Nivolumab and FOLFOX-6 Modified Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Nivolumab in combination with fluoropyrimidine and platinum-based combination chemotherapy for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) with tumour cell programmed death ligand 1 (PD-L1) expression ≥1%.	C15	00844a	Nivolumab: ODMS 1/7/2023 Oxaliplatin: Hospital 5-fluorouracil: Hospital

Note: As the platinum and fluoropyrimidine based chemotherapy is not defined in the EMA licensed indication other evidence based platinum and fluoropyrimidine regimens may be used in combination with nivolumab. Prior therapy with an anti-PD-1 or anti-PD-L1 antibody is an exclusion criteria.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Nivolumab and FOLFOX-6 are administered once every 14 days. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity. The maximum duration of treatment for nivolumab is 24 months. Treatment with FOLFOX-6 is administered until disease progression or unacceptable toxicity.

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab may occur at any time during or after discontinuation of therapy.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Nivolumab	240mg	IV infusion[a]	Infuse over 30 minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm[b]	Every 14 days **for up to 24 months**
1	Oxaliplatin[c]	85mg/m^2	IV infusion	500ml glucose 5% over 2hrs	Every 14 days
1	Folinic Acid[d] (Calcium leucovorin)	400mg/m^2	IV infusion	250ml glucose 5% over 2hrs	Every 14 days
1	5-Fluorouracil[e]	400mg/m^2	IV Bolus	n/a	Every 14 days
1	5-Fluorouracil[e]	2400mg/m^2	Continuous IV infusion	Over 46h in 0.9% NaCl	Every 14 days

[a] Nivolumab must not be administered as an intravenous push or bolus injection.

[b] Nivolumab can be infused directly as a 10mg/mL solution or can be diluted to as low as 1mg/mL with sodium chloride 9mg/mL (0.9%) solution for injection or glucose 50mg/mL (5%) solution for injection.

[c] Oxaliplatin is incompatible with 0.9% NaCl. Do not piggyback or flush lines with normal saline
For oxaliplatin doses ≤ 104mg use 250ml glucose 5%.
Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction
Oxaliplatin administration must always precede the administration of 5-FU.
Oxaliplatin may be given at the same time as Folinic Acid *(Calcium Leucovorin)* using a Y connector.

[d] Folinic Acid *(Calcium Leucovorin)* must be administered prior to fluorouracil. It enhances the effects of fluorouracil by increasing fluorouracil binding to the target enzyme thymidylate synthetase.

Acute neurotoxicity is common with oxaliplatin and can be precipitated on exposure to the cold therefore in this regimen patients should NOT suck on ice chips during the bolus injection of fluorouracil.
[e] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.

ELIGIBILITY:

- Indication as above
- Aged ≥18 years
- ECOG 0-2
- Adequate haematological, hepatic and renal function
- PD-L1 expression ≥1% as demonstrated by a validated test method

CAUTION:

- Patients with clinically significant autoimmune disease
- Previous pelvic radiotherapy
- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)
- Symptomatic peripheral neuropathy

EXCLUSIONS:

- Hypersensitivity to nivolumab, oxaliplatin, 5-fluorouracil or any of the excipients
- Prior therapy with an anti-PD-1 or anti-PD-L1 antibody
- Active or unstable CNS metastases
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids)
- History of interstitial lung disease
- Any active clinically significant infection requiring therapy
- Pregnancy / breastfeeding
- Known dihydropyrimidine dehydrogenase (DPD) deficiency
- Severe renal impairment (creatinine clearance < 30ml/min)
- Peripheral neuropathy with functional impairment prior to first cycle

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- Thyroid function tests
- Virology: All patients should be tested for both HBsAg and HBcoreAb as per local policy and Hepatitis C (HCV RNA)
- DPD testing prior to first treatment with 5-fluorouracil - using phenotype and/or genotype testing unless patient has been previously tested
- Serum cortisol (ideally a morning sample)
- ECG (if patient has compromised cardiac function)
- PD-L1 expression ≥1% as demonstrated by a validated test method

Regular tests:

- FBC, renal, liver profile and glucose prior to each cycle
- TFTs prior to each cycle
- Evaluate for peripheral neuropathy every 2 cycles

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Oxaliplatin and 5-fluorouracil:

- Consider a reduced starting dose of 5-fluorouracil in patients with identified partial DPD deficiency.
    - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring
- Dose reductions to manage chemotherapy-induced adverse reactions are permitted for oxaliplatin and 5-fluorouracil and are outlined in Tables 1-5 below

Nivolumab:

- Dose escalation or reduction is not recommended. Any dose modification should be discussed with a Consultant
- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of nivolumab therapy and institution of systemic high-dose corticosteroid.

- If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use. Nivolumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy
- Guidelines for withholding of doses or permanent discontinuation are described in Table 6 below

Table 1: Dose Reduction Levels for FOLFOX for All Toxicity

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2	Discontinue
Folinic Acid *(Calcium Leucovorin)*	400 mg/m^2	400 mg/m^2	400 mg/m^2	Discontinue
5-Fluorouracil bolus	400 mg/m^2	320 mg/m^2	260 mg/m^2	Discontinue
5-Fluorouracil infusion	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2	Discontinue

Note: Folinic acid is delayed or omitted if bolus 5-fluorouracil is delayed or omitted

Haematological:

Table 2. Dose Modifications for FOLFOX for Haematological Toxicity

Prior to a Cycle (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	**ANC (x 10^9/L)**	**Oxaliplatin**	**5-Fluorouracil**
• If ANC< 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks • ANC ≥ 1.5 within 4 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). • If ANC remains <1.5 after 4 weeks discontinue treatment	1	≥ 1.5	Maintain dose level	Maintain dose level
	2	1.0-1.49	Maintain dose level	Maintain dose level
	3	0.5-0.99	↓ 1 dose level	Maintain dose level
	4	<0.5	↓ 1 dose level	Omit bolus and ↓1 infusion dose level
	Grade	**Platelets (x10^9/L)**	**Oxaliplatin**	**5-Fluorouracil**
• If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks • Platelets ≥ 75 within 4 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). • If platelets remains <75 after 4 weeks discontinue treatment	1	≥ 75	Maintain dose level	Maintain dose level
	2	50-74.9	Maintain dose level	Maintain dose level
	3	10-49.9	↓ 1 dose level	Maintain dose level
	4	<10	↓ 2 dose levels	Maintain dose level

Renal and Hepatic Impairment:

Table 3. Recommended Dose Modifications for FOLFOX in Patients with Renal or Hepatic Impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td rowspan="2">Nivolumab</td><td>Mild-moderate</td><td>No dose adjustment necessary</td><td>Mild</td><td colspan="3">No dose adjustment necessary</td></tr>
<tr><td>Severe</td><td>Has not been studied</td><td>Moderate-severe</td><td colspan="3">Has not been studied

Nivolumab must be administered with caution in patients with:
• moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST)
or
• severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.</td></tr>
<tr><td rowspan="4">Oxaliplatin</td><td>CrCl(ml/min)</td><td>Dose</td><td colspan="4" rowspan="4">No dose adjustment is needed</td></tr>
<tr><td>≥30</td><td>No dose adjustment is needed</td></tr>
<tr><td><30</td><td>Consider 50% of the original dose</td></tr>
<tr><td>Haemodialysis</td><td>Consider 50% of the original dose, haemodialysis within 90 mins after administration.</td></tr>
<tr><td rowspan="4">5-Fluorouracil</td><td colspan="2" rowspan="4">No need for dose adjustment is expected

Haemodialysis: no need for dose adjustment is expected</td><td>Bilirubin (micromol/L)</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td><85</td><td></td><td><180</td><td>100%</td></tr>
<tr><td>>85</td><td>or</td><td>>180</td><td>Contraindicated</td></tr>
<tr><td colspan="4">Clinical decision.
Moderate hepatic impairment; reduce initial dose by 1/3.
Severe hepatic impairment, reduce initial dose by 1/2.
Increase dose if no toxicity</td></tr>
</table>

Management of adverse events:

Table 4: Dose Modification Schedule for FOLFOX Based on Adverse Events

Adverse reactions	Discontinue	Recommended dose modification
*Peripheral neuropathy Grade 2 present at start of cycle Grade 3 • First occurrence • 2nd occurrence • Persistent Grade 4	 Discontinue oxaliplatin Discontinue oxaliplatin	Reduce oxaliplatin by 1 dose level ↓ 1 dose level ↓1 dose level
Laryngo-pharyngeal dysaesthesia		Increase infusion time from 2 to 6 hrs
Stomatitis		Delay treatment until stomatitis reaches level of grade 1 or less
Unexplained respiratory symptoms e.g. Non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates	Discontinue oxaliplatin until interstitial disease or pulmonary fibrosis excluded.	

*Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re- challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed.

Management of adverse events:

Table 5: Dose Modification of FOLFOX for Diarrhoea

Prior to a Cycle (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	Diarrhoea	Oxaliplatin	5-Fluorouracil
• If diarrhoea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 4 times. • If diarrhoea is less than Grade 2 within 4 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. • If diarrhoea remains greater than or equal to Grade 2 after 4 weeks, discontinue treatment.	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Maintain dose level	↓ 1 dose level of IV push and infusional 5-fluorouracil
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level	↓ 1 dose level of IV push and infusional 5-fluorouracil

Table 6: Recommended Treatment Modifications for Nivolumab for Immune-related Adverse Reactions

Immune-related adverse reaction	Severity	Treatment Modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment

Immune-related myocarditis	Grade 2 myocarditis Grade 3 or 4 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence) Grade 4 or recurrent Grade 3 ; persistent Grade 2 or 3 despite treatment modification ; inability to reduce corticosteroid dose to 10mg prednisone or equivalent per day	Withhold dose(s) Permanently discontinue treatment

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Nivolumab: Minimal **(Refer to local policy)**
Oxaliplatin**:** Moderate (**Refer to local policy)**
5-Fluorouracil**:** Low (**Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: Anti-diarrhoeal treatment **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.

Nivolumab:

- **Cardiac adverse events and pulmonary embolism**: Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment
- **Immune related adverse reactions:**

Adverse reaction	**Withhold/ discontinue**	**Recommended action -1st occurrence**
Immune-related pneumonitis Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.		

Grade 2 (symptomatic) If worsening or no improvement occurs despite initiation of corticosteroids	Withhold Permanently discontinue	Initiate corticosteroids at a dose of 1mg/kg/day methylprednisolone (/equivalents) Upon improvement, nivolumab may be resumed after corticosteroid taper Increase corticosteroid dose to 2 to 4mg/kg/day methylprednisolone (/equivalents)
Grade 3 or 4	Permanently discontinue	Initiate corticosteroids at a dose of 2 to 4mg/kg/day methylprednisolone (/equivalents)
Immune-related colitis Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Infectious and disease-related aetiologies should be ruled out. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Consider if patient has persistent colitis despite appropriate colitis therapy		
Grade 2 diarrhoea or colitis If worsening or no improvement occurs despite initiation of corticosteroids	Withhold Permanently discontinue	Initiate corticosteroids at a dose of 0.5 to 1mg/kg/day methylprednisolone (/equivalents) Upon improvement, nivolumab may be resumed after corticosteroid taper Increase corticosteroid dose to 1 to 2mg/kg/day methylprednisolone (/equivalents)
Grade 3 diarrhoea or colitis If worsening or no improvement occurs despite initiation of corticosteroids	Withhold Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone (/equivalents) Upon improvement, nivolumab may be resumed after corticosteroid taper
Grade 4 diarrhoea or colitis	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone (/equivalents)
Immune-related hepatitis Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.		
Grade 2 transaminase or total bilirubin elevation If worsening or no improvement occurs despite initiation of corticosteroids	Withhold Permanently discontinue	Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab may be resumed after corticosteroid taper Increase corticosteroid dose to 1 to 2mg/kg/day methylprednisolone (/equivalents)

Grade 3 or 4 transaminase or total bilirubin elevation	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone (/equivalents)
Immune-related nephritis and renal dysfunction Patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.		
Grade 2 or 3 serum creatinine elevation	Withhold	Initiate corticosteroids at a dose of 0.5 to 1mg/kg/day methylprednisolone (/equivalents) Upon improvement, nivolumab may be resumed after corticosteroid taper
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	Increase corticosteroid dose to 1 to 2mg/kg/day methylprednisolone (/equivalents)
Grade 4 serum creatinine elevation	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone (/equivalents)
Immune-related endocrinopathies Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.		
Symptomatic hypothyroidism	Withhold	Thyroid hormone replacement should be initiated as needed
Symptomatic hyperthyroidism	Withhold	Anti-thyroid medication should be initiated as needed Corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised.
Life-threatening hyperthyroidism or hypothyroidism	Permanently discontinue	
Symptomatic Grade 2 adrenal insufficiency	Withhold	Physiologic corticosteroid replacement should be initiated as needed.
Severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency	Permanently discontinue	Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised
Symptomatic Grade 2 or 3 hypophysitis	Withhold	Hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone (/ equivalents) should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed.
Life-threatening (Grade 4) hypophysitis	Permanently discontinue	Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised

Symptomatic diabetes	Withhold	Insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised.
Life-threatening diabetes	Permanently discontinue	
Immune-related skin adverse reactions		
Grade 3 rash	Withhold	Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2mg/kg/day methylprednisolone equivalents. Rare cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) some of them with fatal outcome have been observed. If symptoms or signs of SJS or TEN appear, nivolumab treatment should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab, permanent discontinuation of nivolumab is recommended. Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents
Grade 4 rash	Permanently discontinue	
Other immune-related adverse reactions For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab should be withheld and corticosteroids administered. Upon improvement, nivolumab may be resumed after corticosteroid taper. Nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.		
Infusion reactions		
Mild or moderate infusion reaction	Caution	May receive nivolumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions
Severe or life-threatening infusion reaction	Discontinue infusion	Administer appropriate medical therapy

Oxaliplatin

- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysaesthesia:** An acute syndrome of laryngopharyngeal dysaesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.
- **Extravasation:** Oxaliplatin causes irritation if extravasated (Refer to local policy).
- **Venous occlusive disease:** A rare but serious complications that has been reported in patients

(0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.

- **Haemolytic Ureamic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

5-Fluorouracil

- **Gastrointestinal toxicity:** Patients treated with fluorouracil should be closely monitored for diarrhoea and managed appropriately.
- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysaesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil.
- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.
- **DPD deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.

DRUG INTERACTIONS:

- No formal pharmacokinetic drug interaction studies have been conducted with nivolumab. Since nivolumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting nivolumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of nivolumab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions
- Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored. Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-fluorouracil regimens.
- Concurrent administration of 5-fluorouracil and phenytoin may result in increased serum levels of phenytoin
- 5-Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil metabolising enzyme DPD.
- Caution should be taken when using 5-fluorouracil in conjunction with medications which may affect DPD activity.

- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Nivolumab Patient Alert Card:
https://www.hpra.ie/img/uploaded/swedocuments/c02753be-51a5-44fd-8117-123823bdcff8.pdf

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Version	Date	Amendment	Approved By
1	27/09/2023		Prof Maccon Keane
1a	20/02/2024	Correction of typo in reimbursement status box.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie