PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Pemigatinib

Cholangiocarcinoma

PROTOCOL REF: MPHAPEMIGA
(Version No. 1.1)

Approved for use in:

Treatment of locally advance or metastatic cholangiocarcinoma where the following criteria are satisfied:

- Relapsed or refractory to at least one prior line of systemic therapy.
- Fibroblast growth factor receptor 2 (FGFR2) receptor positive via genetic screening
- PS 0-2

*********Blueteq registration required*********

Dosage:

Drug	Dosage	Route	Frequency
Pemigatinib	13.5mg	Oral	Days 1 – 14 of a 21 day cycle

- Treatment will be continued until disease progression or unacceptable toxicity, whichever occurs first.
- Dosing delay or discontinuation may be required based on individual safety and tolerability.

Administration and Counselling Points:

- Available as 4.5mg / 9mg / 13.5mg in packs of 14 tablets.
- Alterations to taste is a common side effect of Pemigatinib.
- Should you develop changes to your vision including blurred vision, flashes of light or seeing black spots the clinical team should be informed straight away. An urgent referral to an ophthalmologist may be required.
- Should you develop numbness, tingling around the mouth or muscle cramps you should inform a medical professional straight away. The trust telephone triage line is available.
- Patients should not take grapefruit juice for duration of Pemigatinib treatment.
- Changes to blood phosphate levels are common with Pemigatinib. During treatment your phosphate levels will be monitored regularly. Medication to lower phosphate levels may be required. Diet changes may also be recommended.
- Advice on a low phosphate diet from the Leeds NHS trust can be found at http://flipbooks.leedsth.nhs.uk/LN000458.pdf or by a web search for “low phosphate diet Leeds”.
- Pemigatinib has a moderate influence on the ability to drive and use machines. Adverse reactions such as fatigue and visual disturbances have been associated with pemigatinib. Therefore, caution should be recommended when driving or operating machines.
- If you miss a dose of pemigatinib by 4 hours or more, or if you vomit after taking pemigatinib, do not take another pemigatinib tablet to make up for the missed dose. Take your next dose of pemigatinib at the scheduled time.

- Pemigatinib can cause foetal harm. During treatment and for one week after the last dose, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

Emetogenic risk:

Nausea occurred in around 40% of trial patients. The majority mild to moderate Grade 1 – 2 in severity.

Supportive treatments:

Domperidone 10mg up to THREE times a day when required will be provided with cycle 1.

Mucositis was reported in around 40% of trial patients. The majority mild to moderate Grade 1 – 2 in severity. Should patients experience mucositis, guidance can be found in the Oral Hygiene Policy. Treatment options include:
Gelclair 1 sachet up to THREE times a when required
Benzydamine 0.15% Oral Rinse 15ml to be used every 1.5 to 3 HOURLY when required

Dry eyes occurred in around 30% of trial patients. Symptomatic treatment for dry eyes may be required. The following lubricant eye preparations are routinely available at CCC:
Hypromellose 0.3% eye drops apply 1 drop into both eyes when required.
or
Carbomer 980 0.2% eye drops apply 1 drop into both eyes when required.

Dosing in renal and hepatic impairment:

Renal	Mild or moderate	CrCL ≥30ml/min (Cockcroft-Gault)	No adjustment required
	Severe	CrCL <30ml/min (Cockcroft-Gault)	Reduce dose by one dose level

Hepatic

Mild or Moderate (Child-Pugh A or B)
No dose adjustment required.

Severe (Child-Pugh C)
Withhold until LFTs return to mild or moderate.
Restart with dose reduced by one dose level.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Ongoing
Informed Consent	X						
Clinical Assessment	X	X	X	X	X	X	Every 8 weeks thereafter or as clinically indicated
Ophthalmological Examination including Optical Coherance Tomography (OCT)*	X				X		Prior to initiation then every 2 months for the first 6 months. Then every 3 months thereafter.
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	Every cycle
FBC, U&E, LFTs	X	X	X	X	X	X	Every cycle
Phosphate	X	X	X	X	X	X	Every cycle
Corrected Calcium	X	X	X	X	X	X	Every cycle
CrCl (Cockcroft and Gault)	X						Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal
CT scan	X						Every 6 months/if clinically indicated
ECG							If clinically indicated
Full observations	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	Every cycle
Height recorded	X						
Pregnancy test	X						

During treatment and for one week after, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.
*Pemigatinib can cause serous retinal detachment and therefore opthalmological examination is required prior to initiation of pemigatinib and then whilst on therapy (every 2 months for the first 6 months and every 3 months thereafter).

Interactions:

Use of proton pump inhibitors such as omeprazole or lansoprazole should be avoided in patients receiving pemigatinib.

Concomitant use of pemigatinib with strong CYP3A4 **inhibitors**, including grapefruit juice, should be avoided. CYP3A4 inhibitors are expected to increase Pemigatinib levels and increase side effects. If continuation of a strong CYP3A4 is considered essential Pemigatinib should be reduced by one dose level.

CYP3A4 **inducers** are expected to significantly decrease Pemigatinib levels Concomitant use of Pemigatinib with strong and moderate CYP3A4 **inducers** should be avoided.

Studies suggest moderate CYP3A4 **inducers** reduced Pemigatinib levels by more than 50%.

Use of St. John's wort is a contraindication to Pemigatinib treatment.

Main Toxicities:

Side effects of Pemigatinib were evaluated in the FIGHT-202 clinical trial with the following findings;

- Hyperphosphataemia (60.5%)
- Alopecia (49.7%)
- Diarrhoea (46.9%)
- Nail toxicity (44.9%)
- Fatigue (43.5%)
- Nausea (41.5%)
- Taste alerations (40.8%)
- Mucostitis (37.4%)
- Constipation (36.7%)
- Dry mouth (34.0%)
- Dry eye (27.9%)

- Joint pain (arthralgia) (25.9%)
- Hypophosphataemia (23.1%)
- Dry skin (21.8%)
- Palmar-plantar erythrothema (16.3 %)
- Low serum sodium (hyponatraemia) 10.3%

Dose Modifications and Toxicity Management:

Proceed on day 1 if:-

Platelets	Neutrophils	Creatinine Clearance	Bilirubin	AST/ALT	Alkaline Phosphatase	Phosphate
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≥30 mL/min	<1.5 x ULN*	<10 x ULN	<6 x ULN	≤2.25 mmol/L

* ULN = upper limit of normal

Results outside these parameters should be discussed with a consultant as they indicate the need for a dose reduction.

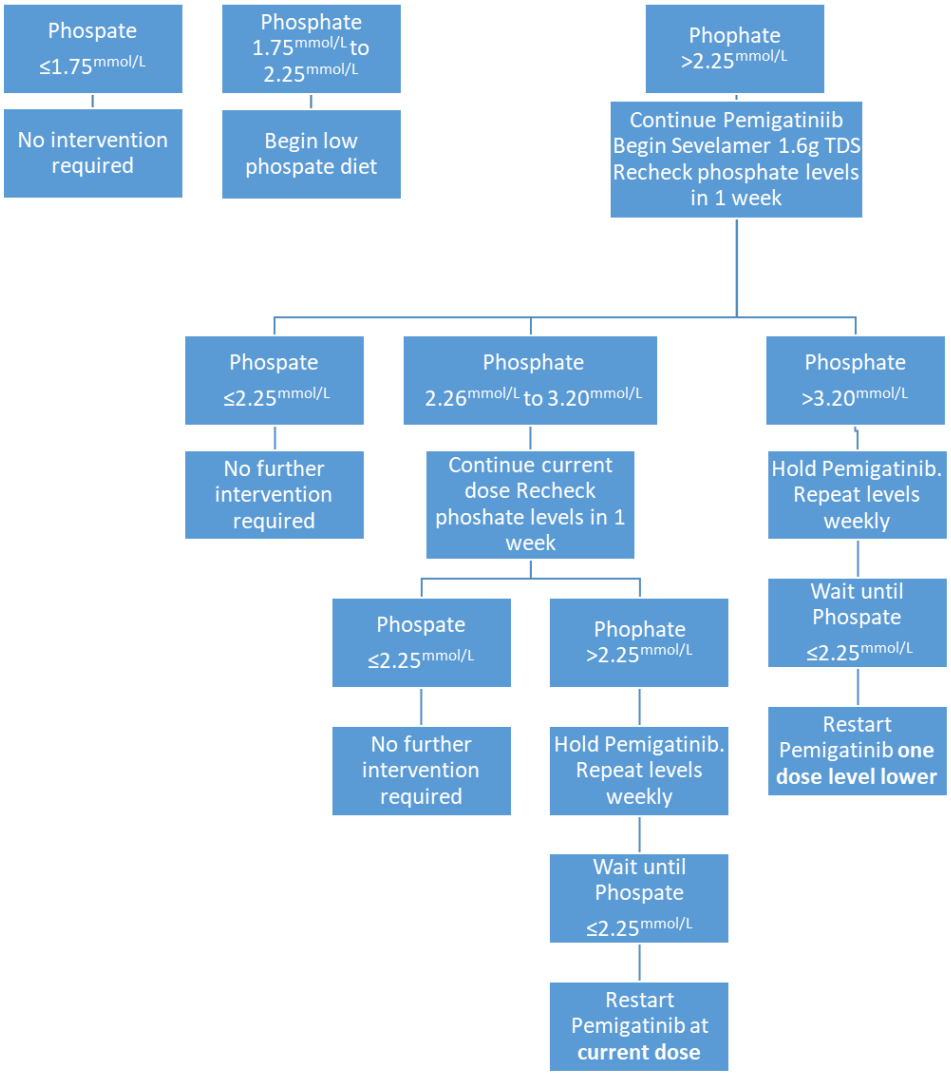
Dose Reduction Steps	Dose
Step 1	13.5mg ONCE daily
Step 2	9mg ONCE daily
Step 3	4.5mg ONCE daily
Step 4	Stop treatment

Haematological toxicity

Pemigatinib does not routinely cause haematological toxicity.

Hyperphosphataemia Management

A rise in serum phosphate is common and may require treatment with the phosphate binder Sevelamer as outlined below.



Treatment should be stopped if a patient has a phosphate >3.20mmol/L on the lowest dose of Pemigatinib.

Sevelamer Dose titration	
Starting dose	Sevelamer 1.6g TDS
At 2 weeks if Phosphate >2.25mmol/L	Sevelamer 2.4g TDS
At 4 weeks if Phosphate >2.25mmol/L	Sevelamer 3.2g TDS
Available as packs of 180 x 800mg tablets	
Sevelamer dose may be continued to be titrated in accordance with phosphate level	
An average dose is considered to be around 2.4g TDS	

Raised serum Creatinine

Pemigatinib treatment commonly leads to a rise in serum creatinine. However, this is not caused by a decrease in renal function. Instead inhibition Pemigatinib inhibits specific renal transporters responsible for removing creatinine leading to a rise in serum creatinine but not a decline in glomerular function. Therefore, once alternative causes have been eliminated intervention may not be required.

Serous Retinal Detachment

Pemitgatinib can lead to serous retinal detachment.

Careful consideration should be prior to treating patients with a history of clinically significant medical eye disorders, such as retinal disorders, including, central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment.

Patients should report any visual changes as outlined in “Administration and Counselling Points:” section above.

Ophthalmological examination including Optical Coherance Tomography (OCT) is required prior to initiation then every 2 months for the first 6 months and then every 3 months thereafter.

Pregnancy and Breast-feeding

Pemigatinib is not recommended during pregnancy. Although there are no available data from the use of pemigatinib in pregnant women, studies in animal have shown reproductive toxicity. During treatment and for one week after, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

It is unknown whether pemigatinib or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with pemigatinib and for one week following completion of therapy.

References:

Abou-Alfa et al. (2020). Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study (FIGHT-202): *The Lancet Oncology*. 21 (5) p671-684.

NICE TA 722 Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. Published: 25 August 2021

Pemigatinib EAMS info including Info for Healthcare Professionals (SPC) and Info for Patients available at; https://www.gov.uk/government/publications/pemigatinib-in-the-treatment-of-cholangioarcinoma [accessed 10/04/2021]

The Leeds Teaching Hospitals NHS Trust. 2018. Phosphate; A basic guide to lowering the phosphate in your diet. Available at http://flipbooks.leedsth.nhs.uk/LN000458.pdf [accessed 30/04/21]

Circulation/Dissemination

Date added into Q-Pulse	23rd November 2021
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Version History

		Author name and designation	Summary of main changes
		Rob Challoner **HPB SRG Pharmacist**	New Regimen Protocol V1.0
		Rob Challoner **HPB SRG Pharmacist**	Regimen amended to reflect new licensing and funding changes. V1.1