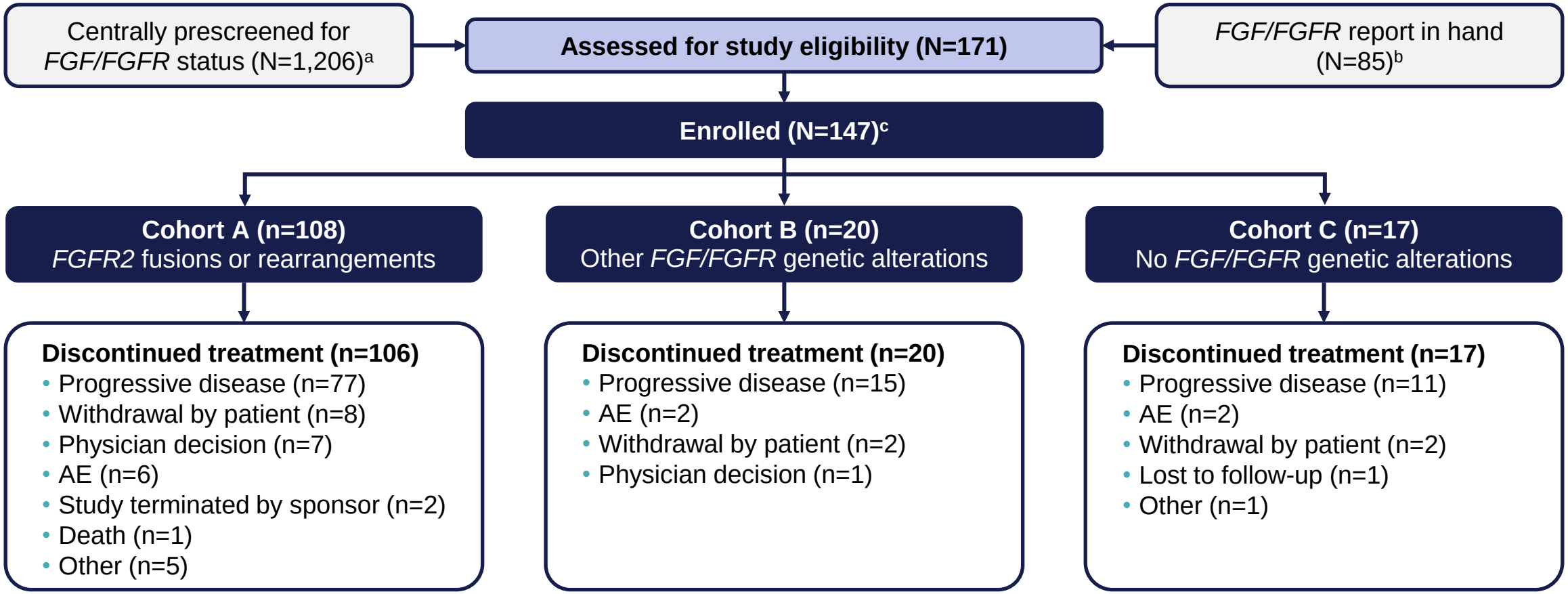
Patient Disposition[1]

fight-202



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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Adverse Events Reported in ≥15% of Patients

fight-202

AE, %	All patients (N=146)[a] All grades[b]	Grades 3/4
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	49	0
Nail toxicity[e]	43	2.1
Dry skin	20	0.7
PPE 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

AE, %	All patients (N=146)[a] All grades[b]	Grades 3/4
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

In all patients treated with pemigatinib, 0.5% experienced pathologic fractures (which included patients with and without cholangiocarcinoma [N=635]).
[a] Data include 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 phosphorus 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 phosphorus 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; PPE, palmar-plantar erythrodysesthesia.
PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023.

Select Laboratory Abnormalities

fight-202

Laboratory abnormality reported in ≥10% (any grade) worsening from baseline in patients, %	All patients (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 serum creatinine:

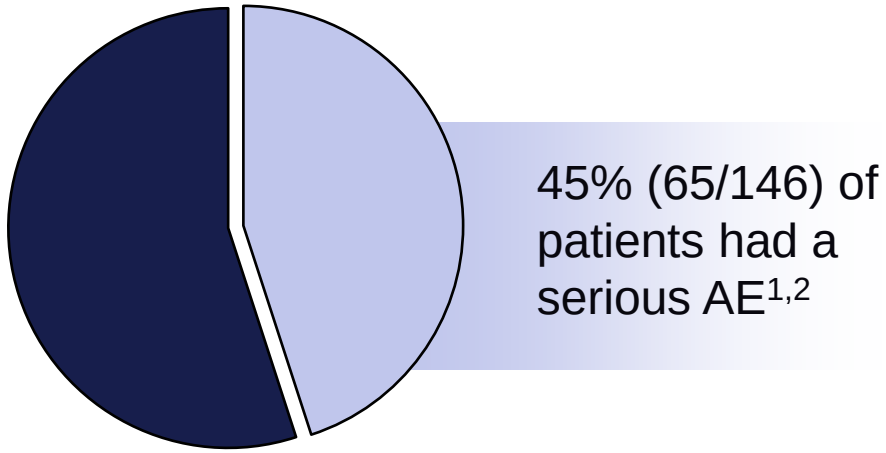
- Within the first 21-day cycle: SCr increased (mean increase of 0.2 mg/dL) and reached steady state by day 8 and then decreased during the 7 days off therapy
- Consider alternative markers of renal function if persistent elevations in serum creatinine are observed

[a] The denominator used to calculate the rate varied from 142 to146 based on the number of patients with a baseline value and ≥1 posttreatment value. [b] Graded per NCI CTCAE 4.03.
[c] Based on CTCAE 5.0 grading. [d] Graded based on comparison to ULN.
ULN, upper limit of normal.
PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023.

Serious or Fatal AEs Reported[1,2]

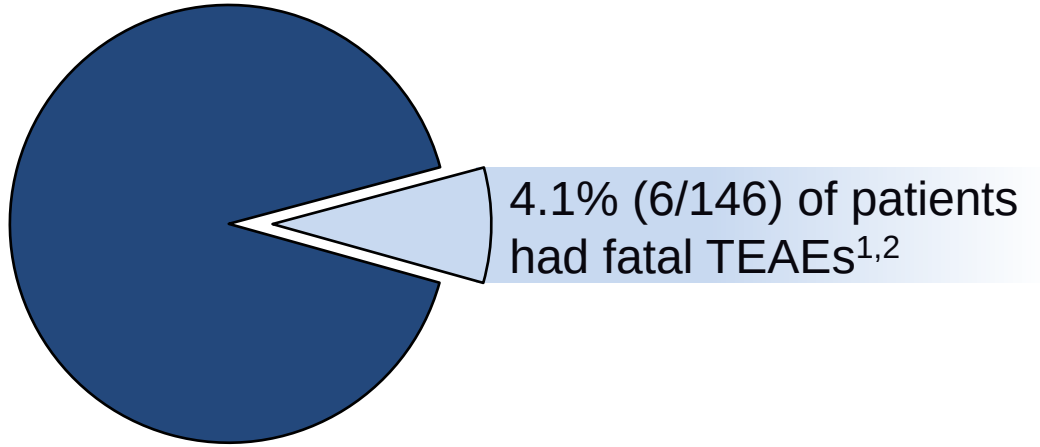
fight-202

Serious AEs



- Most frequent (occurring in >3 patients):[2]
  - Abdominal pain (n=7)
  - Pyrexia (n=7)
  - Cholangitis (n=5)
  - Pleural effusion (n=5)

Fatal TEAEs



- Fatal TEAEs:[2]
  - Failure to thrive (n=2)
  - Bile duct obstruction, sepsis, pleural effusion, and cholangitis (n=1 each)
- No deaths were deemed treatment related by the investigators[2]

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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Dose Modifications and Discontinuations Due to Adverse Reactions

fight-202

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.

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

Pemigatinib in MLNs with *FGFR1* Rearrangement

Study Design

fight-203

Study Design: Monotherapy, open-label study (ClinicalTrials.gov, NCT03011372) to evaluate the efficacy and safety of pemigatinib in patients with MLN with *FGFR1* rearrangement[1]

Select Inclusion Criteria:

- ≥18 years of age
- MLN with variant translocation/*FGFR1* rearrangement[a]
- ≥1 Prior therapy; no prior therapy allowed after protocol amendment
- No prior selective FGFR inhibitor therapy

Pemigatinib 13.5 mg daily
(2 weeks on, 1 week off)

Protocol Amendment 3 allowed pemigatinib 13.5 mg daily on a continuous schedule

- Response (per protocol) → Continue treatment
- Disease progression → Discontinue (safety and survival follow-up)[b]

Primary endpoint:

- Proportion of participants who achieve CR

Secondary endpoints:

- ORR (CR + PR), CCyR or partial CyR (PCyR), and Safety

Assessments:

- Investigator-assessed disease and cytogenetic responses according to protocol-defined criteria including modified response criteria for MDS/MPN,[3] modified Lugano criteria for EMD[4] and cytogenetic criteria
- Responses were also adjudicated retrospectively by a CRC using CRC-defined response criteria[c]
- AEs were assessed using CTCAE v4.03

[a] Based on standard cytogenetic evaluation performed locally. [b] Patients who discontinue and bridge to HSCT are followed up. [c] CRC-defined response criteria were based on local lab and radiologic results and central histopathology review; both local and central cytogenetic results were used by CRC with central results given priority.[1]
AEs, adverse events; CCyR, complete cytogenic response; CR, complete response; CRC, central review committee; CTCAE, common terminology criteria for adverse events; CyR, cytogenic response; ORR, overall response rate; PCyR, partial cytogenic response; PR, partial response.

1. ClinicalTrials.gov. Accessed Sep 2024. https://clinicaltrials.gov/ct2/show/NCT03011372. 2. Gotlib J, et al. ASH 2021. Oral presentation 385. 3. Savona MR, et al. *Blood.* 2015;125:1857–865. 4. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059–068.

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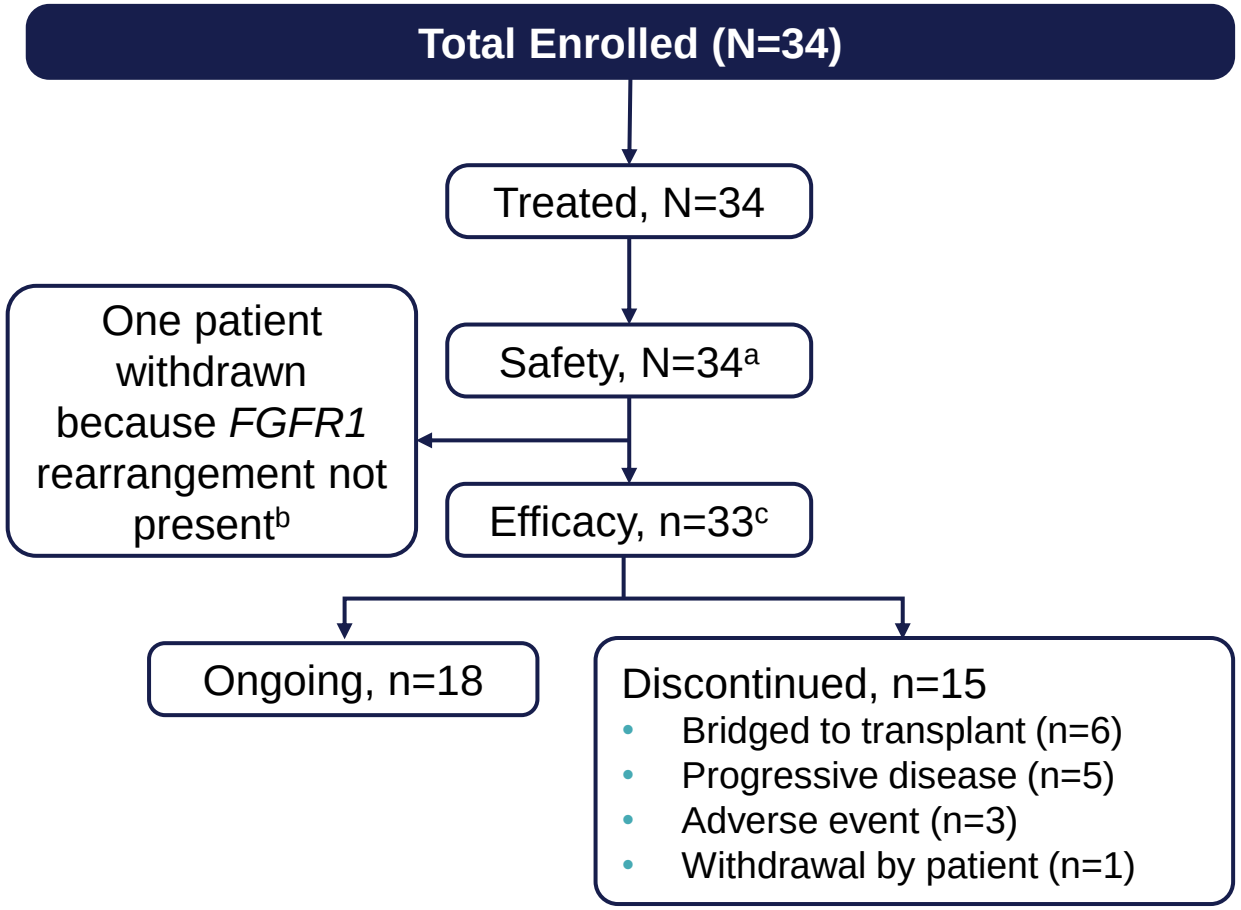
Patient Deposition and Exposure

fight-203

Patient Disposition



Pemigatinib Exposure

Exposure, median (range)	Patients (N=34)
Daily Dose, mg/day	9.5 (4.0-14.7)
Number of treatment cycles completed	10.0 (2.0-65.0)
Duration of treatment, weeks	29.3 (4.3-192.4)

Data cut-off: December 31, 2020.

[a] Safety population included all enrolled patients who received at least one dose of pemigatinib. [b] Physician decision. [c] Efficacy evaluable population included all enrolled patients with an *FGFR1* rearrangement who received at least 1 dose of pemigatinib; 1 patient did not have *FGFR1* rearrangement and was excluded from efficacy analysis.

Gotlib J, et al. ASH 2021. Oral presentation 385.

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Adverse Events Reported in ≥15% of Patients

fight-203

AE, %	All patients (N=34)	
	All grades[a]	Grades 3/4
Metabolism and nutrition disorders		
Hyperphosphatemia[b]	74	2.9
Decreased appetite	24	6
Skin and subcutaneous tissue disorders		
Nail toxicity[c]	62	21
Alopecia	59	0
Rash[d]	35	6
Dry skin[e]	24	0
PPE syndrome[f]	18	9
Gastrointestinal disorders		
Stomatitis[g]	53	15
Diarrhea	50	2.9
Abdominal pain[h]	35	2.9
Constipation	32	2.9
Dry mouth	32	0
Dyspepsia	24	0
Nausea	21	0

AE, %	All patients (N=34)	
	All grades[a]	Grades 3/4
Eye disorders		
Dry eye[i]	50	6
RPED[j]	26	0
Vision blurred	21	2.9
Trichiasis	18	2.9
General disorders		
Fatigue[k]	44	9
Edema peripheral	21	0
Pyrexia	18	2.9
Blood and lymphatic system		
Anemia	35	18
Respiratory/thoracic/mediastinal disorders		
Epistaxis	29	0
Musculoskeletal/connective tissue disorders		
Pain in extremity	26	12
Back pain[l]	24	9
Nervous system disorders		
Dizziness	21	0

In all patients treated with pemigatinib, 0.5% experienced pathologic fractures (which included patients with and without cholangiocarcinoma [N=635]).

[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 ingrowing nail, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail growth abnormal, nail infection, nail pigmentation, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia. [d] Includes dermatitis, dermatitis acneiform, lichen planus, rash, rash macular, and skin exfoliation. [e] Includes dry skin and xerosis. [f] Includes palmar-erythemia, palmer-plantar erythrodysaesthesia, and plantar erythema. [g] Includes aphthous ulcer, cheilitis, lip ulceration, mouth ulceration, pharyngeal inflammation, stomatitis, and tongue ulceration. [h] Includes abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal rigidity. [i] Includes dry eye, keratitis, lacrimation increased, meibomian gland dysfunction, and punctate keratitis. [j] Includes detachment of retinal pigment epithelium, maculopathy, retinal detachment, retinal disorder, retinal thickening, serous retinal detachment, and subretinal fluid. [k] Includes asthenia and fatigue. [l] Includes back pain and spinal pain.

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

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Select Laboratory Abnormalities

fight-203

Laboratory abnormality reported in ≥20% worsening from baseline in patients, %	All patients (N=34)[a]	
	All grades[b]	Grades 3/4
Hematology		
Decreased lymphocytes	65	16
Decreased leukocytes	65	15
Decreased hemoglobin	53	9
Decreased neutrophils	45	12
Decreased platelets	29	15
Chemistry		
Increased phosphate[c]	97	2.9
Increased alkaline phosphatase	62	9
Increased alanine aminotransferase	50	12
Increased aspartate aminotransferase	47	9
Increased creatinine[d]	44	0
Decreased phosphate	41	26
Decreased sodium	41	9
Increased glucose	33	3
Decreased calcium	26	2.9
Increased calcium	26	2.9
Decreased potassium	24	2.9
Increased bilirubin	21	0

Other clinically significant laboratory abnormalities:

- Prothrombin time/international normalized ratio was elevated in 16% (Grade 1 or 2 elevation) of patients
- Uric acid was elevated in 18% of patients, including 2.9% with a Grade 3 or 4 elevation

[a] The denominator used to calculate the rate varied from 31 to 34 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] Graded per NCI CTCAE 5.0. [d] Based on comparison to upper limit of normal.

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

Adverse Event Overview

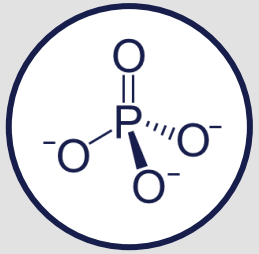
Normal Functions of FGFR Signaling in Cells

Despite roles in promoting tumor growth and metastasis, FGF and its receptors also play roles in normal cellular processes, including:

Organ Development[1]
(eg, heart, lung, eyes)

Angiogenesis[1]

Wound Healing[1]



Phosphate Homeostasis[2]

Cardioprotection[1]

Neuroprotection[1]

Dermal/Skin Cell Homeostasis[3]

Knowledge of normal physiologic functions may help explain the mechanisms of the AEs observed with FGFR inhibition which include ocular toxicities, dermatologic effects, and hypo-/hyperphospatemia[2-4]

1. Raju R, et al. *J Signal Transduction*. 2014;104:1-16. 2. Wohrle S, et al. *J Bone Miner Res*. 2011;26:2486-2497. 3. Grose R, et ad. *EMBO J*. 2007;26:1268-12785. 4. Zhang J, et al. *PLoS One*. 2015;10:e0117089.

Select AEs and Management Strategies

- Ocular Toxicities
- Hyper-/Hypophosphatemia
- Nail Toxicities
- Stomatitis
- Palmar-Plantar Erythrodysesthesia Syndrome
- Considerations for Other Toxicities

Ocular Toxicities

Ocular Toxicities: RPED

- RPED symptoms may include blurred vision, visual floaters, or photopsia[1]

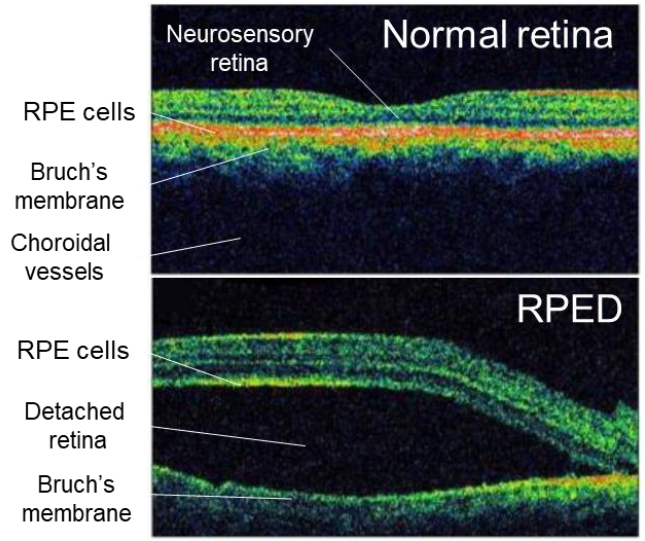
RPED Occurrence[1,2,a]

	Overall	Grade 3/4
Across clinical trials[b]	11%	1.3%
fight-202	4.8%	0.7%
fight-203	26%	–

Across Clinical Trials[1]

- **Overall median time to onset:** 56 days
- **Observed pemigatinib dose modifications:**
  - Dose interruption: 3.1%
  - Dose reduction: 1.3%
  - Discontinuation: 0.2%
- RPED resolved or improved to Grade 1 in 76% of patients who required a dose modification

RPED Presentation[3]



Kim J, et al. Korean J Ophthalmol, 2010;24:245-248. Figure reproduced under the terms of the Creative Commons Attribution NonCommercial 3.0 Unported (CC BY-NC 3.0) license

Potential mechanisms of ocular toxicity

[a] Clinical trials of pemigatinib did not conduct routine monitoring that included OCT to detect asymptomatic RPED; therefore, the incidence of asymptomatic RPED with pemigatinib is unknown. [b] Occurrence among 635 patients who received a starting does of pemigatinib 13.5 mg, regardless of schedule.
OCT, optical coherence tomography; RPED, retinal pigment epithelial detachment.

1. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023. 2. Data on file. Incyte Corporation. 3. Kim J, et al. *Korean J Ophthalmol.* 2010;24:245-248.

Ocular Toxicities: RPED Monitoring and Management

Monitoring

- 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 Modifications

- 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

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

Ocular Toxicities: Dry Eye and Other Reported Ocular Toxicities

- Dry eye symptoms may include recurrent burning, tearing, light sensitivity, and a sensation of foreign-body in eyes[1]

Dry Eye Occurrence[2,3]

	Overall	Grade 3/4
Across clinical trials	31%	1.6%
fight-202	28%	0.7%
fight-203	29%	–

Dry Eye Management Strategies[2]

- Patients should be treated with ocular demulcents (artificial tears) as needed

Other Reported Eye Disorders[2,3]

fight-202	fight-203
Grade 1/2: • Trichiasis: 8.2% • Punctate keratitis: 6.2% • Growth of eyelashes: 5.5% • Trichomegaly: 2.1%	**Grade 1/2:** • Trichiasis: 18% • Blurred vision: 21%
Grade 3/4: • Keratitis: 0.7% • Blurred vision: 0.7%	**Grade 3/4:** • Trichiasis: 2.9% • Blurred vision: 2.9%

Trichiasis is an inward growth of the eyelashes that can lead to irritation of the cornea and conjunctiva and may cause ulcerations[4]

Trichiasis Management Strategies[4]

- Ocular lubricants
- Epilation as needed for prevention of ulcers

1. American Academy of Ophthalmology. Accessed Sep 2024. https://www.aao.org/eye-health/diseases/what-is-dry-eye. 2. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023. 3. Data on file. Incyte Corporation. 4. The College of Optometrists. Accessed Sep 2024. https://www.college-optometrists.org/guidance/clinical-management-guidelines/trichiasis.html.

Hyper-/Hypophosphatemia

Hyper-Phosphatemia: Potential Mechanisms and Occurrence

Potential Mechanisms

- Asymptomatic event often observed with FGFR inhibition therapy[1-4]
  - FGF23 binds to FGFR1 and regulates phosphate excretion; when inhibited, it can lead to phosphate reabsorption[5]
  - Potential complications arising from hyperphosphatemia include soft-tissue mineralization, cutaneous calcification, calcinosis, and nonuremic calciphylaxis[1]

Hyper-phosphatemia Occurrence[1]

Population	Patients experiencing hyperphosphatemia, %	Median time to onset, days (range)	Description
Pemigatinib-exposed across all tumor types (N=635)	93	8 (1-169)	>ULN laboratory abnormality

- Across all tumor types, 33% of patients who received pemigatinib required phosphate-lowering therapy[1]

In fight-202, hyper-phosphatemia[a] was the most common all-cause AE across all cohorts; all cases were reported as Grade 1 or 2[2]

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

1. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023. 2. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684. 3. Chae YK, et al. *Oncotarget*. 2017;8:16052-16074. 4. Hierro C, et al. *Semin Oncol*. 2015;42:801-819. 5. Valle JW, et al. *Cancer Discov*. 2017;7:1-20.

Hyper-Phosphatemia: Monitoring and Management

Monitoring

- Requires regular monitoring of serum phosphate levels to maintain as close to normal range as possible[1]

Management Strategies

- fight-202 management:[2]
  - Low-phosphate diet (n=NR)
  - Phosphate binders (n=27)
    - Lanthanum carbonate: 1.4%
    - Sevelamer (including salts): 13%
    - Calcium acetate: 4.1%
  - Diuretics (n=1)
- fight-203 management:[2]
  - Low-phosphate diet (n=NR)
  - Phosphate binders (n=11)
    - Lanthanum carbonate: 2.9%
    - Sevelamer (including salts): 29.4%
    - Calcium acetate: 2.9%

NR, not reported.

1. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023. 2. Data on file, Incyte Corporation.

Hyper-Phosphatemia: Monitoring and Management (cont)

Pemigatinib Dose Modifications

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 level 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 serum 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 level 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 serum phosphate levels are <7 mg/dL • Permanently discontinue pemigatinib for recurrence of serum phosphate levels >10 mg/dL following 2 dose reductions

Severity as defined by NCI CTCAE v4.03.

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

Hypo-Phosphatemia: Occurrence and Management

Hypo-phosphatemia Occurrence[1,2]

	Overall	Grade 3/4
fight-202[a]	23%	12%
fight-203	11.8%	5.9%

- In the fight-202 study, hypophosphatemia may have resulted from:[3]
  - Continued use of a low phosphate diet or phosphate binders for hyperphosphatemia during off-treatment weeks
  - Negative feedback effects on phosphate homeostasis
- In the fight-202 study, No case was clinically significant/serious; no case led to discontinuation/dose reduction[3]

Pemigatinib Dose Modifications

- In fight-202, 2 patients who had grade 3 AEs were managed with dose interruptions[2]
- In fight-203, no patient required a dose reduction, interruption, or discontinuation[2]

[a] The following MedDRA preferred terms related to hypophosphatemia were combined: blood phosphorus decreased and hypophosphatemia.

1. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023. 2. Data on file, Incyte Corporation. 3. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684

Nail Toxicities

Nail Toxicities: Occurrence

- Nail toxicities included, but were not limited to:[1]
  - Nail discoloration, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia

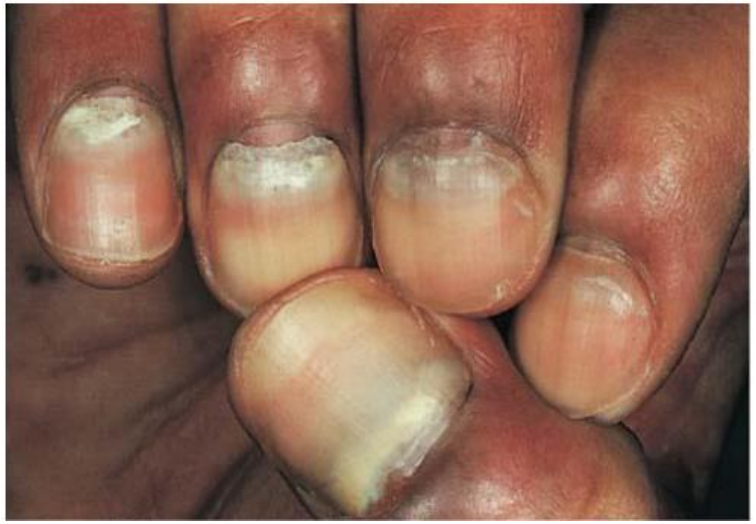
Onychomadesis, an observed nail toxicity, is the proximal separation of the nail plate from the nail matrix[2]

Nail Toxicity Occurrence[1]

	Overall	Grade 3/4
fight-202[a]	43%	2.1%
fight-203[b]	62%	21%

- In fight-202, the median time to onset was 6 months[3]

Onychomadesis Presentation[2]



Reprinted from *Lancet Oncol*, Vol. 16, Robert C, et al, Nail toxicities induced by systemic anticancer treatments, Pages e181-189, Copyright (2015), with permission from Elsevier.

[a] Includes nail toxicity, nail disorder, nail discoloration, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia. [b] Includes ingrowing nail, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail growth abnormal, nail infection, nail pigmentation, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia.

1. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023. 2. Robert C, et al. *Lancet Oncol*. 2015;16:e181-e189. 3. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684.

Nail Toxicities: Management

Management Strategies

- Management for toenail or fingernail issues may include:[1,2]
  - Avoid extended contact with water and use gloves[1,2]
  - Avoid repeated trauma or friction and pressure[2]
  - Use of topical emollients[2]
  - Trim nails regularly[1,2]
  - Avoid nail polish removers and nail hardeners[2]
  - Use of topical steroids and topical antibiotics[1,2]
  - Artificial nails should not be worn or used as they can promote growth of fungal infections[3]
- For nails that are lifting from nail bed, consider referral to a dermatologist (fingernails) or podiatrist (toenails) for removal of the nail to avoid tearing the nail off the nail bed prematurely[2]
  - The new nail may start to grow in before the old nail comes off, so removal of the old nail may assist with palliation of pain at the cuticle

Pemigatinib Dose Modifications

- In fight-202, general nail toxicities led to dose reductions in 5 patients and dose interruptions in 6 patients; onychomadesis led to a dose reduction in 2 patients[4]
- In fight-203, general nail toxicities led to dose reductions in 7 events and dose interruptions in 3 events; there were no dicontinuations[5]

1. Robert C, et al. *Lancet Oncol*. 2015;16:e181-e189. 2. Lacouture ME, et al. *Oncologist*. 2021;26:e316-e326. 3. Subbiah V et al. *Cell Rep Med*. 2023;4(10):101204.
4. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671-684. 5. Data on file, Incyte Corporation.

Stomatitis

Stomatitis: Occurrence and Management

- Stomatitis symptoms include oral inflammation and redness of the oral mucosa or single or multiple painful ulcers[1]

Stomatitis Occurrence[2]

	Overall	Grade 3/4
fight-202	35%	5%
fight-203[a]	53%	15%

Pemigatinib Dose Modifications[2]

- Pemigatinib dose interruption or discontinuation may be required for cases that are grade ≥3/4[b]

Management Strategies

- Preventive strategies include:
  - Dental work aimed at eliminating any existing tooth and/or gum disease before starting treatment[3]
  - Patient education on the importance of oral hygiene, avoidance of salty, spicy, or acidic foods, and hot beverages[3,4]
  - Maintain routine dental visits and use a high-fluoride toothpaste[3]
  - Routine baking soda rinses[4]
- At emergence of grade 1-2 stomatitis, consider:[3]
  - Use of dexamethasone 0.5 mg/5 mL elixir
  - Application with gauze of an augmented betamethasone dipropionate 0.05% gel to the affected surface

[a] Includes aphthous ulcer, cheilitis, lip ulceration, mouth ulceration, pharyngeal inflammation, stomatitis, and tongue ulceration. [b] See full prescribing information for more details on how to manage grade 3/4 AEs.

1. Merck Manuals. Accessed Oct 2023. https://www.merckmanuals.com/professional/dental-disorders/symptoms-of-dental-and-oral-disorders/stomatitis. 2. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023. 3. Lacouture ME, et al. *Oncologist*. 2021;26:e316-e326. 4. Subbiah V et al. *Cell Rep Med*. 2023;4(10):101204.

Palmar-Plantar Erythrodysesthesia Syndrome

Palmar-Plantar Erythrodysesthesia: Occurrence and Management

- PPE produces symmetric and painful erythema of the palms and soles that can progress to blistering desquamation, erosion, ulceration, and the formation of vesicles or bullae[1]

Palmar-Plantar Erythrodysesthesia Occurrence[2]

	Overall	Grade 3/4
fight-202	15%	4.1%
fight-203	18%	9%

Pemigatinib Dose Modifications

- Pemigatinib dose interruption or discontinuation may be required for cases that are grade ≥3/4[a]

Management Strategies[3]

- Prevention strategies may include prophylactic removal of hyperkeratotic areas, application of moisturizing creams containing ≥10% urea, pedicures, and cushioning of callused areas using soft or padded shoes[3]

- Symptomatic management includes:
  - Wound care[1]
  - Use of alcohol-free emollients[1] or keratolytic agents (for grade ≥1)[3]
  - Elevation[1]
  - Pain medication[1]
  - High-potency topical steroids such as fluocinonide 0.05% (for grade ≥2)[3]
  - Limit exposure to heat sources and keep showers and baths short[4]

[a] See full prescribing information for more details on how to manage grade 3/4 AEs.

1. StatPearls. Accessed Sep 2022. https://www.ncbi.nlm.nih.gov/books/NBK459375/. 2. PEMAZYRE (pemigatinib). Prescribing information. Incyte Corporation; June 2023.
3. Lacouture ME, et al. *Oncologist*. 2021;26:e316-e326. 4. Subbiah V et al. *Cell Rep Med*. 2023;4(10):101204.

Considerations for Other Toxicities

General Adverse Reactions: Pemigatinib Dose Modifications

Pemigatinib Dose Recommendations

	CCA with *FGFR2* Fusion or Rearrangement	MLNs with *FGFR1* Rearrangement
Starting Dose	13.5 mg once daily for 14 days, followed by 7 days off, in 21-day cycles	13.5 mg once daily on a continuous basis
1st Dose Reduction	9 mg once daily for first 14 days of each 21-day cycle	9 mg once daily
2nd Dose Reduction	4.5 mg once daily for first 14 days of each 21-day cycle	4.5 mg once daily
3rd Dose Reduction	Discontinue	4.5 mg once daily for first 14 days of each 21-day cycle[a]

[a] Permanently discontinue PEMAZYRE if unable to tolerate 4.5 mg once daily for 14 days of each 21-day cycle.

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

Grade 3/4 Adverse Reactions: Pemigatinib Dose Modifications

Pemigatinib Dose Recommendations

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

Severity as defined by NCI CTCAE v4.03.

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

FOR MEDICAL INFORMATION PURPOSES ONLY.

APPENDIX

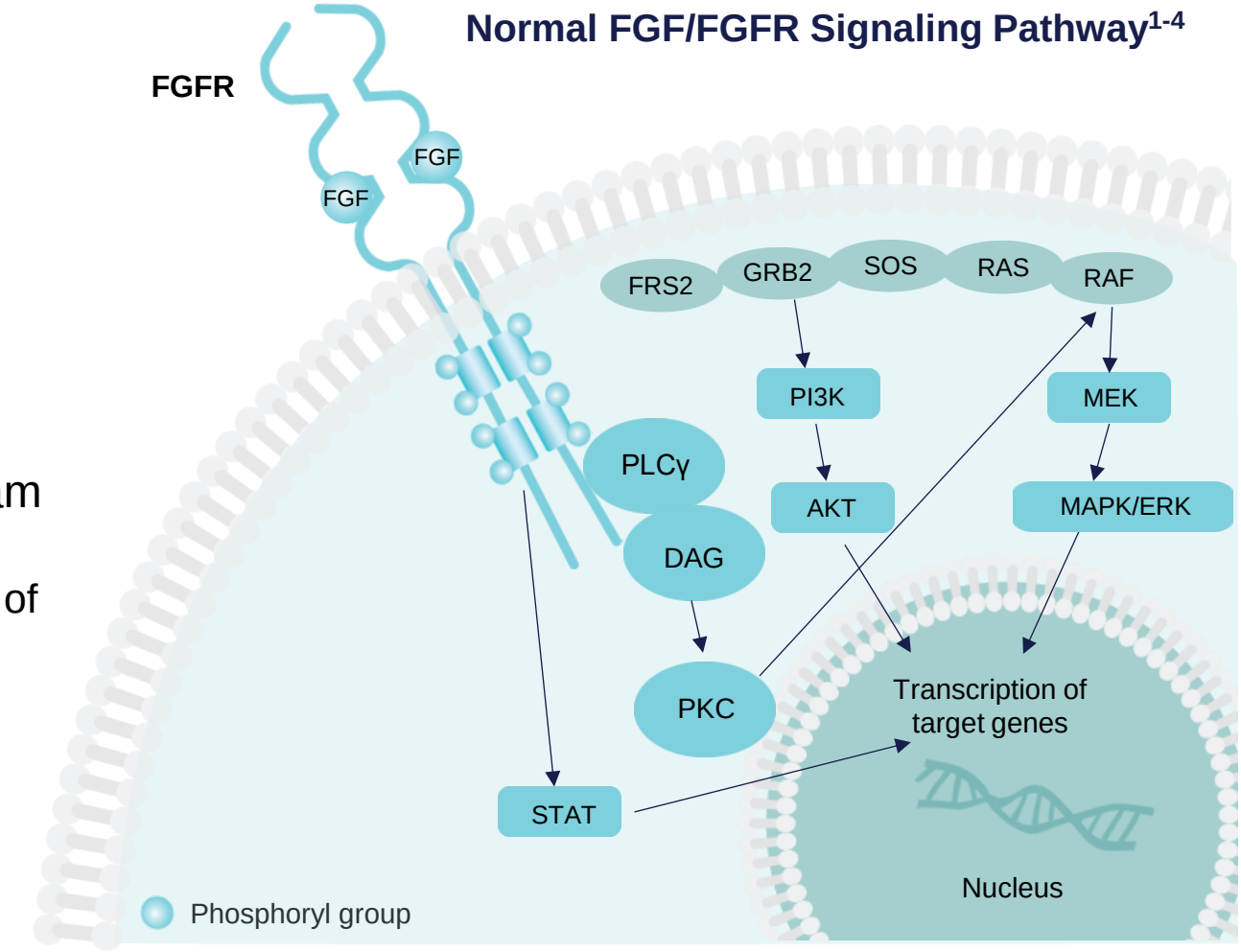
Ocular Toxicities: Potential Mechanisms

BACK

- FGF/FGFR pathway plays an essential role in:
  - DNA synthesis and growth in young RPE cells[1,2]
  - Prevention of apoptosis in mature RPE cells[1,2]

- FGF ligand binding triggers activation of downstream pathways, including MAPK and PI3K
  - Both of these pathways eventually trigger transcription of genes involved in cell survival and proliferation[2]

Normal FGF/FGFR Signaling Pathway[1-4]



AKT, protein kinase B; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FRS2, fibroblast growth factor receptor substrate 2; GRB2, growth factor receptor-bound protein 2; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLCγ, phospholipase C-gamma; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma GTPase; SOS, son of sevenless; STAT, signal transducer and activator of transcription.

1. Babina IS, Turner NC. *Nat Rev Cancer*. 2017;17:318-332. 2. Turner N, Grose R. *Nat Rev Cancer*. 2010;10:116-129. 3. Sarabipour S, Hristova K. *Nat Commun*. 2016;7:10262. 4. Touat M, et al. *Clin Cancer Res*. 2015;21:2684-2694.