Pembrolizumab, oxaliplatin & capecitabine

Indication

First-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10

Untreated HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1

Regimen details

Cycles 1-6:

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion
		Or 395mg	Subcutaneous
1	Oxaliplatin	130mg/m^2	IV infusion
1-21	Capecitabine	625mg/m^2 BD	PO

Cycle 7 onwards:

Day	Drug	Dose	Route
1	Pembrolizumab	400mg	IV infusion
		Or 790mg	Subcutaneous

Cycle frequency

Cycles 1-6: 21 days
Cycle 7 onwards: 42 days

Number of cycles

Oxaliplatin and capecitabine should be stopped after 6 cycles.
Pembrolizumab is continued until radiological or clinical progression, unacceptable toxic effects, for up to 2 years.

Administration

Subcutaneous pembrolizumab

Inject into the subcutaneous tissue of the thigh or abdomen, avoiding the 5 cm area around the navel. Do not inject into skin that is damaged, sore, bruised, scarred, scaly, or has red patches. Rotate injection sites for subsequent injections.

- Inject 395mg over 1 minute
- Inject 790mg over 2 minutes

Intravenous pembrolizumab

Pembrolizumab is administered in 100ml 0.9% sodium chloride over 30 minutes prior to chemotherapy. The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm

Oxaliplatin

Oxaliplatin is administered in 250-500mL glucose 5% over 2 hours. If patients experience laryngo-pharyngeal dyaesthesia (see below), subsequent infusions 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 well advised on precautions to be taken. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

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

Pre-medication
None routinely given

Emetogenicity
This regimen has a moderate emetogenic potential

Additional supportive medication
None required routinely

Extravasation
Oxaliplatin is an exfoliant (group 4).
Pembrolizumab is neutral (group 1)

Investigations – pre first cycle
See standard list of pre-SACT bloods

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Patients require DPD testing prior to administration. Dose adjustments should be made in accordance with local DPD policy.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	48 hours
U+E (including creatinine)	48 hours
LFTs	48 hours
Magnesium	48 hours
Calcium	48 hours

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)	**Oxaliplatin Dose**	**Capecitabine dose**
≥ 1.0	and	≥ 75	100% original dose	100% original dose
0.5 - < 1.0	or	50-74	Delay treatment until count recovery 80% original dose on restart.	Stop and delay until count recovery.

- **Renal impairment**

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

- **Hepatic impairment**

Capecitabine:

Bilirubin	**Oxaliplatin dose**	**Capecitabine dose**
1.5 – x2 ULN	Little information available. Probably no dose reduction necessary, consultant decision	75% original dose
>x2 ULN		Omit

- **Other toxicities**

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

Immune related adverse events (IRAEs)

Consult network guidance for management of IRAEs
https://www.healthierlsc.co.uk/application/files/8916/8744/0377/ESMO_IO_Toxicity_Treatment_Guidance.pdf

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

- **Serious side effects**

Immune related adverse events (IRAEs)
Myelosuppression
Infertility
Allergic reactions
Neurotoxicity
Nephrotoxicity
Severe toxicity due to DPD deficiency (see comments below)

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Diarrhoea
Stomatitis and mucositis
Palmar-plantar erythema
Fatigue

- **Other side effects**

Dysguesia
Headache
Dizziness

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.

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 as been shown when taken in combination of allopurinol. Avoid if possible.
Antacids – the use of antacids with capecitabine can decrease absorption – avoid.

Additional comments

This regimen is contraindicated if known or suspected dihydropyrimidine dehydrogenase (DPD) deficiency

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.

References

- Summary of Product Characteristics Oxaliplatin via www.medicines.org.uk
- Summary of Product Characteristics Capecitabine via www.medicines.org.uk
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.
- https://www.nice.org.uk/guidance/indevelopment/gid-ta10613

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RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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