PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Nivolumab with FOLFOX OR CAPOX Metastatic Squamous Cell Carcinoma of the Oesophagus

PROTOCOL REF: MPHANFCOE
(Version No.: 1.0)

Approved for use in:

Nivolumab in combination with platinum and fluoropyrimidine-based chemotherapy for previously untreated unresectable advanced or recurrent or metastatic squamous cell carcinoma of the oesophagus with a tumour cell PD-L1 expression of ≥1% and a PD-L1 combined positive score of <10

The patient has not received prior treatment with any antibody which targets PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4).

ECOG performance status (PS) 0 or 1.

Please NOTE: for previously untreated advanced or metastatic **HER-2 negative adenocarcinomas of the stomach, gastro-oesophageal junction or oesophagus** please use the alternative protocol

********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

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 symptomatic CNS disease or carcinomatosis meningitis

Dosage:

Nivolumab + FOLFOX

Drug	Dosage	Route	Frequency
Nivolumab	240mg	IV infusion	2 weekly for 12 cycles and then 4 weekly maintenance as 480mg for 2 years*
Oxaliplatin	85mg/m^2		2 weekly for 12 cycles
Folinic Acid	350mg		
Fluorouracil	400mg/m^2		
Fluorouracil	2400mg/m^2		

OR

Nivolumab + CAPOX

Drug	Dosage	Route	Frequency
Nivolumab	360mg	IV infusion	3 weekly for 6 cycles and then 480mg 4 weekly maintenance for 2 years*
Oxaliplatin	130 mg/m^2	IV infusion	3 weekly for 6 cycles
Capecitabine	625 mg/m^2 twice a day	PO	21 days continuous for 6 cycles

*To continue until disease progression or unacceptable toxicity or after 2 years of treatment whichever is first, regardless of any treatment breaks

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:

Nivolumab – neutral

Oxaliplatin- irritant

Fluorouracil- irritant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'.

Dosing in renal and hepatic impairment:

<table>
<tr><td rowspan="4">Renal</td><td>Oxaliplatin</td><td>GFR ≥ 30 ml/min: no dose adjustment is needed
GFR < 30 ml/min and haemodialysis: consider 50% of the original dose.</td></tr>
<tr><td>Fluorouracil</td><td>No dose adjustment is needed</td></tr>
<tr><td>Capecitabine</td><td><table><tr><th>GFR (mL/min)</th><th>Capecitabine dose</th></tr><tr><td>≥ 60</td><td>100% dose</td></tr><tr><td>50 to 59</td><td>100% dose</td></tr><tr><td>30 to 49</td><td>75% dose</td></tr><tr><td>< 30</td><td>Omit</td></tr></table></td></tr>
<tr><td>Nivolumab (prior to start of treatment ONLY/Baseline)</td><td>eGFR < 30ml/min - limited data use with caution</td></tr>
</table>

Hepatic	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
	Nivolumab (prior to start of treatment ONLY/Baseline)	Administered with caution in patients with: Moderate (total bilirubin > 1.5 -3 × ULN and any AST) or Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment. * Within normal limits or high

Patient Counselling Points

Nivolumab

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

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.
- 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:

2-weekly Nivolumab + FOLFOX for **12 cycles**

Day(s)	Drug	Dose	Route	Diluent and rate
1	Nivolumab	240mg	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
1	**Dexamethasone**	8mg	PO	30 minutes before chemotherapy
	Ondansetron	16mg	PO	30 minutes before chemotherapy
	CHANGE ADMINISTRATION LINE BEFORE STARTING OXALIPLATIN INFUSION			
1	**Oxaliplatin**	85mg/m^2	IV	500mL Glucose 5% infusion over 2 hours
Oxaliplatin and Folinic Acid given at same time concomitantly				
1	**Folinic Acid**	350mg	IV	250mL Glucose 5% infusion over 2 hours

	Fluorouracil	400mg/m^2	IV	Bolus over 5 minutes
1	**Fluorouracil**	2400mg/m^2	IV	46 hour continuous infusion in Sodium Chloride 0.9%

Followed by maintenance single agent Nivolmab

Drug	Dosage	Route	Frequency
Nivolumab	480mg	IV infusion	4 weekly to complete 2 years**

OR

3-weekly Nivolumab+ CAPOX for **6 cycles**

Day	Drug	Dosage	Route	Diluent and Rate
1	Nivolumab	360mg	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 NIVOUMAB HAS BEEN ADMINISTERED FIRST			
	Oxaliplatin	130mg/m^2	IV infusion	500mL Glucose 5% infusion over 2 hours
Days 1 to 21	**Capecitabine**	625 mg/m^2	PO	Twice daily, morning and evening continuously

Followed by maintenance single agent Nivolumab

Drug	Dosage	Route	Frequency
Nivolumab	480mg	IV infusion	4 weekly to complete 2 years**

**To continue until disease progression or unacceptable toxicity or after 2 years of treatment. NHS England expects the 4-weekly dosing of nivolumab to be used once chemotherapy has been discontinued.

If toxicities present, the immunotherapy can be held at the consultant's discretion

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.
Oxaliplatin
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.
Nivolumab
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.

Nivolumab	
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	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Colitis occurred in 1% of patients (including G3 in 0.5%).	
Other Immune-Mediated Toxicities: Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia	Monitor LFTs, biochemistry, cortisol and TFTs regularly Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

<table>
<tr><td colspan="2">Capecitabine / Fluorouracil</td></tr>
<tr><td colspan="2"><u>DPD deficiency – leads to severe early fluorouracil/capecitabine toxicity, affects approximately 3% of population, may be life threatening.</u></td></tr>
<tr><td>Chest pain, coronary artery spasm</td><td>Stop fluorouracil, standard angina investigations, refer to clinical team, if symptoms persist stop permanently</td></tr>
<tr><td>Stomatitis</td><td>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</td></tr>
<tr><td>Diarrhoea</td><td>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</td></tr>
<tr><td>PPE</td><td>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.</td></tr>
<tr><td colspan="2">Oxaliplatin</td></tr>
<tr><td>General toxicities</td><td>Infusion reactions, neurotoxicity, myelosuppression, mucositis, diarrhoea, nausea and vomiting</td></tr>
<tr><td>Neurotoxicity – see notes below for specific cases</td><td>
<table>
<tr><td>Neurotoxicity</td><td>Oxaliplatin dose</td></tr>
<tr><td>Grade 1 any duration or grade 2 < 7days but resolving before next cycle</td><td>85mg/m^2</td></tr>
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<table>
<tr><td></td><td>
<table>
<tr><td>Grade 2 persisting for 7 days or Grade 3 resolved by next cycle</td><td>65mg/m^2</td></tr>
<tr><td>Grade 3 persisting to next cycle or any grade 4</td><td>Stop oxaliplatin</td></tr>
</table>
If oxaliplatin is discontinued, review the infusional dose of fluorouracil and consider increasing to 2800mg/m^2</td></tr>
<tr><td>Acute cold related dysaesthesia (CRD)</td><td>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)</td></tr>
<tr><td>Laryngopharyngeal dysaesthesia</td><td>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)</td></tr>
<tr><td>Cumulative dose related sensory neuropathy</td><td>Usually occurs after a cumulative dose of 800mg/m^2. It can occur after treatment is completed, is usually reversible taking about 3-5 months to recover</td></tr>
<tr><td>Allergic reactions during infusion</td><td>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.</td></tr>
</table>

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)

Nivolumab + FOLFOX

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x	Review pre c2	x* keep this review if immunotherapy added form C2		Every 6-12 weeks thereafter or as clinically indicated (alternate cycle) can go 12 weeks if well maintained on treatment in selected cases
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
OTR	x	x	x	x	Prior to treatment with nivolumab **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	Prior to each SACT containing nivolumab
FBC, U&E, renal profile, bone profile, magnesium, LFTs	x	x	x	x	Prior to treatment

Lipid profile (cholesterol)	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 (*BP, hear rate, temperature, respiratory rate and O_2 sats*)	x	x	x	x	Every cycle
Creatinine Clearance (Cockcroft and Gault)	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	Every cycle
Height recorded	x				

OR

Nivolumab + CAPOX

	Pre	Cycle 1	Cycle 2	Prior to cycle 3	Cycle 3	Ongoing
Informed Consent	x					
Clinical Assessment	x		Review pre c2	x* keep this review if immunotherapy added form C2		Every 6-12 weeks thereafter or as clinically indicated (-alternate cycle) can go 12 weeks if well maintained on treatment in selected cases
SACT Assessment (to include PS and toxicities)	x	x	x		x	Every cycle**
OTR	x		x		x	Every cycle prior to Nivolumab 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	Prior to every cycle containing nivolumab
Lipid profile (cholesterol)	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 (*BP, heart rate, temperature, respiratory rate and O_2 sats*)	x	x	x	x	x	Every cycle
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					

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	TS
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≤1.5 x ULN or baseline	<3 x ULN	<5 x ULN	<5 x ULN	W ch

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 x10^9/L) or thrombocytopenia (<50 x 10^9/L)	65mg/m^2 (metastatic) 75mg/m^2 (adjuvant)	80% bolus and infusion

Toxicity management:

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Please refer to the CCC clinical network immunotherapy acute oncology guidelines on the intranet for more detailed information

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to ≤ grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 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.

Fluorouracil dose reductions for non haematological toxicity

	Non haematological toxicities (diarrhoea, stomatitis, PPE)			
grade	0-1	2	3	4
1st occurrence	100%	80%	50%	Stop treatment
2nd occurrence	80%	70%	50%	Stop treatment
3rd 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. Last updated 17th May 2021.

Fluorouracil 25mg/ml injection, Summary of Product Characteristics, Hospira UK Limited. Available from www.medicines.org.uk/emc/medicine. Last updated 17th May 2021.

Keytruda 25mg/mL, Summary of Product Characteristics, Merck Sharp & Dohme (UK) Limited. Available from 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.

Oxaliplatin Hospira 5mglml concentrate for solution for infusion, Summary of Product Characteristics, Hospira UK Limited. Available from www.medicines.org.uk/emc/medicine. Last updated 13th April 202.

Circulation/Dissemination

Date added into Q-Pulse	5th July 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
Jan 2023	1.0	**Gabriella Langton**	New Regimen Protocol Version 1.0