

Systemic Anti Cancer Therapy Protocol

## Pembrolizumab with FOLFOX OR CAPOX Advanced Oesophageal or Gastro-oesophageal Adenocarcinoma

PROTOCOL REF: MPHAPFCO  
(Version No.: 1.0)

### Approved for use in:

Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy is recommended as **first line** treatment of unresectable locally advanced or metastatic **oesophageal adenocarcinoma OR HER-2 negative gastro-oesophageal adenocarcinoma** either of which expresses PD-L1 with a combined positive score of 10% or more.

ECOG performance status (PS) 0 or 1.

Please NOTE: use pembrolizumab in combination with cisplatin and fluorouracil protocol for **advanced or metastatic oesophageal squamous carcinoma**.

**\*\*\*\*\*Blueteq registration is required\*\*\*\*\***

### Exclusions

History of pneumonitis, organ transplantation, autoimmune disorders, HIV infection, active hepatitis B or C infection

Active infection requiring systemic treatment

Less than 4 weeks from major surgery

Issue Date: 16 <sup>th</sup> March 2022 Review: 1 <sup>st</sup> March 2025	Page 1 of 22	Protocol reference: MPHAPFCO	
Author: Hala Ghoz	Authorised by: Aileen McCaughey, Arvind Arumainathan, Chris Lube, Helen Flint, Zahed Khan, Jo McCaughey		Version No: 1.0

History of clinically severe autoimmune disease (can proceed with immunotherapy if well controlled autoimmune disease at the discretion of the clinical team, this needs to be documented on Meditech)

Patient with active CNS disease or carcinomatosis meningitis

## Dosage:

### Pembrolizumab + FOLFOX

Drug	Dosage	Route	Frequency
Pembrolizumab	400mg	IV infusion	6 weekly for 2 years*
Oxaliplatin	85mg/m <sup>2</sup>		2 weekly for 12 cycles
Folinic Acid	350mg		
Fluorouracil	400mg/m <sup>2</sup>		
Fluorouracil	2400mg/m <sup>2</sup>		

OR

### Pembrolizumab + CAPOX

Drug	Dosage	Route	Frequency
Pembrolizumab	400mg	IV infusion	6 weekly for 2 years*
	OR		OR
	200mg**		3 weekly for 2 years*
Oxaliplatin	130 mg/m <sup>2</sup>	IV infusion	3 weekly for 6 cycles
Capecitabine	625 mg/m <sup>2</sup> twice a day	PO	21 days continuous for 6 cycles

\*To continue until disease progression or unacceptable toxicity or after 2 years of treatment (to complete 35 x 3-weekly cycles or its equivalent if 6-weekly dosing is used) whichever is first.

\*\*Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 3-weekly regimen may be used.

## Supportive Treatments:

Metoclopramide 10mg oral tablets, up to 3 times a day or as required (total of 5 days supply)

Dexamethasone tablets 4mg twice daily for 3 days

Ondansetron 8mg twice a day for 3 days when required for nausea and vomiting.

## Extravasation risk:

Pembrolizumab – neutral

Oxaliplatin- irritant

Fluorouracil- irritant

Refer to the CCC policy for the '[Prevention and Management of Extravasation Injuries](#)'.

## Dosing in renal and hepatic impairment:

<b>Renal</b>	Oxaliplatin	GFR $\geq$ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min and haemodialysis: consider 50% of the original dose.		
	Fluorouracil	No dose adjustment is needed		
	Capecitabine	<b>GFR (mL/min)</b>	<b>Capecitabine dose</b>	
		$\geq$ 60	100% dose	
		50 to 59	100% dose	
30 to 49		75% dose		
< 30	Omit			
Pembrolizumab (prior to start of treatment ONLY/Baseline)	GFR $\geq$ 10ml/min proceed with treatment GFR < 10ml/min- use with caution.			
<b>Hepatic</b>	Oxaliplatin	No dose adjustment is needed		

	Fluorouracil	Mild (bilirubin >1.0-1.5 x ULN and any AST or bilirubin ≤ULN and AST >ULN) and moderate ( bilirubin 1.5-3 x ULN, with normal or raised AST)- no dose adjustment Severe (bilirubin >3.0-10 x ULN, with normal or raised AST) - not recommended.
	Capecitabine	No dose adjustment required for hepatic impairment at baseline BUT if bilirubin increases to 3 times ULN or ALT/AST to 2.5 times ULN subsequent to treatment then omit capecitabine until liver function recovers
	Pembrolizumab (prior to start of treatment ONLY/Baseline)	Administered with caution in patients with: Moderate (total bilirubin > 1.5 -3 x ULN and any AST) or Severe (total bilirubin > 3 x ULN and any AST*) hepatic impairment. * Within normal limits or high

## Patient Counselling Points

### Pembrolizumab

Women of childbearing potential should use effective contraception throughout treatment and for at least 5 months following the last dose of pembrolizumab.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection / sepsis

### Capecitabine

- Tablets should be taken 12 hours apart, swallowed whole with plenty of water within 30 minutes of a meal.

Issue Date: 16 <sup>th</sup> March 2022 Review: 1 <sup>st</sup> March 2025	Page 4 of 22	Protocol reference: MPHAPFCO
Author: Hala Ghoz	Authorised by: Aileen McCaughey, Arvind Arumainathan, Chris Lube, Helen Flint, Zahed Khan, Jo McCaughey	Version No: 1.0

- Do not add doses missed due to toxicity onto the end of the cycle. Continue according to the treatment plan and stop taking on the originally scheduled day.
- Take missed doses if remembered within 2 hours of the normal scheduled time. Otherwise continue with the next scheduled dose. Do not double up missed doses
- In case of swallowing difficulties the tablets may be dissolved in 200ml warm water. Once dissolved stir the contents with a spoon and drink immediately. Wash well and reserve the glass and spoon for chemotherapy administration only.

## Administration:

### 6-weekly Pembrolizumab + FOLFOX for 12 cycles

Day(s)	Drug	Dose	Route	Diluent and rate
1	Pembrolizumab	400mg	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
1,15 and 29	<b>Dexamethasone</b>	8mg	PO	30 minutes before chemotherapy
	<b>Ondansetron</b>	16mg	PO	30 minutes before chemotherapy
	CHANGE ADMINISTRATION LINE BEFORE STARTING OXALIPLATIN INFUSION			
1,15 and 29	<b>Oxaliplatin</b>	85mg/m <sup>2</sup>	IV	500mL Glucose 5% infusion over 2 hours
Oxaliplatin and Folinic Acid given at same time concomitantly				
1,15 and 29	<b>Folinic Acid</b>	350mg	IV	250mL Glucose 5% infusion over 2 hours
	<b>Fluorouracil</b>	400mg/m <sup>2</sup>	IV	Bolus over 5 minutes
1 to 2 15 to 16 29 to 30	<b>Fluorouracil</b>	2400mg/m <sup>2</sup>	IV	46 hour continuous infusion in Sodium Chloride 0.9%

## Followed by maintenance single agent Pembrolizumab

Drug	Dosage	Route	Frequency
Pembrolizumab	400mg	IV infusion	6 weekly to complete 2 years**
Pembrolizumab	200mg*	IV infusion	3 weekly to complete 2 years**

OR

## 3-weekly Pembrolizumab + CAPOX for 6 cycles

Day	Drug	Dosage	Route	Diluent and Rate
1	Pembrolizumab	200mg*	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
	Dexamethasone	8mg	PO	30 minutes before chemotherapy
	Ondansetron	16mg	PO	30 minutes before chemotherapy
	CHANGE ADMINISTRATION LINE BEFORE STARTING OXALIPLATIN INFUSION WHEN PEMBROLIZUMAB HAS BEEN ADMINISTERED FIRST			
	Oxaliplatin	130mg/m <sup>2</sup>	IV infusion	500mL Glucose 5% infusion over 2 hours
Days 1 to 21	Capecitabine	625 mg/m <sup>2</sup>	PO	Twice daily, morning and evening continuously

## Followed by maintenance single agent Pembrolizumab

Drug	Dosage	Route	Frequency
Pembrolizumab	400mg	IV infusion	6 weekly to complete 2 years**

Pembrolizumab	200mg*	IV infusion	3 weekly to complete 2 years**
---------------	--------	-------------	-----------------------------------

OR

6-weekly Pembrolizumab + CAPOX for **6 cycles**

Day(s)	Drug	Dosage	Route	Diluent and Rate
1	Pembrolizumab	400mg	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
1 and 22	<b>Dexamethasone</b>	8mg	PO	30 minutes before chemotherapy
	<b>Ondansetron</b>	16mg	PO	30 minutes before chemotherapy
CHANGE ADMINISTRATION LINE BEFORE STARTING OXALIPLATIN INFUSION WHEN PEMBROLIZUMAB HAS BEEN ADMINISTERED FIRST				
1 and 22	<b>Oxaliplatin</b>	130mg/m <sup>2</sup>	IV infusion	500mL Glucose 5% infusion over 2 hours
1 to 21 and 22 to 42	<b>Capecitabine</b>	625 mg/m <sup>2</sup>	PO	Twice daily, morning and evening continuously

Followed by maintenance single agent Pembrolizumab

Drug	Dosage	Route	Frequency
Pembrolizumab	400mg	IV infusion	6 weekly to complete 2 years**
Pembrolizumab	200mg*	IV infusion	3 weekly to complete 2 years**

\*Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 3 weekly regimen may be used.\*

\*\*To continue until disease progression or unacceptable toxicity or after 2 years of treatment (to complete 35 x 3-weekly cycles or its equivalent if 6-weekly dosing is used) whichever is first.

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.). Please refer to the CCC [Hypersensitivity; Management Prevention Policy](#)

For management of **acute cold related dysaesthesia (CRD) or laryngopharyngeal dysaesthesia** as a result of oxaliplatin administration, please refer to 'Main Toxicities' section.

## Interactions:

Refer to [SmPC](#) for full list of interactions

Capecitabine/fluorouracil
Phenytoin – potentially toxic levels of phenytoin have been reported- monitor carefully
Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH
Sorivudine and analogues – Potentially fatal interaction – avoid completely
Allopurinol – reduced efficacy of capecitabine – avoid
Increased risk of agranulocytosis with clozapine.
Cimetidine, metronidazole and interferone may increase the plasma level of 5-fluorouracil, thereby increasing the toxicity of 5-fluorouracil.
Fluorouracil enhances the action of other cytostatic drugs and irradiation therapy.
Avoid live vaccines.

Issue Date: 16 <sup>th</sup> March 2022 Review: 1 <sup>st</sup> March 2025	Page 8 of 22	Protocol reference: MPHAPFCO
Author: Hala Ghoz	Authorised by: Aileen McCaughey, Arvind Arumainathan, Chris Lube, Helen Flint, Zahed Khan, Jo McCaughey	Version No: 1.0

<b>Oxaliplatin</b>
Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval (amiodarone, citalopram, domperidone) and those with electrolyte disturbances such as hypokalemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, oxaliplatin treatment should be discontinued.
<b>Pembrolizumab</b>
No known interactions

## Main Toxicities:

For full details on assessment and management of immune-related toxicities refer to [CCC Immuno-Oncology toxicity specific guidance for adverse event management](#).

<b>Pembrolizumab</b>	
Immune-Mediated Pneumonitis  Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%).	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Immune-Mediated Colitis  Colitis occurred in 1% of patients (including G3 in 0.5%).	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

<p>Other Immune-Mediated Toxicities:</p> <p>Hypophysitis</p> <p>Nephritis</p> <p>Hyperthyroidism or Hypothyroidism</p> <p>Less frequently:</p> <p>Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia</p>	<p>Monitor LFTs, biochemistry, cortisol and TFTs regularly</p> <p>Refer to Immuno-Oncology toxicity specific guidance for adverse event management</p>
<p>Other non-immune adverse events:</p> <p>Fatigue, anaemia</p> <p>Cough, dyspnoea</p> <p>Nausea, decreased appetite</p> <p>Pruritis, rash</p> <p>Constipation, diarrhoea</p> <p>Arthralgia</p>	<p>Refer to Immuno-Oncology toxicity specific guidance for adverse event management</p>
<p>Laboratory abnormalities:</p> <p>Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia</p>	<p>Refer to Immuno-Oncology toxicity specific guidance for adverse event management</p>
<p>Capecitabine / Fluorouracil</p>	

<u>DPD deficiency – leads to severe early fluorouracil/capecitabine toxicity, affects approximately 3% of population, may be life threatening.</u>					
Chest pain, coronary artery spasm	Stop fluorouracil, standard angina investigations, refer to clinical team, if symptoms persist stop permanently				
Stomatitis	If mouth ulcers or > grade 2 symptoms develop treat symptomatically, delay treatment until resolved to grade 1 and reduce fluorouracil doses by 20%. See table				
Diarrhoea	Treat diarrhoea between cycles symptomatically. If diarrhoea has not resolved by next cycle delay treatment by 1 week. If diarrhoea remains troublesome or more than 1 delay is required reduce both fluorouracil bolus and infusion doses by 20% and continue at the lower dose unless further toxicity occurs - See table				
PPE	Treat symptomatically, delay treatment until resolved to grade 1. Reduce fluorouracil doses (bolus and infusion) by 20% for subsequent doses if persistent troublesome PPE. See table below.				
<b>Oxaliplatin</b>					
General toxicities	Infusion reactions, neurotoxicity, myelosuppression, mucositis, diarrhoea, nausea and vomiting				
Neurotoxicity – see notes below for specific cases	<table border="1"> <thead> <tr> <th>Neurotoxicity</th> <th>Oxaliplatin dose</th> </tr> </thead> <tbody> <tr> <td>Grade 1 any duration or grade 2 &lt; 7days but resolving before next cycle</td> <td>85mg/m<sup>2</sup></td> </tr> </tbody> </table>	Neurotoxicity	Oxaliplatin dose	Grade 1 any duration or grade 2 < 7days but resolving before next cycle	85mg/m <sup>2</sup>
Neurotoxicity	Oxaliplatin dose				
Grade 1 any duration or grade 2 < 7days but resolving before next cycle	85mg/m <sup>2</sup>				

	Grade 2 persisting for 7 days or Grade 3 resolved by next cycle	65mg/m <sup>2</sup>
	Grade 3 persisting to next cycle or any grade 4	Stop oxaliplatin
	If oxaliplatin is discontinued, review the infusional dose of fluorouracil and consider increasing to 2800mg/m <sup>2</sup>	
Acute cold related dysaesthesia (CRD)	Transient paraesthesia of hands and feet as well as laryngopharyngeal dysaesthesia (unpleasant sensations in throat) is common. Onset is during or within hours of infusion and it resolves in minutes or days. Symptoms are exacerbated by cold – advise patients on suitable precautions e.g. avoid cold drinks. Should not require dose reduction, but if troublesome then infusion duration can be increased to 6 hours (or 4 hours where oncologist and treating team agree dependent on severity of reaction and tolerability of the infusion over this time)	
Laryngopharyngeal dysaesthesia	Stop infusion, provide symptomatic treatment. Resume at slower infusion rate. Give subsequent infusions over 6 hours (or 4 hours where oncologist and treating team agree dependent on severity of reaction and tolerability of the infusion over this time)	
Cumulative dose related sensory neuropathy	Usually occurs after a cumulative dose of 800mg/m <sup>2</sup> . It can occur after treatment is completed, is usually reversible taking about 3-5 months to recover	
Allergic reactions during infusion	Stop the infusion and call for help. Follow trust anaphylaxis policy. Treat with IV corticosteroid and antihistamine.	

	Discuss continuing with fluorouracil alone or re-challenge with the consultant.
--	---

## Investigations and treatment plan (please refer to the appropriate investigations table as per regimen used):

**If suspicion of endocrinopathies:** request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

### Pembrolizumab + CAPOX

	Pre	Cycle 1	Cycle 2	Prior to cycle 3	Cycle 3	Ongoing
Informed Consent	x					
Clinical Assessment	x			x*		Every 12 weeks thereafter or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x		x	Every cycle**
OTR	x		x		x	Every cycle prior to pembrolizumab treatment. Not required for CAPOX ONLY treatment Go-ahead NOT required
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (AST, ALT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x	x		x	Every cycle
Lipid profile (cholesterol)	x				x	At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x					At baseline then if clinically indicated
Full set of observations ( <i>BP, heart rate, temperature, respiratory rate and O<sub>2</sub> sats</i> )	x	x	x	x	x	Every cycle

Issue Date: 16 <sup>th</sup> March 2022 Review: 1 <sup>st</sup> March 2025	Page 14 of 22	Protocol reference: MPHAPFCO
Author: Hala Ghaz	Authorised by: Aileen McCaughey, Arvind Arumainathan, Chris Lube, Helen Flint, Zahed Khan, Jo McCaughey	Version No: 1.0

# PROTOCOL



The Clatterbridge  
Cancer Centre  
NHS Foundation Trust

Creatinine Clearance (Cockcroft and Gault)	x					Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline
Dihydropyrimidine dehydrogenase (DPD) deficiency test	x					This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.
CT scan**	x					Every 12 weeks/if clinically indicated
Trop-T, CK, pro-BNP	x					At baseline and thereafter as clinically indicated (ECG to be reviewed by clinical team)
ECG	x					
Weight recorded	x	x	x		x	Every cycle
Height recorded	x					

OR

Issue Date: 16 <sup>th</sup> March 2022 Review: 1 <sup>st</sup> March 2025	Page 15 of 22	Protocol reference: MPHAPFCO
Author: Hala Ghaz	Authorised by: Aileen McCaughey, Arvind Arumainathan, Chris Lube, Helen Flint, Zahed Khan, Jo McCaughey	Version No: 1.0

## Pembrolizumab + FOLFOX

	Pre	Cycle 1	Cycle 1 day 15	Prior to cycle 1 day 29	Cycle 1 day 29	Cycle 2	Ongoing
Informed Consent	x						
Clinical Assessment	x			x*		x	Every 12 weeks thereafter or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x		x	x	Every cycle
OTR/ Go-ahead	x					x	Prior to treatment with Pembrolizumab Every 6 weeks
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (AST, ALT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x				x	Every 6 weeks Prior to each SACT containing Pembrolizumab
FBC, U&E, renal profile, bone profile, magnesium, LFTs			x	x	x		Prior to treatment with FOLFOX ONLY
Lipid profile (cholesterol)	x					x	At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x						At baseline then if clinically indicated
Full set of observations ( <i>BP, hear rate, temperature, respiratory rate and O<sub>2</sub> sats</i> )	x	x	x	x	x	x	Every cycle
Creatinine Clearance (Cockcroft and Gault)	x	x	x		x	x	Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline

Dihydropyrimidine dehydrogenase (DPD) deficiency test	x						This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.
CT scan**	x						Every 12 weeks/if clinically indicated
Trop-T, CK, pro-BNP	x						At baseline and thereafter as clinically indicated (ECG to be reviewed by clinical team)
ECG	x						
Weight recorded	x	x	x		x	x	Every cycle
Height recorded	x						

Formal medical review (can be virtual) to assess the tolerability of treatment and whether treatment should continue (as per NHS England criteria).

**\*\*Monitor for symptoms of cardiotoxicity (peripheral oedema, progressive breathlessness, chest pain- please hold treatment and refer patient back to clinical team as a matter of urgency)**

Pregnancy test if applicable

## Dose Modifications and Toxicity Management:

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of doses are contained in dose modifications.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the [CCC Immuno-Oncology toxicity specific guidance for adverse event management](#).

## Treatment Threshold

Administer treatment on day 1 if:

Platelets	Neutrophils	Serum Creatinine	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
$\geq 75 \times 10^9/L$	$\geq 1.0 \times 10^9/L$	$\leq 1.5 \times \text{ULN}$ or baseline	$< 3 \times \text{ULN}$	$< 5 \times \text{ULN}$	$< 5 \times \text{ULN}$	Within range or no change from base line

ULN = upper limit of normal

**Platelets must be within normal range prior to Cycle 1.**

If platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need assessment and chemotherapy dose reduction as follows

Lowest count since previous cycle	Oxaliplatin dose	Fluorouracil dose
Grade 3 / 4 neutropenia ( $< 1.0 \times 10^9/L$ ) or thrombocytopenia ( $< 50 \times 10^9/L$ )	65mg/m <sup>2</sup> (metastatic) 75mg/m <sup>2</sup> (adjuvant)	80% bolus and infusion

Issue Date: 16 <sup>th</sup> March 2022 Review: 1 <sup>st</sup> March 2025	Page 18 of 22	Protocol reference: MPHAPFCO	
Author: Hala Ghaz	Authorised by: Aileen McCaughey, Arvind Arumainathan, Chris Lube, Helen Flint, Zahed Khan, Jo McCaughey		Version No: 1.0

## Toxicity management:

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Toxicity Grade	Action
<b>Grade 1</b> Mild	Continue treatment increase monitoring and provide symptomatic treatment.
<b>Grade 2</b> Moderate	Withhold treatment until resolved to $\leq$ grade 1.  Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
<b>Grade 3 and Grade 4</b> Severe	Withhold treatment.  Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion.  Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

Issue Date: 16 <sup>th</sup> March 2022 Review: 1 <sup>st</sup> March 2025	Page 19 of 22	Protocol reference: MPHAPFCO
Author: Hala Ghoz	Authorised by: Aileen McCaughey, Arvind Arumainathan, Chris Lube, Helen Flint, Zahed Khan, Jo McCaughey	Version No: 1.0

## Fluorouracil dose reductions for non haematological toxicity

	Non haematological toxicities (diarrhoea, stomatitis, PPE)			
grade	0-1	2	3	4
1 <sup>st</sup> occurrence	100%	80%	50%	Stop treatment
2 <sup>nd</sup> occurrence	80%	70%	50%	Stop treatment
3 <sup>rd</sup> occurrence	50%	50%	50%	Stop treatment

## References:

Capecitabine Accord 150mg fil-coated tablets, Summary of Product Characteristics, Accord Healthcare Limited. Available from [www.medicines.org.uk/emc/medicine](http://www.medicines.org.uk/emc/medicine). Last updated 17<sup>th</sup> May 2021.

Fluorouracil 25mg/ml injection, Summary of Product Characteristics, Hospira UK Limited. Available from [www.medicines.org.uk/emc/medicine](http://www.medicines.org.uk/emc/medicine). Last updated 17<sup>th</sup> May 2021.

Keytruda 25mg/mL, Summary of Product Characteristics, Merck Sharp & Dohme (UK) Limited. Available from [www.medicines.org.uk/emc/medicine](http://www.medicines.org.uk/emc/medicine). Last updated 21st September 2021

Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.

NICE TA737 Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer. Published: 20 October 2021

Oxaliplatin Hospira 5mg/ml concentrate for solution for infusion, Summary of Product Characteristics, Hospira UK Limited. Available from [www.medicines.org.uk/emc/medicine](http://www.medicines.org.uk/emc/medicine). Last updated 13<sup>th</sup> April 202.

Sun, J.M., Shen, L., Shah, M.A., Enzinger, P., Adenis, A., Doi, T., Kojima, T., Metges, J.P., Li, Z., Kim, S.B. and Cho, B.C., 2021. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *The Lancet*, 398(10302), pp.759-771.

Issue Date: 16 <sup>th</sup> March 2022 Review: 1 <sup>st</sup> March 2025	Page 21 of 22	Protocol reference: MPHAPFCO	
Author: Hala Ghoz	Authorised by: Aileen McCaughey, Arvind Arumainathan, Chris Lube, Helen Flint, Zahed Khan, Jo McCaughey		Version No: 1.0

# PROTOCOL

## Circulation/Dissemination

Date added into Q-Pulse	16 <sup>th</sup> March 2022
Date document posted on the Intranet	N/A

## Version History

Date	Version	Author name and designation	Summary of main changes
March 2022	1.0	Hala Ghoz Protocols Pharmacist	New Regimen Protocol Version 1.0

Issue Date: 16 <sup>th</sup> March 2022 Review: 1 <sup>st</sup> March 2025	Page 22 of 22	Protocol reference: MPHAPFCO
Author: Hala Ghoz	Authorised by: Aileen McCaughey, Arvind Arumainathan, Chris Lube, Helen Flint, Zahed Khan, Jo McCaughey	Version No: 1.0