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FGFR2 Gene Fusion Testing Clinical Guidance Document

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Guideline version	Date	Summary of amendments
V0.1	12/10/21	
V0.2	08/11/21	Addition of information to prescribing section
V0.3	23/11/21	Review of references and addition of phosphate dietary information sheet
V1.0	23/11/21	Final version
V2.0	29/06/23	Addition of cytopathological sample preparation guidelines and updated pathology laboratory email addresses

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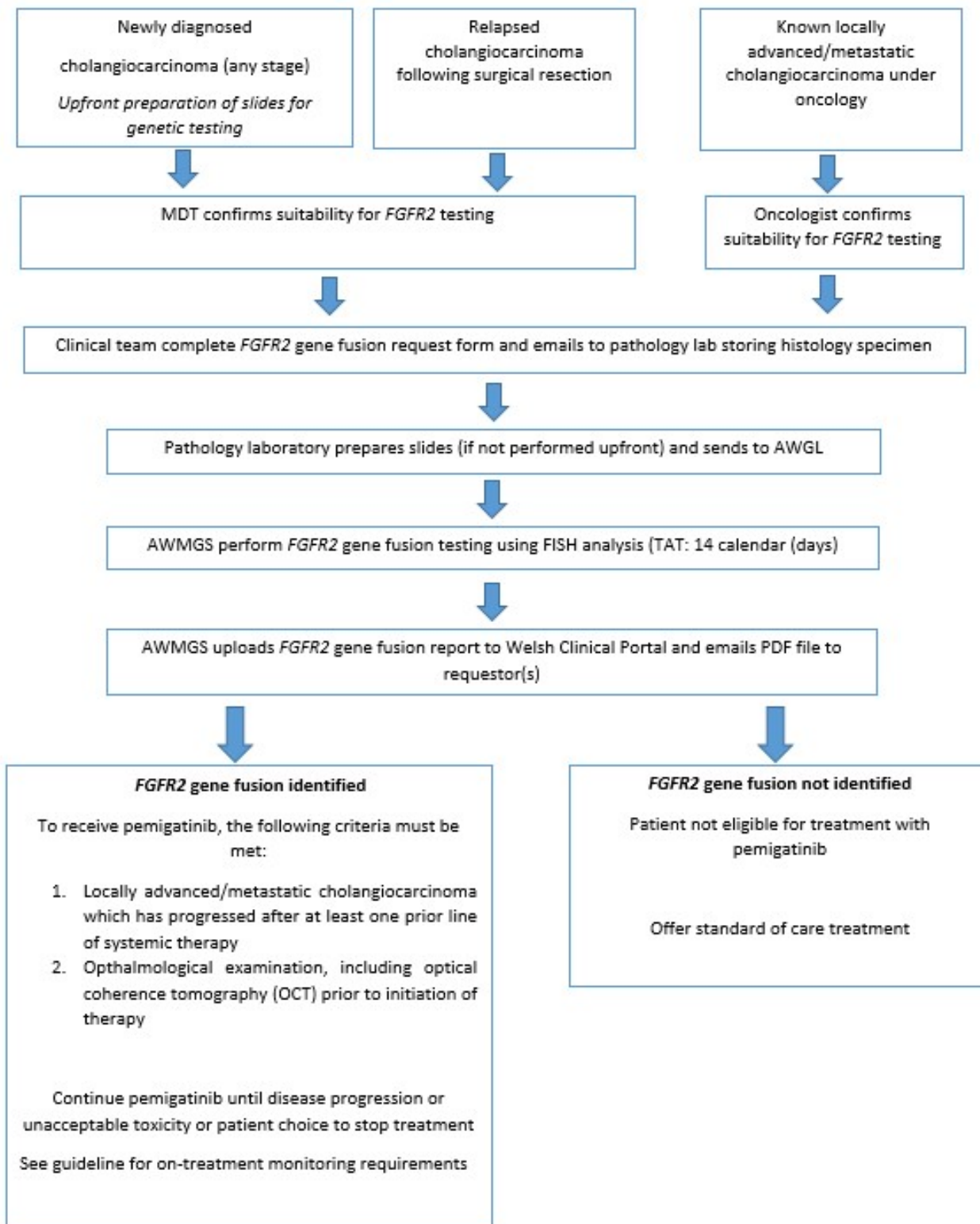
Purpose and summary of document

The aim of this document is to provide clinical staff with guidance on the *FGFR2* gene fusion testing pathway.

The guidance is relevant to all staff involved with the management of patients with locally advanced or metastatic cholangiocarcinoma.

These patients may be eligible to receive pemigatinib, an oral tyrosine kinase inhibitor, if their tumour is found to have a *FGFR2* gene fusion. This guideline summarises the prescribing information and recommended baseline investigations and on-treatment monitoring requirements for this drug.

FGFR2 gene fusion testing request algorithm



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Background

Cholangiocarcinoma is a type of cancer that develops from the epithelial lining of the bile ducts. It has historically been reported as a rare cancer although both the global and UK incidence rates are increasing; the age-standardised incidence in England in 2017 was reported at 4.3 per 100,000 (Genus et al., 2019). It represents a group of heterogeneous tumours, classified as intrahepatic or extrahepatic (perihilar or distal) based on the location of the tumour within the biliary tract. Surgery remains the only curative treatment however this is an option for only around 30% of patients with a 60% relapse rate (Banales et al., 2020).

First-line treatment for locally advanced or metastatic cholangiocarcinoma is gemcitabine and cisplatin combination chemotherapy (Valle, 2010). There is no clearly established standard-of-care treatment after failure of first-line chemotherapy, and the efficacy of second-line chemotherapy regimens for advanced biliary cancer remains low (Lamarca et al., 2020; Lamarca & Valle, 2020). Current second-line treatment options include chemotherapy with folinic acid, 5-fluorouracil and oxaliplatin (FOLFOX) plus active symptom control (ASC) (Lowery et al., 2019); if further chemotherapy is not deemed suitable, ASC alone is offered. Treatment options for cholangiocarcinoma have not improved in over a decade.

Comprehensive genomic profiling has identified several potentially actionable oncogenic alterations in patients with cholangiocarcinoma. The fibroblast growth factor receptor (FGFR) family comprises several subtypes of transmembrane tyrosine kinase receptors, FGFR 1-4 (Ross et al., 2014). Somatic alterations in *FGFR* genes can lead to aberrant FGFR signalling, which can drive tumorigenesis by enhancing cellular proliferation, migration, survival and invasion, as well as angiogenesis. In cholangiocarcinoma, *FGFR2* gene fusions and rearrangements are found almost exclusively in intrahepatic tumours, occurring in 10–16% of patients (Graham et al., 2014).

NICE has recently recommended pemigatinib, within its marketing authorisation, as an option for treating adults with locally advanced or metastatic cholangiocarcinoma with an *FGFR2* fusion or rearrangement that has progressed after systemic therapy (NICE, 2021). Appendix 1 provides further detail on these decision, taken from the NICE final appraisal document. It should be noted that to be eligible for pemigatinib, patients will be identified by the presence of an *FGFR2* variant and not by the anatomical subtype of cholangiocarcinoma; it may be used in both intrahepatic and extrahepatic cholangiocarcinoma.

Pemigatinib is a selective, potent, oral competitive tyrosine kinase inhibitor (TKI) of the FGFR1, FGFR2, and FGFR3 receptors (Liu et al., 2015). The FIGHT-202 study evaluated the safety and anti-tumour activity of pemigatinib in patients with locally advanced or metastatic cholangiocarcinoma, with or without *FGFR* alterations (Abou-Alfa et al., 2020). This was a phase 2, single-arm, non-randomised, open label study in people with advanced or surgically unresectable cholangiocarcinoma that had not responded to previous therapy. The clinical evidence from the latest available data cut-off (March 2019) suggests a median progression-free survival of 6.9 months and the median overall survival of 21.1 months. As this is a single-

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arm study, it does not provide evidence of the relative effectiveness of pemigatinib compared with current treatment options.

However the NICE appraisal document acknowledges that performing studies for advanced chemo-refractory cholangiocarcinoma is difficult because of the rarity of this cancer (NICE, 2021). There is an urgent unmet need for people with advanced cholangiocarcinoma with *FGFR2* fusions or rearrangements after systemic chemotherapy; access to pemigatinib therefore represents an opportunity for further disease-modifying treatment in this population (NICE, 2021).

Eligibility criteria for FGFR2 gene fusion testing

Given the aggressive nature of cholangiocarcinoma and that most patients present with advanced disease, **the All Wales Genomics Oncology Group (AWGOG) recommends the upfront testing of all newly diagnosed cholangiocarcinoma (regardless of stage and anatomical site) in patients deemed suitable for treatment.** This approach aims to identify patients who are eligible to receive pemigatinib at the earliest opportunity in the treatment pathway.

It is appreciated that histological confirmation of cholangiocarcinoma can be diagnostically challenging. The need for *FGFR2* gene fusion testing should be discussed at the diagnostic MDT with the decision to proceed based on the clinical, radiological and histopathological features of the individual case. If the patient has undergone surgery, testing should be preferentially performed on the surgical specimen. Cytological cell blocks can be tested if solid tissue is not available. **Wherever possible, upfront preparation of slides for genetic testing should be performed at the time of initial morphological assessment. Use of IHC should be limited on liver cores containing morphological adenocarcinoma in order to preserve tissue for biomarker testing.**

Patients diagnosed with cholangiocarcinoma prior to the implementation of routine *FGFR2* testing should have genetic testing performed at an appropriate time in the pathway e.g. at the point of relapse for patients initially treated with surgery or as soon as possible for patients with locally advanced or metastatic disease who have received first-line systemic treatment.

As pemigatinib is a second-line treatment, it may not be necessary to wait for the results prior to referral to an oncologist. **However MDTs should have an agreed process in place regarding which team member(s) is responsible for receiving and signing off *FGFR2* gene fusion test results to ensure the *FGFR2* status is documented appropriately in the patient record.**

It is not necessary for patients to sign a consent form in order to proceed with *FGFR2* gene fusion testing. However, where appropriate, the clinical team should inform the patient as to the rationale for testing and the likelihood of detecting a *FGFR2* gene fusion.

FGFR2 gene fusion testing request process

FGFR2 gene fusion testing is performed on the diagnostic histological specimen which requires preparation (slide cutting and tumour assessment) by the local pathology laboratory storing the sample. The slides should then be sent to the All Wales Medical Genomics Laboratory (AWGL) in Cardiff for analysis. **Requests should therefore not be made directly to the AWGL as samples are not stored here and histopathology services are unavailable in this laboratory.**

Testing should be made using the appropriate AWGL request form which is available under the 'Cholangiocarcinoma' section of the 'Solid Tumour' tab <https://medicalgenomicswales.co.uk/index.php/health-professional-information/a-z-of-services#Solid>

The patient demographic information and requestor's name and email address should be entered in the appropriate sections. In order to reduce turnaround times, it is recommended that the form is then emailed to the local pathology laboratory storing the diagnostic specimen which is to be tested. The majority of laboratories now have generic emails addresses, the accounts for which are checked on a daily basis (see table 1). If a generic address is not available, the request should be sent to a named individual at the local pathology laboratory who knows to expect the request and initiate the required sample preparation, thus avoiding unnecessary delays.

University Healthboard	Generic email address(es)
Aneurin Bevan	ABB.HistReferralRGW@wales.nhs.uk
Betsi Cadwaladr	BCU.CellPathMolecular@wales.nhs.uk
Cwm Taf Morgannwg	CTM.CellularPathologyMolecularRequests@wales.nhs.uk
Cardiff and Vale	mg.cellpath@wales.nhs.uk
Hywel Dda	WWGH.Histology@wales.nhs.uk (laboratory) HDD.Secretaries@wales.nhs.uk (secretaries)
Swansea Bay	SBUResearch.Histology@wales.nhs.uk

Table 1: Generic email address details for healthboards

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N.B. It is not necessary to ask the patient to sign the test request form to indicate their consent for the test to be undertaken. This is a standard pre-printed AWMGS request form.

The pathology laboratory should prepare the sample in line with the AWGL recommendations (see 'Histopathological sample preparation requirements' section). The laboratory should complete the request form and send a paper copy of the form with the prepared slides directly to the AWGL as soon as possible.

Upon receipt of the sample at AWGL, the result will be available within 14 calendar days. Hard copies of the report will be emailed to the requesting clinician (as listed on the request form) as a PDF file and also uploaded to the Welsh Clinical Portal system.

The contact details for the AWGL are as follows:

All Wales Genetics Laboratory

Institute of Medical Genetics

University Hospital of Wales

Heath Park

Cardiff CF14 4XW

Telephone: 02921845347

Email address: Admin.Genetics.cav@wales.nhs.uk

Website: <http://www.medicalgenomicswales.co.uk>

Opening hours: Monday – Friday 8.30am – 5:00pm

FGFR2 gene fusion testing for privately funding patients

FGFR2 gene fusion testing is a WHSSC-funded service and is routinely available for cholangiocarcinoma patients in Wales. However, it is also available for privately funding patients. Please contact the AWGL directly for further details.

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Histopathological sample preparation requirements

The local pathology laboratory housing the diagnostic specimen should prepare the sample as follows before sending the slides to AWGL with the request form:

FISH requirements	1 x H&E stained slide with area of highest neoplastic cell content CLEARLY circled
	3 x 3-4 μ m sections (singly mounted) on charged/adhesion slides for FISH testing

Please note that AWGL will be returning all unused slides to the referring pathology laboratory to file as part of the archive.

Cytopathological sample preparation requirements

In cases where there is not enough cytological material to create a histological cell block for the histopathological sample preparation requirements above but the MDT opinion is that the case clinically and radiologically fits with that of a cholangiocarcinoma, the local pathology laboratory can provide a cytological sample instead. It is preferable to have at least 100 cells in the preparation, however this should not impede a pathology laboratory from sending slides for FGFR2 gene fusion testing.

The local pathology laboratory housing the diagnostic specimen should prepare the sample as follows before sending the slides to AWGL with the request form:

FISH requirements	2 x air-dried cytospin prepared samples on charged/adhesion slides for FISH testing
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The cytospin slides should be air-dried and no fixative used. If sample has been placed into a cytological fixative prior to the cytospin slides being created, please make AWGL aware on the request form.

Please note that AWGL will be returning all unused slides to the referring pathology laboratory to file as part of the archive.

Interpreting a FGFR2 gene fusion test result

The following section provides information on how to interpret the genetics report.

Appendix 2 includes examples of *FGFR2* gene fusion reports.

1. *FGFR2* gene fusion/rearrangement identified

The 'Karyotype' comment will state that the patient may respond to FGFR2 inhibitors and that a *FGFR2* gene rearrangement has been detected.

The report will give further information about the implications for treatment e.g. *Patients with cholangiocarcinoma harbouring a FGFR2 gene rearrangement have been reported to respond to treatment with a FGFR2 inhibitor. Pemigatinib is recommended as an option for treating locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after systemic therapy in adults.*

2. No *FGFR2* gene fusion/rearrangement detected

The 'Karyotype' comment will state that the patient has a reduced likelihood of response to FGFR2 inhibitors as no evidence of a *FGFR2* gene rearrangement has been detected.

The report will give further information about the implications for treatment e.g. *Current clinical evidence suggests that this patient would be unlikely to benefit from treatment with FGFR2 inhibitors.*

If a *FGFR2* gene fusion is not identified, the patient is not eligible for treatment with pemigatinib. The treating clinician should consider whether the patient is a suitable candidate for any alternative treatments (including clinical trials) or offer best supportive care.

3. No *FGFR2* gene fusion/rearrangement detected despite low neoplastic cell content

The 'Karyotype' comment will state that the patient has a reduced likelihood of response to FGFR2 inhibitors as no evidence of a *FGFR2* gene rearrangement has been detected.

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The report will give further information about the implications for treatment e.g. *The low neoplastic cell content of this sample was noted during analysis but the cellularity was sufficient to exclude the presence of a FGFR2 gene rearrangement. Current clinical evidence suggests that this patient would be unlikely to benefit from treatment with FGFR2 inhibitors.*

If a *FGFR2* gene fusion is not identified, the patient is not eligible for treatment with pemigatinib. The treating clinician should consider whether the patient is a suitable candidate for any alternative treatments (including clinical trials) or offer best supportive care.

4. Failed report - insufficient material for FISH analysis

The 'Karyotype' comment will state that the *FGFR2* FISH test failed.

This reason for test failure will be given and appropriate next steps described e.g. *the neoplastic cell content, cellularity or tissue quality was insufficient for this FISH analysis. If an alternative sample is available, we would be happy to test tissue from an alternate block.*

Additional material will be required in order to proceed with any further analysis. This may require a dialogue between the requesting clinician, local pathology laboratory and AWGL to ascertain whether a further biopsy is clinically indicated or technically possible.

It may not be possible to establish the *FGFR2* status using the histological tissue testing approach if a re-biopsy is not possible/appropriate or if repeated testing attempts fail; pemigatinib cannot be prescribed in this situation.

Eligibility criteria for treatment with Pemigatinib

The patient must meet the following criteria in order to receive pemigatinib:

1. Diagnosis of locally advanced or metastatic cholangiocarcinoma which has progressed after at least one prior line of systemic therapy*
2. Evidence of a *FGFR2* gene fusion in tumour specimen
3. Ophthalmological examination, including optical coherence tomography (OCT) prior to initiation of therapy.

*The indication for treatment is specified within the SPC for pemigatinib; it does not specify whether patients are eligible for treatment if first-line therapy is discontinued to due toxicity as this was not an inclusion criteria in the clinical trials. However, in such instances pemigatinib should be considered if no suitable alternative first-line therapy is available.

The patient should provide written consent to treatment prior to cycle 1.

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Pemigatinib prescribing information

Detailed prescribing information is provided in appendix 3.

Treatment with pemigatinib should continue until disease progression, or unacceptable toxicity develops, or if the patient chooses to stop treatment.

Baseline investigations and on-treatment monitoring for pemigatinib

Table 2 summarises the required baseline investigations and on-treatment monitoring for patients receiving pemigatinib.

Pemigatinib can cause hyperphosphataemia and hypophosphataemia. Management advice for this toxicity is summarised in appendix 3 with a patient information leaflet on dietary advice provided in appendix 4.

Investigation		Baseline	On-treatment
Bloods	FBC	✓	Every 3 weeks
	U+Es and LFTs	✓	Every 3 weeks
	Serum calcium and phosphate	✓	At 2 week toxicity check, and every 3 weeks
Ophthalmology	Ophthalmological examination including optical coherence tomography (OCT)	✓	Every 2 months for the first 6 months of treatment, then every 3 months thereafter, and urgently at any time if visual symptoms develop
Imaging	Radiological imaging of disease status	As per local guidelines	As per local guidelines – minimum every 3 months or as clinically indicated
Pregnancy test		✓	

Table 2: Baseline and on-treatment monitoring

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Ross JS, Wang K, Gay L, Al-Rohil R, Rand JV, Jones DM, Lee HJ, Sheehan CE, Otto GA, Palmer G, Yelensky R, Lipson D, Morosini D, Hawryluk M, Catenacci DV, Miller VA, Churi C, Ali S, Stephens PJ. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. *Oncologist.* 2014; 19(3):235-42.

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Valle, J, Wasan H, Palmer, DH et al. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. *NEJM*. 2010; 362:1273-1281.

Appendix 1 Summary of NICE clinical effectiveness evidence for pemigatinib

NICE approved pemigatinib from clinical data from one study suggesting it may be more effective than current treatments. FIGHT-202 was a phase 2, single-arm, non-randomised, open label study in people with advanced or surgically unresectable cholangiocarcinoma that had not responded to previous therapy.

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Only cohort A of FIGHT-202, which included people with *FGFR2* fusion or rearrangement, was relevant to the NICE appraisal. The committee noted that, because FIGHT-202 was a single-arm study, it did not provide evidence of the relative effectiveness of pemigatinib compared with current treatment options. But it acknowledged that doing studies for advanced chemorefractory cholangiocarcinoma is difficult because of the rarity of this cancer. It concluded that, in the absence of direct evidence, indirect comparisons were needed to assess the relative effectiveness of pemigatinib compared with the comparators.





The ERG highlighted that cohort A of FIGHT-202 was a subset of the population in the marketing authorisation. It highlighted that 98% of people in cohort A had intrahepatic disease. However, the marketing authorisation and the NICE scope include people with non-intrahepatic disease. The company stated that there is no biological reason that pemigatinib would not provide benefit to people with non-intrahepatic cholangiocarcinoma with *FGFR2* fusion or rearrangement. The clinical experts advised that about 40% of people with advanced cholangiocarcinoma have intrahepatic disease. However, they explained that, in advanced cancer, it is difficult to differentiate intrahepatic disease from other subtypes. They advised that *FGFR2* fusion or rearrangement can be present in non-intrahepatic disease but it is uncommon. To be eligible for pemigatinib, people will be identified by the presence of an *FGFR2* fusion or rearrangement and not by the disease subtype. The committee concluded that the population in cohort A of FIGHT-202 was appropriate for decision making. The comparative evidence from ABC-06 is appropriate for decision making but has limitations.

No studies directly compared pemigatinib with treatments currently used in the NHS. The main comparative evidence was from ABC-06. This was a phase 3, randomised, open label study of mFOLFOX+ASC or Best Supportive Care (BSC) alone for people with locally advanced or metastatic biliary tract cancers previously treated with gemcitabine plus cisplatin chemotherapy. Not knowing the *FGFR2* mutation status in the ABC-06 population was a significant limitation but its relevance as a prognostic marker remains uncertain. The committee acknowledged that because of the rarity of the cancer, the data on the comparators from ABC-06 were the best available evidence.





In the absence of direct comparative evidence, the estimate of the relative treatment effect of pemigatinib compared with mFOLFOX+ASC and BSC alone was based on an unanchored matching adjusted indirect comparison of patient-level data from FIGHT-202 and data from ABC-06. The weightings were derived using a propensity score logistic regression model adjusted for selected prognostic factors. The weighted hazard ratios for overall survival and progression-free survival are considered confidential by the company and exact results have not been reported. In general, the results were more favourable for pemigatinib. The hazard ratio for overall survival was lower for pemigatinib compared with mFOLFOX+ASC and BSC alone. The hazard ratio for progression-free survival was also lower for pemigatinib compared with mFOLFOX+BSC. The committee concluded that the matching adjusted indirect comparison suggests pemigatinib was more effective than the comparators, but that this was uncertain.

Appendix 2 Examples of *FGFR2* genetic testing reports

1. 'FGFR2 rearrangement detected' report

<p>   </p> <p style="text-align: center;"> Cytogenetics Section Genetic Diagnostic Laboratory </p> <p> Not Specified N/a Not Specified </p> <table border="1" style="width: 100%;"> <thead> <tr> <th colspan="2" style="text-align: center;">CYTOGENETIC ANALYSIS</th> </tr> </thead> <tbody> <tr> <td>Name: JONES</td> <td>Lab No: M21-5860</td> </tr> <tr> <td>A Dumi</td> <td>Date of Birth: 01/01/2018</td> </tr> <tr> <td>Address: I dummy address record</td> <td>NHS No: 1112223334</td> </tr> <tr> <td></td> <td>Hospital: Not Specified</td> </tr> <tr> <td></td> <td>Ward/Clinic: OPD</td> </tr> <tr> <td>SA37 0EX</td> <td>Consultant: Not Specified</td> </tr> <tr> <td>Sample Type: Malignancy Tissue</td> <td>Sub-type: Biopsy slides</td> </tr> <tr> <td>Indication: Cholangiocarcinoma</td> <td>Date Collected: 31/08/2021</td> </tr> <tr> <td></td> <td>Date Received: 31/08/2021</td> </tr> </tbody> </table> <p style="text-align: center;">REPORT</p> <p>Karyotype: This patient may respond to FGFR2 inhibitors. Evidence of a FGFR2 gene rearrangement detected.</p> <p>Reason for referral: FGFR2 gene-fusion analysis requested on this ## sample.</p> <p>Fluorescence in situ hybridisation (FISH) analysis was carried out on the tumour sample provided from this patient (block no. 9). The area of highest neoplastic cell content (estimated at 9%), as assessed by a pathologist, was analysed using the Zytovision ZytoLight SPEC FGFR2 dual colour break apart probe.</p> <p>FISH analysis showed evidence of a FGFR2 gene rearrangement in ##/## (%) nuclei examined.</p> <p>Patients with Cholangiocarcinoma harbouring a FGFR2 gene rearrangement have been reported to respond to treatment with a FGFR2 inhibitor. Pemigatinib is recommended as an option for treating locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after systemic therapy in adults (1,2)</p> <p>The reported results are dependent upon the analysed tissue representing the molecular makeup of the tumour in this patient.</p>	CYTOGENETIC ANALYSIS		Name: JONES	Lab No: M21-5860	A Dumi	Date of Birth: 01/01/2018	Address: I dummy address record	NHS No: 1112223334		Hospital: Not Specified		Ward/Clinic: OPD	SA37 0EX	Consultant: Not Specified	Sample Type: Malignancy Tissue	Sub-type: Biopsy slides	Indication: Cholangiocarcinoma	Date Collected: 31/08/2021		Date Received: 31/08/2021	<p>   </p> <p style="text-align: center;"> Cytogenetics Section Genetic Diagnostic Laboratory </p> <p>Technical information: FGFR2 FISH analysis method: Please note that this FISH test has not been accredited by UKAS. FISH studies on a minimum of 100 cells and a scan of the marked area, using the Zytovision ZytoLight SPEC FGFR2 dual colour break apart probe. Partner genes cannot be identified in rearrangement-positive samples using these probes. Laboratory guidelines state that if the average percent positive cells is <15%, the sample is considered negative. If the average percent positive cells is >15% the sample is considered positive.</p> <p>The implication of this result for this patient should be determined in the context of this patient's full clinical details.</p> <p>References 1) Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. <i>Lancet Oncol.</i> 2020; 21(5):671-84. 2) https://www.nice.org.uk/guidance/ta722/resources/pemigatinib-for-treating-relapsed-or-refractory-advanced-cholangiocarcinoma-with-fgfr2-fusion-or-rearrangement-pdf-8261190679749</p> <p>Email report to:</p> <p>Cytogeneticist: Hannah Jones Head of Section: Holly Lewis Report Date: 31/08/2021</p>
CYTOGENETIC ANALYSIS																					
Name: JONES	Lab No: M21-5860																				
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Sample Type: Malignancy Tissue	Sub-type: Biopsy slides																				
Indication: Cholangiocarcinoma	Date Collected: 31/08/2021																				
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2. 'FGFR2 rearrangement not detected' report

 		 	
<p>Not Specified N/a Not Specified</p>		<p>Cytogenetics Section Genetic Diagnostic Laboratory</p>	
<p>Technical information: FGFR2 FISH analysis method: Please note that this FISH test has not been accredited by UKAS. FISH studies on a minimum of 100 cells and a scan of the marked area, using the Zytovision ZytoLight SPEC FGFR2 dual colour break apart probe. Partner genes cannot be identified in rearrangement-positive samples using these probes. Laboratory guidelines state that if the average percent positive cells is <15%, the sample is considered negative. If the average percent positive cells is >15% the sample is considered positive.</p> <p>The implication of this result for this patient should be determined in the context of this patient's full clinical details.</p> <p>References: 1) References re treatment response: FGFR2 - Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. <i>Lancet Oncol.</i> 2020; 21(5):671-84.</p> <p>Email report to:</p>			
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Address:	1 dummy address record	NHS No:	1112223334
		Hospital:	Not Specified
	SA37 0EX	Ward/Clinic:	OPD
Sample Type:	Malignancy Tissue	Consultant:	Not Specified
Indication:	Cholangiocarcinoma	Sub-type:	Biopsy slides
		Date Collected:	31/08/2021
		Date Received:	31/08/2021

REPORT

Karyotype: This patient has a reduced likelihood of response to FGFR2 inhibitors. No evidence of a FGFR2 gene rearrangement detected.

Reason for referral: FGFR2 gene-fusion analysis requested on this ## sample.

Fluorescence in situ hybridisation (FISH) analysis was carried out on the tumour sample provided from this patient (block no. #). The area of highest neoplastic cell content (estimated at #%), as assessed by a pathologist, was analysed using the Zytovision ZytoLight SPEC FGFR2 dual colour break apart probe.





FISH analysis showed no evidence of a rearrangement of the FGFR2 gene with this probe.

#Copy number changes of the FGFR2 probe were detected, however the clinical significance is not known at the present time.#

Current clinical evidence suggests that this patient would be unlikely to benefit from treatment with FGFR2 inhibitors (1).

The reported results are dependent upon the analysed tissue representing the molecular makeup of the tumour in this patient.

3. 'No FGFR2 rearrangement detected despite low neoplastic cell content' report

 		 	
<p>Not Specified N/a Not Specified</p>		<p>Cytogenetics Section Genetic Diagnostic Laboratory</p>	
<p>The reported results are dependent upon the analysed tissue representing the molecular makeup of the tumour in this patient.</p> <p>Technical information: FGFR2 FISH analysis method: Please note that this FISH test has not been accredited by UKAS. FISH studies on a minimum of 100 cells and a scan of the marked area, using the Zytovision ZytoLight SPEC FGFR2 dual colour break apart probe. Partner genes cannot be identified in rearrangement-positive samples using these probes. Laboratory guidelines state that if the average percent positive cells is <15%, the sample is considered negative. If the average percent positive cells is >15% the sample is considered positive.</p> <p>The implication of this result for this patient should be determined in the context of this patient's full clinical details.</p> <p>References: 1) References re treatment response: FGFR2 - Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. <i>Lancet Oncol.</i> 2020; 21(5):671-84.</p> <p>Email report to:</p>			
<p>Cytogeneticist: Hannah Jones Head of Section: Holly Lewis Report Date: 31/08/2021</p>			

CYTOGENETIC ANALYSIS			
Name:	JONES	Lab No:	M21-5860
	A Dumi	Date of Birth:	01/01/2018
Address:	1 dummy address record	NHS No:	1112223334
		Hospital:	Not Specified
	SA37 0EX	Ward/Clinic:	OPD
Sample Type:	Malignancy Tissue	Consultant:	Not Specified
Indication:	Cholangiocarcinoma	Sub-type:	Biopsy slides
		Date Collected:	31/08/2021
		Date Received:	31/08/2021

REPORT

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Reason for referral: FGFR2 gene-fusion analysis requested on this ## sample.

Fluorescence in situ hybridisation (FISH) analysis was carried out on the tumour sample provided from this patient (block no. #). The area of highest neoplastic cell content (estimated at #%), as assessed by a pathologist, was analysed using the Zytovision ZytoLight SPEC FGFR2 dual colour break apart probe.





FISH analysis showed no evidence of a rearrangement of the FGFR2 gene with this probe.

The low neoplastic cell content of this sample (#%) was noted during analysis but the cellularity was sufficient to exclude the presence of a FGFR2 gene rearrangement.

#Copy number changes of the FGFR2 probe were detected, however the clinical significance is not known at the present time.#

Current clinical evidence suggests that this patient would be unlikely to benefit from treatment with FGFR2 inhibitors (1).

4. 'FGFR2 FISH fail report'

<p>   </p> <p style="text-align: center;"> geneteg feddygol GWASANAETH I GYMRU </p> <p style="text-align: center;"> medical genetics SERVICE FOR WALES </p> <p style="text-align: center;"> <i>Cytogenetics Section</i> Genetic Diagnostic Laboratory </p> <p> Not Specified N/a Not Specified </p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2" style="text-align: center;">CYTOGENETIC ANALYSIS</th> </tr> </thead> <tbody> <tr> <td style="width: 50%;">Name: JONES</td> <td style="width: 50%;">Lab No: M21-5860</td> </tr> <tr> <td>Address: A Dumi</td> <td>Date of Birth: 01/01/2018</td> </tr> <tr> <td></td> <td>NHS No: 1112223334</td> </tr> <tr> <td></td> <td>Hospital: Not Specified</td> </tr> <tr> <td></td> <td>Ward/Clinic: OPD</td> </tr> <tr> <td></td> <td>Consultant: Not Specified</td> </tr> <tr> <td>Sample Type: Malignancy Tissue</td> <td>Sub-type: Biopsy slides</td> </tr> <tr> <td>Indication: Cholangiocarcinoma</td> <td>Date Collected: 31/08/2021</td> </tr> <tr> <td></td> <td>Date Received: 31/08/2021</td> </tr> </tbody> </table> <p style="text-align: center;">REPORT</p> <p>Karyotype: FGFR2 FISH test fail.</p> <p>Reason for referral: FGFR2 gene-fusion analysis requested on this ## sample.</p> <p>We regret that Fluorescence in situ hybridisation (FISH) analysis of the tumour sample from the above patient has failed on repeated attempts.</p> <p>The neoplastic cell content #and/ cellularity #and/ tissue quality of this sample (block number #) was insufficient for this FISH analysis. If an alternative sample is available, we would be happy to test tissue from an alternate block.</p> <p>Technical information: FGFR2 FISH analysis method: Please note that this FISH test has not been accredited by UKAS. FISH studies on a minimum of 100 cells and a scan of the marked area, using the Zytovision ZytoLight SPEC FGFR2 dual colour break apart probe. Partner genes cannot be identified in rearrangement-positive samples using these probes. Laboratory guidelines state that if the average percent positive cells is <15%, the sample is considered negative. If the average percent positive cells is >15% the sample is considered positive.</p>	CYTOGENETIC ANALYSIS		Name: JONES	Lab No: M21-5860	Address: A Dumi	Date of Birth: 01/01/2018		NHS No: 1112223334		Hospital: Not Specified		Ward/Clinic: OPD		Consultant: Not Specified	Sample Type: Malignancy Tissue	Sub-type: Biopsy slides	Indication: Cholangiocarcinoma	Date Collected: 31/08/2021		Date Received: 31/08/2021	<p>   </p> <p style="text-align: center;"> geneteg feddygol GWASANAETH I GYMRU </p> <p style="text-align: center;"> medical genetics SERVICE FOR WALES </p> <p style="text-align: center;"> <i>Cytogenetics Section</i> Genetic Diagnostic Laboratory </p> <p>The implication of this result for this patient should be determined in the context of this patient's full clinical details.</p> <p>Email report to:</p> <p> Cytogeneticist: Hannah Jones Head of Section: Holly Lewis Report Date: 31/08/2021 </p>
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Appendix 3 Pemigatinib prescribing information

Drugs/Dosage	Pemigatinib	13.5mg	Oral	ONCE daily for 14 days followed by 7 days off therapy (21 day cycle)
Administration	<ul style="list-style-type: none"> Licensed in over 18 years old adults only Pemigatinib is available as 4.5mg, 9mg and 13.5mg tablets Pemigatinib is for oral use. The tablets should be taken at approximately the same time every day Pemigatinib may be taken with or without food. Patients should not crush, chew, split or dissolve the tablets <p><u>Missed dose(s)</u></p> <p>If a dose of pemigatinib is missed by 4 or more hours or vomiting occurs after taking a dose, an additional dose should not be administered and dosing should be resumed with the next scheduled dose.</p> <p><u>Patient counselling/ advice</u></p> <p>Low Phosphate diet: Issue a low phosphate diet sheet before starting treatment and counsel that patients only need to follow it when advised to by their oncologist (serum phosphate level rises to >1.77 mmol/L)</p> <p>Driving advice: Advise not to drive or use machinery if they experience any ophthalmic side effects, such as blurred vision, or if they see black spots, or experience visual distortions such as intermittent flashing lights.</p> <p>Preventing dry eye: Consider hypromellose eye drops and/or simple eye ointment in order to prevent dry eye.</p> <p>Anti-emetics are not routinely required.</p>			
Main Toxicities	<p>Hyperphosphataemia, alopecia, diarrhoea, nail toxicity, fatigue, nausea, dysgeusia, stomatitis, constipation, dry mouth, dry eye, arthralgia, hyponatraemia, hypophosphataemia, dry skin and PPE.</p> <p>Common eye disorders include serious retinal detachment, punctate keratitis, blurred vision and trichiasis.</p> <p><u>Serous retinal detachment reactions</u> may present with symptoms such as blurred vision, visual floaters, or photopsia.</p>			

Baseline pre-treatment investigations	<ul style="list-style-type: none"> Ophthalmological examination: Optical Coherence Tomography (OCT) Pregnacy test to exclude pregnancy FBC, LFTs & U&Es, calcium & phosphate 	
Regular Investigations	Optical Coherence Tomography	Every 2 months for the first 6 months of treatment, every 3 months afterwards, and urgently at any time for visual symptoms.
	FBC	Every 3 weeks
	LFTs & U&Es	Every 3 weeks
	Calcium & phosphate	At 2 week toxicity check, and every 3 weeks, plus as table below
Clinical review requirements	<ul style="list-style-type: none"> Perform toxicity review, including calcium & phosphate, 2 weeks after initiation Then review every 21 days Continue until loss of clinical benefit or unacceptable toxicity 	
End of treatment review	Continue until loss of clinical benefit or unacceptable toxicity.	

Management of toxicities: Dose modifications or interruption of dosing should be considered for the management of toxicities.

Dose modification levels for pemigatinib

Dose	Dose reduction levels	
	First	Second
13.5 mg taken orally once daily for 14 days followed by 7 days off therapy	9 mg taken orally once daily for 14 days followed by 7 days off therapy	4.5 mg taken orally once daily for 14 days followed by 7 days off therapy
Treatment should be permanently discontinued if patient is unable to tolerate 4.5 mg pemigatinib once daily.		

Serum phosphate levels

Hyperphosphataemia: Reported in 60% of cases with 27% with level > 2.26mmol/L and usually develops within the first 15 days.

Management Advice: Dietary phosphate restriction and/or administration of phosphate-lowering therapy along with the 1-week dose holiday were effective strategies for managing this on-target effect of pemigatinib.

Prolonged hyperphosphataemia can cause precipitation of calcium-phosphate crystals that can lead to hypocalcaemia, soft tissue mineralization, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias.

Hypophosphataemia: \geq Grade 3 in 12.3% of patients.

Management advice: Discontinue phosphate-lowering therapy and diet during pemigatinib-treatment breaks or if serum phosphate level falls below normal range.

Severe hypophosphataemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and haemolytic anaemia.

For patients presenting with hyperphosphataemia or hypophosphataemia, additional close monitoring and follow-up is recommended regarding dysregulation of bone mineralization.

Pemigatinib dose modifications/phosphate advice dependent on phosphate levels

Phosphate level	Pemigatinib dose modification
<0.8 mmol/l	<ul style="list-style-type: none"> Discontinue / interrupt any low phosphate diet and phosphate-lowering therapy Pemigatinib to be continued at current dose
>1.77mmol/L - \leq 2.26mmol/L	<ul style="list-style-type: none"> Advise starting a low phosphate diet, (if not already); or to continue on low phosphate diet (check that patient has low phosphate diet sheet; refer to dietitian as necessary) Pemigatinib should be continued at current dose
>2.26mmol/L – \leq 3.23mmol/l	<ul style="list-style-type: none"> Ensure patient is following a low phosphate diet Continue pemigatinib and initiate phosphate-lowering therapy, such as, calcium acetate 1000mg TDS with meals Weekly serum phosphate and adjust dose of phosphate lowering therapy* until level returns to <2.26 mmol/l <p><u>If phosphate levels do not return to <2.26 mmol/l within two weeks of starting phosphate lowering therapy, withhold pemigatinib.</u></p> <p>Re-start pemigatinib at the same dose when phosphate level returns to <2.26 mmol/l.</p> <ul style="list-style-type: none"> If recurrence of serum phosphate at >2.26 mmol/l while on phosphate-lowering therapy, reduce pemigatinib by one dose level
>3.23mmol/L	<ul style="list-style-type: none"> Ensure patient is following a low phosphate diet Continue pemigatinib and initiate phosphate-lowering therapy, such as, calcium acetate 1000mg TDS with meals Weekly serum phosphate and adjust dose of phosphate lowering therapy* until level returns to <2.26 mmol/l <p><u>If phosphate level remains >3.23 mmol/l for one week, withhold pemigatinib</u></p>

	<p>Re-start pemigatinib one dose level lower once serum phosphate is <2.26 mmol/l.</p> <ul style="list-style-type: none"> If there is recurrence of serum phosphate at >3.23 mmol/l following 2 pemigatinib dose reductions, permanently discontinue pemigatinib 										
<p>*Discontinuing phosphate-lowering therapy and low phosphate diet should be considered during the 7 day pemigatinib breaks, or if serum phosphate level falls below the normal range (i.e. < 0.8 mmol/l).</p>											
Dysregulation of bone mineralization	<p>For patients presenting with hyperphosphataemia or hypophosphataemia, additional close monitoring and follow-up is recommended regarding dysregulation of bone mineralization. The method of monitoring is not defined by the drug company and is at physician discretion.</p>										
<p>Serous retinal detachment</p> <p>Pemigatinib can cause serous retinal detachment reactions, which may present with symptoms such as blurred vision, visual floaters, or photopsia. This can moderately influence the ability to drive and use machines.</p> <p>Ophthalmological examination, including optical coherence tomography (OCT) should be performed prior to initiation of therapy and every 2 months for the first 6 months of treatment, every 3 months afterwards, and urgently at any time for visual symptoms. For serous retinal detachment reactions, the dose modification guidelines should be followed.</p> <p>Careful consideration should be taken with patients that have clinically significant medical eye disorders, such as retinal disorders, including but not limited to, central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment.</p> <p>Table showing dose modifications for serous retinal detachment</p> <table border="1"> <thead> <tr> <th>Adverse reaction</th> <th>Pemigatinib dose modification</th> </tr> </thead> <tbody> <tr> <td>Asymptomatic</td> <td>Pemigatinib should be continued at current dose</td> </tr> <tr> <td>Moderate decrease in visual acuity (best corrected visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline); limiting instrumental activities of daily living</td> <td> <ul style="list-style-type: none"> Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib should be resumed at the next lower dose level If it recurs or symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered based on clinical status </td> </tr> <tr> <td>Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or >3 lines decreased vision from baseline up to 20/200); limiting activities of daily living</td> <td> <ul style="list-style-type: none"> Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib may be resumed at 2 dose levels lower If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered, based on clinical status </td> </tr> <tr> <td>Visual acuity worse than 20/200 in affected eye; limiting activities of daily living</td> <td> <ul style="list-style-type: none"> Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib may be resumed at 2 dose levels lower </td> </tr> </tbody> </table>		Adverse reaction	Pemigatinib dose modification	Asymptomatic	Pemigatinib should be continued at current dose	Moderate decrease in visual acuity (best corrected visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline); limiting instrumental activities of daily living	<ul style="list-style-type: none"> Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib should be resumed at the next lower dose level If it recurs or symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered based on clinical status 	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or >3 lines decreased vision from baseline up to 20/200); limiting activities of daily living	<ul style="list-style-type: none"> Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib may be resumed at 2 dose levels lower If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered, based on clinical status 	Visual acuity worse than 20/200 in affected eye; limiting activities of daily living	<ul style="list-style-type: none"> Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib may be resumed at 2 dose levels lower
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Dry eyes	Consider hypromellose eye drops and / or simple eye ointment to prevent or treat dry eye, as needed
Increased creatinine	<p>Pemigatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine; this may occur due to inhibition of renal transporters OCT2 and MATE1 and may not affect glomerular function.</p> <p>Within the first cycle, serum creatinine increased (mean increase 20 µmol/L) and reached steady state by Day 8, and then decreased during the 7 days off therapy.</p> <p>Alternative markers of renal function should be considered if persistent elevations in serum creatinine are observed.</p>
Renal Impairment	<p>Dose adjustment is not required for patients with mild, moderate renal impairment or End Stage Renal Disease (ESRD) on haemodialysis.</p> <p>For patients with <u>severe</u> renal impairment (CrCl <30ml/min): if taking 13.5 mg pemigatinib once daily, reduce to 9 mg once daily OR if taking 9 mg pemigatinib once daily reduce to 4.5 mg once daily.</p>
Hepatic Impairment	<p>Dose adjustment is not required for patients with mild or moderate hepatic impairment.</p> <p>For patients with <u>severe</u> hepatic impairment (Childs-Pugh Class C): if taking 13.5 mg pemigatinib once daily, reduce to 9 mg once daily OR if taking 9 mg pemigatinib once daily reduce to 4.5 mg once daily.</p>
Embryo-foetal toxicity	<p>Pemigatinib can cause foetal harm when administered to a pregnant woman.</p> <p>Pregnant women should be advised of the potential risk to the foetus.</p> <p>Women of childbearing potential should be advised to use effective contraception during treatment with pemigatinib and for 1 week after the last dose.</p> <p>Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with pemigatinib and for at least 1 week after the last dose.</p> <p>Women of childbearing age being treated with pemigatinib should be advised not to become pregnant and men being treated with pemigatinib should be advised not to father a child during treatment.</p>
<p>Combination with strong CYP3A4 inhibitors</p> <p>(correct as 11-11-21 – Please check up to date interaction checkers before prescribing)</p>	<p>Concurrent use of strong CYP3A4 inhibitors should be avoided during treatment with pemigatinib.</p> <p><u>Strong CYP3A4 inhibitors:</u> - Clarithromycin, grapefruit juice, telithromycin, nefazodone, itraconazole, ketoconazole, posaconazole, voriconazole, atazanavir, darunavir, indinavir, idelalisib, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, boceprevir,</p>

	<p>cobicistat, danoprevir, elvitegravir, paritaprevir and (ombitasvir and/or dasabuvir), telaprevir, verapamil, diltiazem.</p> <p>If co-administration with a strong CYP3A4 inhibitor is necessary, the dose of patients who are taking 13.5 mg pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg pemigatinib once daily should be reduced to 4.5 mg once daily. Co-administer with caution.</p>
<p>Combination with strong or moderate CYP3A4 inducers</p> <p>(correct as 12-11-21 – Please check up to date interaction checkers before prescribing)</p>	<p>Concomitant use of pemigatinib with strong or moderate CYP3A4 inducers should be avoided.</p> <p><u>Strong CYP3A4 inducers</u>: apalutamide, carbamazepine, enzalutamide, mitotane, fosphenytoin, phenytoin, primidone, rifampin, rifamycin, rifabutin, St. John's wort.</p> <p><u>Moderate CYP3A4 inducers</u>: bosentan, efavirenz, etravirine, phenobarbital, primidone, dronaderone</p> <p>St John's Wort is contraindicated.</p>
<p>Combination with proton pump inhibitors</p> <p>(correct as 12-11-21 – Please check up to date interaction checkers before prescribing)</p>	<p>Concomitant use of pemigatinib with proton pump inhibitors should be avoided.</p>
<p>Documented drug –drug interactions (see Stockley's for up to date list)</p> <p>List correct as of 12-11-21</p>	<p>No advice from manufacturer but drugs thought to increase exposure to pemigatinib include: aprepitant, crizotinib, netupitant.</p> <p>Methadone – pemigatinib may decrease efficacy of methadone.</p> <p>Dabrafenib – pemigatinib may decrease efficacy of dabrafenib.</p> <p>The following drugs should be given at least 6 hours before or 6 hours after pemigatinib – sirolimus, rivaroxaban, everolimus, digoxin, and colchicine.</p> <p>Pemigatinib might increase exposure to the active metabolite of cyclophosphamide and ifosfamide – manufacturer advises monitoring.</p>

References for Prescribing Section

Abou-Alfa, G et al; Lancet 2020; 21 (5): 671 – 684

	Paper Ref:
Wales Cancer Network	FGFR2

CYP3A4 inhibitors & inducers: <https://www.ebmconsult.com/articles/medications-inhibitors-CYP3A4-enzyme>

eBNF https://bnf.nice.org.uk/interaction/pemigatinib-2.html#bnf_i1633485663927 [last accessed 12-11-21]

Incyte Biosciences. SPC Pemigatinib. <https://www.medicines.org.uk/emc/product/12814/smpc> [Last accessed 06-10-21]

Royal Surrey NHS. Pemigatinib protocol.

<https://www.royalsurrey.nhs.uk/download.cfm?doc=docm93jjjm4n12894.pdf&ver=32464> [Last accessed 6-10-21]

Stockley's Drug Interactions

online. <https://www.medicinescomplete.com/#/interactions/stockley?terms=pemigatinib> [last accessed 12-11-

Appendix 4 Patient information leaflet – phosphate dietary advice

Managing your hyperphosphatemia

You have been given this leaflet because you have been asked to follow a low-phosphate diet by your doctor. This leaflet includes basic information on how to manage a low-phosphate diet.

This document was produced by the pharmaceutical company Incyte.








i **Hyperphosphatemia** (pronounced HY-per-FOS-fa-TEE-mee-uh) is a condition which occurs when the levels of a mineral called phosphate in your blood are too high. Phosphate is an important mineral that the body needs for strong bones and teeth.¹ Sometimes, as a side effect of certain medications, a condition occurs when the levels of this mineral become too high. This condition is known as hyperphosphatemia.² In most cases of hyperphosphatemia you will not have any symptoms, but if left uncontrolled it can increase your risk of bone pain or heart disease in the future.¹

You can help manage this condition by making some changes to your diet.

The amount of phosphate in your diet can be reduced by following these two steps:

1. Reduce your intake of foods containing added phosphate (phosphate additives)
 - Phosphate additives are often found in processed foods. You should try to reduce the amount of processed food (e.g., tins and packets) you eat and choose fresh food (e.g., fruits/vegetables and lean meats), where possible.^{1,3}
 - Food labels will tell you if a product contains phosphate additives. Read the labels carefully and try to avoid ingredients with the term "phos" included.
2. Reduce your intake of foods naturally high in phosphate
 - Phosphate occurs naturally in many foods and foods that are high in protein are often high in phosphates. This includes foods such as meat, eggs, and dairy.^{1,3}
 - As these foods play an important role in your diet, you should not remove them completely. Instead, try to replace some high-phosphate foods for other foods that are naturally lower in phosphate.

Examples of high-phosphate and low-phosphate foods are shown below. Please note this is not an exhaustive list, if you are unsure about specific foods you should speak to your doctor or dietitian.

	High-phosphate foods ^{1,3}	Low-phosphate foods ^{1,3}
 Dairy and eggs	Milk and yoghurt (from animal and soy sources) Hard cheese, ricotta, cottage cheese, fat-free cream cheese Ice cream or frozen yoghurt Egg yolks	Alternative milks (e.g., rice or oat milks) Regular and low-fat cream cheese Sorbet or frozen fruit Egg whites
 Meat and fish	Organ meats/offal (e.g., liver and kidney), processed meats (e.g., sausages and bacon), prawns, sardines, crab, lobster, pilchards, herring	All fresh meat and poultry, cod, haddock, mackerel, farmed and fresh salmon or tuna, trout, fish fingers and fish cakes
 Starchy foods	Whole grains, including wholegrain breads, crackers, cereal, rice, and pasta Biscuits, muffins, pancakes, or waffles Dried peas (split, black-eyed), chickpeas, beans (black, lima, kidney, navy, pinto), or lentils Soups made with high phosphate ingredients (e.g., milk, dried peas, beans, lentils)	Refined grains, including white bread, crackers, cereals, rice, pasta and potatoes (including crisps) Homemade refined (white) bread rolls, bagels, or English muffins Green peas (canned, frozen), green beans Soups made with low phosphate ingredients (e.g., broth or water-based)
 Snacks	Nuts and seeds (including nut butters) Chocolate (including chocolate drinks)	Popcorn, jam, jelly, or honey Sweets (e.g., hard boiled sweets or gum drops)
 Drinks	Colas and other artificially flavoured waters, bottled teas (if a term in the ingredients list contains the letters "phos")	Lemon-lime fizzy drink, ginger ale, or plain water

References: 1. The Leeds Teaching Hospital NHS Trust. A basic guide to lowering phosphate in your diet. Information for patients. Review date May 2021 2nd edition (version 1). Produced by Medical Illustration Services. MID code: 20180516_000/RC2; 2. Malipal A. et al. Prevention and treatment of FGFR inhibitor-associated toxicities. *Crit Rev Oncol Hematol*. 2020;155:303091 doi: 10.1016/S1532-0196(20)30309-1; 3. DiAlessandro CD, et al. The "phosphorus pyramid": a visual tool for dietary phosphate management in dialysis and CKD patient. *BMC Nephrol*. 2015;16:9 doi: 10.1186/s12917-016-016-9.



If you require further support or information, please speak to your doctor.
They will be able to advise you on the right type of diet for you.

ELP/PM4/NP/21/0017 + UK/PM4/NP/21/0046 + Date of preparation: October 2021

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1110 Mages, Switzerland

