Nivolumab 480mg, CISplatin 80mg/m^2 and 5-Fluorouracil Infusional 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	00832a	Nivolumab: ODMS 1st July 2023 CISplatin: N/A 5-Fluorouracil: N/A

* This applies to post 2012 indications only.

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 is administered on Day 1; treatment with nivolumab is administered until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.

CISplatin is administered on Day 1 and 5-Fluorouracil 800 mg/m^2 per day is given by continuous intravenous (IV) infusion on Days 1–5 of each cycle, as detailed in Table 1. Alternatively, 5-Fluorouracil may be administered at a dose of 1000 mg/m^2 per day given by continuous IV infusion on Days 1–4 of each cycle as detailed in Table 2 below.

Treatment with CISplatin and 5-Fluorouracil is administered until disease progression or unacceptable toxicity.

Each cycle is 28 days.

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 the systemic anti-cancer therapy (SACT) is administered.

Table 1: Treatment schedule for Nivolumab 480mg, CISplatin 80mg/m^2 and 5-Fluorouracil 800mg/m^2/day Days 1-5

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Nivolumab	480mg	IV infusion[1]	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^2	Every 28 days **for up to 24 months**
2	1	CISplatin	80mg/m^2	IV infusion	1000mL NaCl 0.9% over 1 hour[3,4]	Every 28 days
3	1-5	5-Fluorouracil[5]	800mg/m^2/day (total dose = 4000mg/m^2 over 120 hours)	Continuous IV infusion over 5 days	Infusor pump	Every 28 days

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

[2] 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.

[3] **Pre and post hydration therapy required for CISplatin**

See local hospital policy recommendations.

Suggested prehydration for CISplatin therapy:

- Administer 10mmol magnesium sulphate (MgSO4) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL NaCl 0.9% over 60 -120 minutes. (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above.

Post hydration: Administer 1000 mL 0.9% NaCl over 60 minutes.

[4] Mannitol 10% may be used as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload.

[5] 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.

Table 2: Alternate Treatment schedule for Nivolumab, CISplatin 80mg/m^2 and 5-Fluorouracil 1000mg/m^2/day Days 1-4

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Nivolumab	480mg	IV infusion[1]	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^2	Every 28 days **for up to 24 months**
2	1	CISplatin	80mg/m^2	IV infusion	1000mL NaCl 0.9% over 1 hour[3,4]	Every 28 days
3	1-4	5-Fluorouracil[5]	1000mg/m^2/day (total dose = 4000mg/m^2 over 96 hours)	Continuous IV infusion over 4 days	Infusor pump	Every 28 days

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

[2] 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.

[3] **Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:
- Administer 10mmol magnesium sulphate (MgSO4) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL NaCl 0.9% over 60-120 minutes. (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above.
Post hydration: Administer 1000 mL 0.9% NaCl over 60 minutes.

[4] Mannitol 10% may be used as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload.

[5] 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
- PD-L1 expression ≥1% as demonstrated by a validated test method
- Adequate haematological, hepatic and renal function

CAUTION:

- Moderate/severe renal impairment (CrCl < 40 mL/min)
- Patients with clinically significant autoimmune disease

EXCLUSIONS:

- Hypersensitivity to nivolumab, CISplatin, 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

- 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)
- Symptomatic interstitial lung disease
- Symptomatic CNS metastases
- Any active clinically significant infection requiring therapy
- Pregnancy / breastfeeding
- Significant hearing impairment / tinnitus
- Pre-existing neuropathies ≥ grade 2
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency where used in combination with 5-Fluorouracil

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 (TFTs)
- Virology: All patients should be tested for both HBsAg and HBcoreAb as per local policy and Hepatitis C (HCV RNA)
- PD-L1 testing with the DAKO autostainer using the 28-8 Pharm DX antibody on the request of a Consultant Medical Oncologist where there is an intention to treat with nivolumab in line with this licensed indication
- Audiology and creatinine clearance if clinically indicated
- 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.

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Glucose prior to each cycle
- TFTs every 4 weeks

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

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 3 below

CISplatin 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 CISplatin and 5-Fluorouracil and are outlined in Table 4, 5 and 6 below

Table 3: Recommended Treatment Modifications for Nivolumab

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 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).

Haematological:

Table 4: Dose modification of CISplatin and 5-Fluorouracil for Haematological Toxicity

ANC (x 10^9/L		Platelets (x 10^9/L	Dose
≥ 1.5	and	≥ 100	100%
1 to < 1.5	or	75 to <100	**Delay**[a] then 100% for 1st event[b]
<1	or	<75	**Delay**[a] then 75%

[a]Delay until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L.
[b]Consider dose reduction to 75% for subsequent events and/ or prolonged delays of more than 2 weeks.

Renal and Hepatic Impairment:

Table 5: Dose modification in renal and 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[a]</td><td colspan="2" rowspan="2">No dose adjustment is needed</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="6">CISplatin[b]</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="4" rowspan="6">No need for dose adjustment is expected.</td></tr>
<tr><td>≥60</td><td>100%</td></tr>
<tr><td>50-59</td><td>75% of the original dose</td></tr>
<tr><td>40-49</td><td>50% of the original dose</td></tr>
<tr><td><40</td><td>Not recommended</td></tr>
<tr><td>Haemodialysis</td><td>50% of the original dose may be considered</td></tr>
<tr><td rowspan="4">5-Fluorouracil[c]</td><td colspan="2" rowspan="2">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>Haemodialysis</td><td>No need for dose adjustment is expected</td><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 33%.
Severe hepatic impairment, reduce initial dose by 50%.
Increase dose if no toxicity.</td></tr>
<tr><td colspan="7">[a]Dose modifications from Giraud et al 2023
[b] Dose modifications from Giraud et al 2023
[c]Dose modications for 5-Fluorouracil for renal impairment from Giraud et al 2023, hepatic impairment from North London Cancer Network</td></tr>
</table>

Management of adverse events:

Table 6: Dose modification schedule based on adverse events induced by CISplatin and 5-Fluorouracil

Adverse Event	Dose Modification
Stomatitis or Diarrhoea	
Grade 2	Reduce dose of 5-Fluorouracil to 75%
Grade ≥3	Discontinue or delay until toxicity resolved then resume at 50%.
Hand-foot syndrome	
Grade 2	Reduce dose of 5-fluorouracil to 75% until resolved then consider increasing dose by 100%
Grade 3	Delay until resolved then resume at 75%
Neurotoxicity	
Grade ≥ 2	Omit CISplatin

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)**
CISplatin: High **(Refer to local policy)**
5-fluorouracil: Low **(Refer to local policy)**

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

- 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 for nivolumab

OTHER SUPPORTIVE CARE:

- Hydration pre and post CISplatin administration (**Refer to local policy** or see recommendations above)
- Anti-diarrhoeal treatment **(Refer to local policy)**
- Mouth care **(Refer to local policy)**

ADVERSE EFFECTS

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

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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10. CISplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. Last updated

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Version	Date	Amendment	Approved By
1	28/06/2023		Prof Maccon Keane
1a	08/01/2024	Formatting changes and grammatical corrections.	NCCP
2	17/07/2024	Updated CISplatin pre-hydration wording. Updated cautions and exclusions section. Updated renal and hepatic dose modificacions sections to align with Giraud et al 2023. Removed drug interactions, adverse effects and regimen specific complications in line with NCCP standardisation.	Prof Maccon Keane
2a	03/03/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.