Pembrolizumab, CISplatin and 5-Fluorouracil Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Pembrolizumab is indicated, in combination with CISplatin and 5-fluorouracil, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1.	C76	00706a	Pembrolizumab: ODMS 20/12/2021 CISplatin: Hospital 5-fluorouracil: Hospital

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.

Treatment is administered every 21 days for up to a maximum of 6 cycles in combination with CISplatin and 5-fluorouracil then, followed by maintenance therapy of pembrolizumab every 21 days until disease progression or unacceptable toxicity develops.

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

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab[1]	200mg	IV infusion	100ml 0.9% NaCl over 30 minutes using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.	Every 21 days
2	1	CISplatin	100mg/m^2	IV Infusion	1000ml NaCl 0.9% over 2 hours (Pre and Post hydration therapy required)[2,3]	Every 21 days **cycles 1-6**
2	1-4	5-Flourouracil[4,5]	1,000 mg/m^2/day	IV infusion	1000ml 0.9% NaCl over 22 hours	Every 21 days **cycles 1-6**

[1]Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml

[2]**Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:
- Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins

[3]Mannitol 10% may be used to 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

[4]Alternatively 5-Flourouracil may be administered at 2000mg/m^2 over 48 hours on day 1 and day 2 and then repeated on day 3 and day 4 for a total dose of 4000mg/m^2 over 96 hours

[5]See dose modifications section for patients with identified partial DPD deficiency

ELIGIBILITY:

- Indications as above
- Histologically or cytologically confirmed recurrent or metastatic head and neck squamous cell carcinoma considered incurable by local therapies
- ECOG Status 0-2
- PD-L1 with a combined positive score (CPS) ≥ 1 as demonstrated by a validated assay method
- Adequate haematological, hepatic and renal function

CAUTION:

- History of serious autoimmune disease

EXCLUSIONS:

- Hypersensitivity to pembrolizumab, CISplatin, 5-fluorouracil or any of the excipients
- Has received prior therapy with an anti-PD-1 or anti-PD-L1 antibody
- Progressive disease within six months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC
- 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 or pneumonitis
- Any active clinically significant infection requiring therapy
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus
- Known complete DPD deficiency where used in combination with 5-fluorouracil
- Pregnancy
- Breast feeding

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
- PD-L1 expression using a validated test method
- 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

Regular tests:

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

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 4).
- Any dose modification should be discussed with a Consultant.

CISplatin and 5-fluorouracil dose modifications:

- Treatment may be delayed to allow sufficient time for recovery.
- Treatment should be discontinued after 2 dose reductions, please refer to table 1 for dose levels.
- 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.
- Any dose modification should be discussed with a Consultant.

Table 1: Dose reduction levels for CISplatin and 5-fluorouracil

Drug	Dose level 0	Dose level- 1	Dose level -2	Dose level-3
CISplatin	100mg/m^2	80mg/m^2 (20% decrease)	64mg/m^2 (20% decrease)	Discontinue
5-fluorouracil	1000mg/m^2/day	800mg/m^2/day (20% decrease)	640mg/m^2/day (20% decrease)	Discontinue

Haematological:

Table 2: Dose modification for haematological toxicity induced by CISplatin and 5-fluorouracil

ANC ($x10^9$/L)	Recommended Dose	Platelets ($x10^9$/L)	Recommended Dose
≥1.0	100% dose	≥75	100% dose
0.5-0.99	Delay treatment until recovery to ≥ 1 $x10^9$/L and consider the use of G-CSF as per local policy.	50-75	Delay treatment until recovery to ≥75 x 10^9/L.
<0.5	Delay treatment until recovery to ≥ 1 $x10^9$/L, reduce by 1 dose level, and consider G-CSF as per local policy.	<50	Delay treatment until recovery to ≥75 x 10^9/L and reduce by 1 dose level.

Febrile neutropenia	Number of Occurrences	Recommended Dose
	1	Reduce by 1 dose level and consider the use G-CSF and antibiotics.
	2	Reduce by 1 dose level and consider prophylactic antibiotics for subsequent cycles. The use of G-CSF should be strongly considered as per local policy.
	3	Discontinue platinum

If toxicity does not resolve within 12 weeks of last infusion or if >2 dose level reductions are exceeded both platinum and 5-fluorouracil should be discontinued.

Renal and Hepatic Impairment:

Table 3: Recommended dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
Pembrolizumab	**Mild/ Moderate**	No dose adjustment required.	**Mild**			No dose adjustment required
	Severe	Has not been studied.	**Moderate/Severe**			Has not been studied
CISplatin	**CrCl (ml/min)**	**Dose**	No dose modifications for hepatic impairment			
	≥60	100%				
	45-59	75%				
	<45	Hold CISplatin or delay with additional IV fluids.				
5-Fluorouracil	Consider dose reduction in severe renal impairment only		**Bilirubin**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	Contra-indicated
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2.			

Management of immune-related adverse events:

Table 4: 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 or4 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 4.

Management of adverse events:

Table 5: Dose modification for non-haematological toxicity induced by CISplatin and 5-fluorouracil

Toxicity	Grade	Recommended Dose
Increased creatinine	2-4	Hold until toxicity resolves to Grade 0-1, change treatment of CISplatin to CARBOplatin. Reduce 5-fluorouracil by 1 Dose Level. If toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions are exceeded CISplatin and 5-fluorouracil should be discontinued.
Peripheral neuropathy	≥ 2	Omit CISplatin and consider substituting CISplatin with CARBOplatin.
Mucositis Diarrhoea	2-4	Hold 5-fluorouracil until toxicity resolves to Grade 0-1, reduce by 1 Dose Level. If toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions are exceeded 5-fluorouracil should be discontinued.
Hand-foot syndrome	2	Hold 5-fluorouracil until toxicity resolves to Grade 0-1. If toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions are exceeded 5-fluorouracil should be discontinued.
	3-4	Hold 5-fluorouracil until toxicity resolves to Grade 0-1, reduce by 1 Dose Level. If toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions are exceeded 5-fluorouracil should be discontinued.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Pembrolizumab: Minimal (**Refer to local policy)**
CISplatin: High (**Refer to local policy)**
5-Fluorouracil: Low **(Refer to local policy)**

PREMEDICATIONS:

Hydration pre and post CISplatin administration **(Reference local policy or see recommendations above).**

OTHER SUPPORTIVE CARE: None usually required

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 appropriately.

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.

CISplatin

- **Renal toxicity**: Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage**: These are associated with CISplatin therapy. They should be assessed by history prior to each cycle.

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.
- **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.

- **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.

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 pharmacodynamics activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.
- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimes.
- Concurrent administration of 5-fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- 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

HCP 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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