Nivolumab and FOLFOX-6 Modified Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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 01/07/2023 Oxaliplatin: N/A 5-Fluorouracil: N/A
Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy for first line treatment of adult patients with HER-2 negative advanced or metastatic gastric cancer (GC), gastroesophageal junction cancer (GEJC) or esophageal adenocarcinoma (EAC), whose tumours express PD-L1 (CPS) ≥5.	C15/16	00844b	N/A

*This applies to post 2012 indications

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.

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 2 hours	Every 14 days
1	Folinic Acid[d] (Calcium leucovorin)	400mg/m^2	IV infusion	250mL glucose 5% over 2 hours	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 46 hours 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 NaCl 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-Fluorouracil.
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 5-Fluorouracil. It enhances the effects of fluorouracil by increasing 5-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 5-Fluorouracil.

[e] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indication as above
- Aged ≥18 years
- ECOG 0-2
- Adequate haematological, hepatic and renal function

OSCC indication:

- PD-L1 expression ≥1% as demonstrated by a validated test method.

GC/GEJC/EAC indication:

- PD-L1 expression (CPS) ≥5 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
- Any active clinically significant infection requiring therapy
- Active or unstable CNS metastases
- Immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisoLONE/daily (or steroid equivalent, excluding inhaled or topical steroids)

EXCLUSIONS:

- Hypersensitivity to nivolumab, oxaliplatin, 5-fluorouracil or any of the excipients
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is Available on the NCCP website
- History of interstitial lung disease
- Pregnancy / breastfeeding
- Known dihydropyrimidine dehydrogenase (DPD) deficiency
- Peripheral neuropathy with functional impairment prior to first cycle

GC/GEJC/EAC indication:

- Known HER-2 positive status

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- Thyroid function tests
- DPD testing prior to first treatment with 5-Fluorouracil - using phenotype and/or genotype testing unless patient has been previously tested
    - In patients with moderate or severe renal impairment, blood uracil levels used for dihydropyrimidine dehydrogenase (DPD) phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment.
- ECG (if patient has compromised cardiac function)
- PD-L1 testing with the DAKO autostainer using the 28-8 pharmDX antibody on the request of a consultant medical oncologist where there is an intention to treat with nivolumab in line with this licensed indication

GC/GEJC/EAC indication:

- HER 2 testing using 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
- Cortisol as clinically indicated

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 Nivolumab and 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 colspan="2" rowspan="2">No dose adjustment is needed

Haemodialysis: No need for dose adjustment is expected</td><td>Mild/Moderate</td><td colspan="3">No dose adjustment is needed</td></tr>
<tr><td>Severe</td><td colspan="3">No need for dose adjustment is expected</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 minutes 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>
<tr><td colspan="6">Nivolumab: Renal and hepatic – Giraud et al 2023
Oxaliplatin: Renal and hepatic - Giraud et al 2023
5-Fluorouracil: Renal - Giraud et al 2023, hepatic – North London Cancer Network 2009</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.

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 Grade 3 or 4 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis Grade 3 diarrhoea or colitis Grade 4 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete Withhold dose(s) until symptoms resolve and management with corticosteroids is complete Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation Grade 4 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 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 Permanently discontinue treatment

Immune-related skin adverse reactions	Grade 3 rash Grade 4 rash Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete Permanently discontinue treatment 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:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

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

For information:
Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: Not usually required

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

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **Dihydropyrimidine dehydrogenase (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 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for 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
2	13/08/2024	Reviewed. New indication added (844b). Updated eligibility, exclusions, testing sections. Renal/hepatic dose modifications for nivolumab aligned to Giraud et al 2023 recommendations. Regimen updated as per NCCP standardisation.	Prof Maccon Keane
3	16/04/2025	Updated exclusions and cautions section. Updated baseline testing section including inclusion of PD-L1 testing recommendation. Updated regular testing section.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie