Nivolumab and XELOX Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
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	00843a	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 XELOX are administered once every 21 days. Treatment with nivolumab is administered until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression. Treatment with oxaliplatin and capecitabine is administered until disease progression or unacceptable toxicity.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Nivolumab	360mg	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 21 days **for up to 24 months**
1	Oxaliplatin[c]	130mg/m^2	IV infusion	500mL glucose 5% over 2 hours	Every 21 days
1-14	Capecitabine	1000mg/m^2 Twice Daily[d,e,f]	PO with food	N/A	Every 21 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.

[d] The dose to be administered should consider the available tablet strengths.

Please refer to the NCCP DOSE BANDING TABLES HERE for capecitabine.
Tablets should be swallowed whole with plenty of water with food or within 30 minutes of eating. Tablets should not be crushed or cut.

[e] total daily dose = 2000mg/m^2

[f] 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 (CPS) ≥5 as demonstrated by a validated test method
- Adequate haematological, hepatic and renal function

CAUTION:

- Patients with clinically significant autoimmune or cardiovascular disease

EXCLUSIONS:

- Hypersensitivity to nivolumab, oxaliplatin, capecitabine or any of the excipients
- Known HER-2 positive status
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is available here
- 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
- Severe leucopenia, neutropenia or thrombocytopenia
- Severe renal impairment (creatinine clearance below 30mL/min [Cockcroft and Gault] at baseline
- Peripheral neuropathy with functional impairment prior to first cycle
- Known dihydropyrimidine dehydrogenase (DPD) deficiency

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.
- 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 capecitabine - using phenotype and/or genotype testing unless patient has been previously tested
- Serum cortisol (ideally a morning sample)
- HER2 testing using a validated test method
- PD-L1 expression using a validated test method
- INR tests if patient is on warfarin (as clinically indicated)

Regular tests:

- FBC, renal, liver profile and blood glucose prior to each cycle
- TFTs prior to each cycle
- INR tests if patient is on warfarin (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 capecitabine

- Consider a reduced starting dose of capecitabine 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
- Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction)
- Once the dose has been reduced, it should not be increased at a later time
- For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption
- Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs
- Doses of capecitabine omitted for toxicity are not replaced
- Dose reductions to manage chemotherapy-induced adverse reactions for oxaliplatin and capecitabine and are outlined in Tables 1-7 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 8 below

Haematological:

- Patients with baseline neutrophil counts <1.5x10^9/L and/or platelet counts of <100x10^9/L should not be treated with capecitabine

Table 1: Dose reduction levels for oxaliplatin and capecitabine for non-neurologic toxicity

Drug	Dose	Dose -1	Dose-2	Dose-3
Oxaliplatin	130 mg/m^2	100 mg/m^2	85 mg/m^2	Discontinue
Capecitabine	1000mg/m^2 BD	750 mg/m^2 BD	500 mg/m^2 BD	Discontinue

Table 2: Dose Modifications for oxaliplatin and capecitabine for Haematological Toxicity

Prior to a Cycle (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	ANC (x 10^9/L)	Oxaliplatin	Capecitabine
	1	≥1.2	Maintain dose level	Maintain dose level
	2	1-1.19	Maintain dose level	Maintain dose level

• If ANC< 1.2 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 times • ANC ≥ 1.2 within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). • If ANC remains < 1.2 after 2 weeks discontinue treatment	3	0.5-0.99	↓ 1 dose level	↓ 1 dose level
	4	<0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade	**Platelets ($x10^9$/L)**	**Oxaliplatin**	**Capecitabine**
• If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks • Platelets ≥ 75 within 2 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 2 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	↓ 1 dose level
	4	<10	↓ 2 dose levels	↓ 2 dose levels

Renal and Hepatic Impairment:

Table 3: Dose modification of nivolumab, capecitabine and oxaliplatin in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment	
Nivolumab	No dose adjustment is needed Haemodialysis: No need for dose adjustment is expected	**Mild/Moderate**	No dose adjustment is needed
		Severe	No need for dose adjustment is expected

Capecitabine*	**CrCl (mL/min)**	**Dose**	No dose adjustment is needed	
	51-80	No dose adjustment is needed		
	30-50	75% of the original dose		
	<30	Not recommended		
	Haemodialysis	Not recommended		
Oxaliplatin	**CrCl (mL/min)**	**Dose**	No dose adjustment is needed	
	≥30	No dose adjustment is needed		
	<30	Consider 50% of the original dose		
	Haemodialysis	Consider 50% of the original dose, haemodialysis within 90 minutes after administration.		
*Reference Table 4 for dose modification of capecitabine in treatment related hepatotoxicity				
Renal and hepatic dose modifications as per Giraud et al 2023				

Treatment related hepatotoxicity

Table 4: Dose modification of capecitabine in treatment related hepatotoxicity

Bilirubin		**ALT, AST**	**Dose Modification**
> 3 x ULN	**or**	> 2.5 x ULN	Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN

Management of adverse events:

Non-Haematological and Non-neurological Toxicities:

If Grade 2, 3 or 4 toxicities occur, daily administration of capecitabine should be immediately interrupted until these symptoms resolve or decrease in intensity to grade 1.

Table 5: Dose Modifications for Oxaliplatin and Capecitabine for Non-Haematologic, Non-Neurologic Toxicity

Prior to a Cycle (Day 1)			**Dose Level for Subsequent Cycles**	
Diarrhoea	**Grade ****		**Oxaliplatin**	**Capecitabine**
• If diarrhoea grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks maximum 2 times. • If diarrhoea < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the Highest grade experienced. • If diarrhoea remains Grade 2 after 2 weeks, discontinue treatment.	1	Increase of < 4 stools/day over baseline	Maintain dose level	Maintain dose level
	2	Increase of 4 to 6 stools/day over baseline	Maintain dose level	Maintain dose level
	3	Increase of ≥7 stools/day	Maintain dose level	↓ 1 dose level
	4	[a]Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support. Urgent intervention indicated	↓ 1 dose level	↓ 2 dose levels*
Stomatitis	**Grade ****		**Oxaliplatin**	**Capecitabine**
• If stomatitis ≥ Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. • If stomatitis < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. • If stomatitis remains ≥Grade 2 after 2 weeks,	**1**	Asymptomatic or mild symptoms; intervention not indicated	Maintain dose level	Maintain dose level
	2	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Maintain dose level	Maintain dose level
	3	Severe pain; interfering	Maintain dose level	↓ 1 dose level

discontinue treatment.		with oral intake		
	4	[a]As above but mucosal necrosis and/or requires enteral support, dehydration. Urgent intervention indicated	↓ 1 dose level	↓ 2 dose levels*
Palmar-Plantar Erythrodysaesthesia (Hand-Foot Syndrome)	**Grade ****		**Oxaliplatin**	**Capecitabine**
• If hand-foot skin reaction ≥ Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. • If hand-foot skin reaction is < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced • If hand-foot skin reaction remains ≥ Grade 2 after 2 weeks, discontinue treatment.	**1**	Minimal skin changes or dermatitis (e.g., erythema, oedema, or hyperkeratosis) without pain	Maintain dose level	Maintain dose level
	2	Skin changes (e.g., peeling, blisters, bleeding, fissures, oedema, or hyperkeratosis) with pain; limiting instrumental ADL	Maintain dose level	Maintain dose level
	3	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, oedema, or hyperkeratosis) with pain; limiting self-care ADL	Maintain dose level	↓ 1 dose level
***If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.** **AE Grading CTCAEv5.0				

Neurologic Toxicity

Table 6: Dose reduction levels for oxaliplatin for Neurologic Toxicity

Drug	Dose	Dose -1	Dose-2	Dose-3
Oxaliplatin	130 mg/m^2	100 mg/m^2	65 mg/m^2	Discontinue

If patient has both neurologic and non-neurologic toxicity, the final dose of oxaliplatin is the LOWER of the dose adjustments (i.e. if haematologic toxicity mandates dose –2 reduction (85 mg/m^2) and neurologic toxicity mandates dose –2N reduction (65 mg/m^2), then 65 mg/m^2 is given

Table 7: Dose Modifications for oxaliplatin for Neurologic Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1-7 days	> 7 days	
1	Maintain dose level	Maintain dose level	Maintain dose level
2	Maintain dose level	Maintain dose level	↓ 1 neurotoxicity dose level
3	↓ 1 neurotoxicity dose level	↓ 1 neurotoxicity dose level	Discontinue therapy
4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Laryngo-pharyngeal dysaesthesia	Increase infusion time from 2 to 6 hrs	N/A	N/A

Table 8: 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 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	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

	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	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	Withhold dose(s) Permanently discontinue treatment

	recurrent Grade 3 ; persistent Grade 2 or 3 despite treatment modification ; inability to reduce corticosteroid dose to 10mg prednisone or equivalent per day	

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5).

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting linked here

Nivolumab: Minimal **(Refer to local policy)**

Oxaliplatin**:** Moderate (**Refer to local policy)**

Capecitabine: Minimal to 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) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

PREMEDICATIONS: Not usually required

OTHER SURPORTIVE CARE:

Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see 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 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

REFERENCES:

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Version	Date	Amendment	Approved By
1	13/08/2024		Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.