Pembrolizumab and FOLFOX-6 Modified Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved Reimbursement Status*
Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy, for the first line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with CPS≥10[i]	C15/ C16	00839a	Pembrolizumab: ODMS 01/06/2023 Oxaliplatin, 5-fluorouracil: N/A

*This is for 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 pembrolizumab. 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.

Pembrolizumab is administered on day 1, oxaliplatin, folinic acid and 5-fluorouracil are administered on days 1, 15, and 29 of a 42 day cycle. Treatment is administered for 4 cycles, followed by maintenance single agent pembrolizumab until disease progression or unacceptable toxicity occurs.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Pembrolizumab	400mg	IV infusion	100ml 0.9% NaCl over 30 minutes[a, b]	Every 42 days
1, 15, 29	Oxaliplatin	85mg/m^2	IV infusion	500ml glucose 5% over 2hrs[c]	Every 42 days **Cycles 1-4 only**
1, 15, 29	Folinic Acid[d] (Calcium leucovorin)	400mg/m^2	IV infusion	250ml glucose 5% over 2hrs	Every 42 days **Cycles 1-4 only**
1, 15, 29	5-Fluorouracil[e]	400mg/m^2	IV Bolus	n/a	Every 42 days **Cycles 1-4 only**
1, 15, 29	5-Fluorouracil[e]	2400mg/m^2	Continuous IV infusion	Over 46h in 0.9% NaCl	Every 42 days **Cycles 1-4 only**
[a] Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml.					
[b] Administer using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.					
[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 5-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 5-fluorouracil.
[e] See dose modifications section for patients with identified partial DPD deficiency.

ELIGIBILITY:

- Indication as above
- Histologically or cytologically confirmed locally advanced unresectable or metastatic oesophageal carcinoma or gastro-oesophageal junction (GEJ) carcinoma (Siewert Type 1)
- Aged ≥ 18 years
- ECOG status 0-2
- PD-L1 with a combined positive score (CPS) ≥10 as demonstrated by a validated assay method
- Adequate organ function

CAUTION:

- History of serious 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 pembrolizumab, oxaliplatin, 5-fluorouracil or to any of the excipients
- Known HER-2 positive GEJ carcinoma
- Has received 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
- Peripheral neuropathy with functional impairment prior to first cycle
- Known complete DPD deficiency

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 Screen: Hepatitis B (HBsAg, HbcoreAb) and Hepatitis C
- HER 2 testing of GEJ using a validated test method
- PD-L1 testing with the DAKO autostainer using the 22C3 Pharm DX antibody on the request of a Consultant Medical Oncologist where there is an intention to treat with pembrolizumab in line with this licensed indication
- DPD testing prior to first treatment with 5-fluorouracil using phenotype and / or genotype testing unless patient has been previously tested
- ECG (if patient has compromised cardiac function)

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Glucose prior to each cycle
- Thyroid function tests every 3 to 6 weeks
- 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.

Pembrolizumab dose modifications:

- Dose reduction is not recommended for pembrolizumab
- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of pembrolizumab therapy and institution of systemic high-dose corticosteroid (see Table 6 below)

Oxaliplatin and 5-fluorouracil dose modifications:

- Dose reductions to manage chemotherapy-induced adverse reactions are permitted for oxaliplatin and 5-fluorouracil (see Tables 1-5 below)
- 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

Table 1: Dose Reduction Levels for Oxaliplatin and 5-Fluorouracil

Drug	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 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 in patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment			
Pembrolizumab	No dose adjustment is needed Haemodialysis: no need for dose adjustment is expected		**Mild**	No dose adjustment is needed		
			Moderate/Severe	No need for dose adjustment is expected		
Oxaliplatin	**CrCl(ml/min)**	**Dose**	No dose adjustment needed			
	≥30	No dose adjustment required				
	<30	Consider 50% of original dose				
	Haemodialysis	Consider 50% of original dose, haemodialysis within 90 mins after administration				
5-Fluorouracil	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		**Bilirubin** (micromol/L)		**AST**	**Dose**
			<85		<180	100%
			>85	**or**	>180	Contraindicated
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 33%. Severe hepatic impairment; reduce initial dose by 50%. Increase dose if no toxicity.			

Management of adverse events:

Table 4: Dose modifications for oxaliplatin for 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	 ↓ 1 dose level ↓1 dose level Discontinue oxaliplatin Discontinue oxaliplatin	Reduce oxaliplatin by 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 modifications for oxaliplatin and 5-fluorouracil 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 pembrolizumab

Immune-related adverse reactions	Severity (NCI-CTCAE v.4 grading)	Treatment modification
Pneumonitis	Grade 2	Withhold*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold* For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise, treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.

Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions**	Based on severity and type of reaction (grade 2 or Grade 3)	Withhold*
	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome Grade 4 or recurrent Grade 3	Permanently discontinue
Infusion-related reactions	Grade 3 or 4	Permanently discontinue

* Until adverse reactions recover to Grade 0-1. If treatment related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of pembrolizumab or if corticosteroid dosing cannot be reduced to ≤ 10mg prednisone or equivalent per day within 12 weeks, pembrolizumab should be permanently discontinued.
**Pembrolizumab should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-related adverse reactions, unless otherwise specified in Table 1.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Pembrolizumab: 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.

Pembrolizumab:

- **Immune-mediated adverse reactions:** Most immune-related adverse reactions occurring during treatment with pembrolizumab are reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month.
  Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones. Specific guidelines for management of Immune Mediated Adverse Events are available.
- **Infusion-related reactions**: Severe infusion-related reactions have been reported in patients receiving pembrolizumab. For severe infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued. Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

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 5-fluorouracil should be closely monitored for diarrhoea and managed appropriately.

- **Hand-foot syndrome (HFS):** 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 5-fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-fluorouracil, should be carefully monitored during therapy.
- **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:

- No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-fluorouracil regimes.
- 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 dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using 5-fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase 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

Patient Guide
https://www.hpra.ie/img/uploaded/swedocuments/896369cd-ec45-4e3a-978f-bacea851002e.pdf
Patient Alert Card
https://www.hpra.ie/img/uploaded/swedocuments/874908fb-698e-472d-91d5-dc3a1f14a8f7.pdf

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Version	Date	Amendment	Approved By
1	15/08/2023		Prof Maccon Keane
1a	26/01/2024	Clarification of EMA MA update	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] [i]EMA indication until 23/11/2023. HSE approved Reimbursement Status: ODMS from 01/06/2023. Centralised funding can be claimed by publicly funded hospitals via the ODMS.

To note the EMA license was amended on 23/11/2023

- *Pembrolizumab, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10*
    - *(HSE approved Reimbursement Status: ODMS from 01/06/2023)*

- *Pembrolizumab, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1*
    - *HSE reimbursement assessment ongoing see here)*