Pembrolizumab, Oxaliplatin and Capecitabine (Oesophageal or Gastro-oesophageal)

Indication

Previously untreated advanced oesophageal or HER-2 negative gastro-oesophageal adenocarcinoma which expresses PD-L1 with a combined positive score of ≥ 10

(NICE TA737)

ICD-10 codes

Codes prefixed with C15 and C16.

Regimen details

Cycles 1-8

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion
1	Oxaliplatin	130mg/m^2	IV infusion
1-21	Capecitabine	625mg/m^2 BD	PO

All patients must have documented DPYD status and capecitabine doses adjusted accordingly prior to commencing treatment as per local practice.

Cycle 9 onwards – Pembrolizumab maintenance

Day	Drug	Dose	Route
1	Pembrolizumab	200mg every 3 weeks Or 400mg every 6 weeks	IV infusion

Cycle frequency

Pembrolizumab, Oxaliplatin & Capecitabine – 21 days
Pembrolizumab maintenance – 21 or 42 days as above

Number of cycles

Oxaliplatin & Capecitabine: Maximum of 8 cycles
Pembrolizumab: Until unacceptable toxicity, disease progression or to a maximum of 2 years

Administration

Pembrolizumab should be administered in 100mL sodium chloride 0.9% over 30 minutes. Pembrolizumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 5.0µm). After the infusion the line should be flushed with 30mL sodium chloride 0.9%.

Patients should be monitored every 30 minutes during the infusion (blood pressure, pulse and temperature) and for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

Oxaliplatin is administered in 250-500mL glucose 5% over 2 hours. If patients experience laryngo-pharyngeal dyaesthesia (see below), subsequent infusions should be should be given over 4-6 hours.

Oxaliplatin is not compatible with sodium chloride 0.9%. Lines must not be piggybacked or flushed with sodium chloride 0.9% immediately after the infusion.

Patients should be observed closely for platinum hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of oxaliplatin. Facilities for the treatment of hypotension and bronchospasm must be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy: the infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Chlorphenamine 10mg IV may be administered.
Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of oxaliplatin and appropriate therapy.

Oxaliplatin may cause transient paraesthesia of hands and feet and laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patients should be advised on precautions to be taken. This does not require treatment discontinuation or dose reduction but subsequent infusions should be given over 4 - 6 hours.

Capecitabine is available as 150mg and 500mg tablets.
Tablets should be taken after food, within 30 minutes of a meal, and swallowed whole with a glass of water.

Capecitabine should be banded as per national dose banding: https://www.england.nhs.uk/publication/national-dose-banding-table-capecitabine/

Pre-medication

Patients who have previously experienced Grade 1 or 2 platinum hypersensitivity should receive the following premedication:
- 45 minutes prior to Oxaliplatin: Dexamethasone 20mg IV
- 30 minutes prior to Oxaliplatin: Chlorphenamine 10mg IV and consider H2 antagonist as per local practice

Patients who develop peripheral neuropathy may be considered for calcium gluconate 1g and magnesium sulphate 1g given together in 250mL 5% glucose IV over 20 minutes pre- and post-oxaliplatin infusion. Caution is required in giving this treatment to patients with known hypercalcemia or those receiving therapy with digoxin or thiazide diuretics.

Emetogenicity

This regimen has a moderate emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.
Loperamide if required.

Extravasation

Pembrolizumab is neutral (Group 1)
Oxaliplatin is an exfoliant (Group 4).

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
Thyroid function	14 days
Glucose	14 days
Cortisol	At consultant discretion

DPYD status must be available prior to starting Capecitabine treatment as per local practice.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Calcium	7 days
Thyroid function	6 weekly
Glucose	As clinically indicated
Cortisol	As clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Bilirubin	< 1.5 x ULN
Creatinine Clearance (CrCl)	> 50mL/min

Dose modifications

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Dose**
≥ 1.0	and	≥ 75	100%
0.5 - < 1.0	or	50-74	Withhold treatment. Delay until count recovery Resume with Oxaliplatin 100mg/m^2, Capecitabine 100% dose

- **Renal impairment**

Pembrolizumab: The safety and efficacy of pembrolizumab has not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment.
Discuss with consultant if CrCl <30mL/min.

CrCl (mL/min)	**Oxaliplatin dose**	**Capecitabine dose**
> 50	100%	100%
30-49	75%	75%
< 30	omit	contraindicated

- **Hepatic impairment**

Pembrolizumab: The safety and efficacy of pembrolizumab has not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. See below for management of hepatitis.

Oxaliplatin: Little information available. Probably no dose reduction necessary, consultant decision.

Capecitabine: Lack of information available. In patients with mild to moderate hepatic dysfunction due to liver metastases (bilirubin < 3 x ULN and/or AST/ALT < 5 x ULN) no dose reduction is usually necessary – discuss with consultant

- **Other toxicities**

Pembrolizumab:
Patients must be advised to seek specialist advice if they experience side effects as these can worsen rapidly. Immune reactions may occur during or after completion of treatment.

Toxicity	Definition	Action
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 or recurrent grade 3	Permanently discontinue pembrolizumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to ≤ grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue pembrolizumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 3 (creatinine > 3 x ULN)	Permanently discontinue pembrolizumab
Endocrine	Symptomatic hypophysitis	Withhold until symptoms resolve to ≤ grade 1
	Type 1 diabetes with grade > 3 hyperglycaemia (glucose > 13.9 mmol/L) or ketoacidosis	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hyperthyroidism ≥ grade 3	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hypothyroidism	Continue and manage with replacement therapy
Hepatitis	AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ grade 1
	AST/ALT > 5 x ULN or Bilirubin > 3 x ULN	Permanently discontinue pembrolizumab
	If liver metastasis with baseline AST/ALT 3-5 x ULN: - If AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until resolves to ≤ grade 1
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome	Permanently discontinue

Pembrolizumab should be permanently discontinued if:
- Grade 4 toxicity (except for endocrinopathies that are controlled with replacement hormones)
- Corticosteroid dosing cannot be reduced to ≤10 mg prednisolone or equivalent per day within 12 weeks
- Treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose
- Any event occurs a second time at Grade ≥ 3 severity

Capecitabine:
Other toxicities should be managed by symptomatic treatment and/or dose modification (i.e. by treatment interruption or undertaking a dose reduction). Once the dose has been reduced, it should not be increased at a later time.

Dose modifications should be made as per the following table:

Toxicity grade	1st occurrence	2nd occurrence	3rd occurrence	4th occurrence
0-1	100%	100%	100%	100%
2	Delay then 100%	Delay then 75%	Delay then 50%	Discontinue
3	Delay then 75%	Delay then 50%	Discontinue	
4	Delay then 50%	Discontinue		

Any delays should be until the toxicity has resolved to grade 0-1.

Oxaliplatin:
Neurological toxicity:
If neurological symptoms occur, use the following oxaliplatin dose adjustments:

Toxicity grade	Oxaliplatin dose
1	100%
2 (persisting until next cycle)	100mg/m^2
3 (>7 days but resolved before next cycle)	100mg/m^2
3 (persisting until next cycle) or 4	Discontinue

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Allergic reactions
Neurotoxicity
Cardiomyopathy
Nephrotoxicity
Severe toxicity due to DPD deficiency
Pneumonitis
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Laryngopharyngeal dysaesthesia
Nausea and vomiting
Diarrhoea
Stomatitis and mucositis
Palmar-plantar erythema

Alopecia
Fatigue
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Rash, pruritus
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism

- **Other side effects**

Dysguesia
Arthralgia

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Pembrolizumab:
Corticosteroids: use of systemic corticosteroids at baseline, 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.

Oxaliplatin:
Avoid nephrotoxic agents as these may increase toxicity of oxaliplatin.

Capecitabine:
Folinates: Avoid concomitant use of folinic and folic acid – enhanced toxicity of capecitabine.

Co-trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.

Phenytoin and fosphenytoin – toxicity has occurred during concomitant capecitabine therapy – monitor levels regularly.

Sorivudine and its analogues – co-administration causes increased toxicity which may be fatal.

Allopurinol – A decrease in capecitabine activity has been shown when taken in combination of allopurinol. Avoid if possible.

Antacids – the use of antacids with capecitabine can decrease absorption – avoid.

Additional comments

Dose related peripheral sensory neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

Women of child bearing potential should use effective contraception during treatment and for at least 4 months after the last dose of Pembrolizumab.

References

- Summary of Product Characteristics Oxaliplatin (Accord) accessed 26 May 2022 via www.medicines.org.uk
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- Summary of Product Characteristics Pembrolizumab (MSD) accessed 26 May 2022 via www.medicines.org.uk
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- Sun, J-M. *et al.* Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021 398(10302):759-771

Written/reviewed by: Dr E Cattell (Consultant Oncologist, Taunton and Somerset NHS Foundation Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

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