PEMBROLIZUMAB (Keytruda) OXALIPLATIN CAPECITABINE

INDICATION (ICD10) C15, C16

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

For previously untreated advanced oesophageal or HER-2 negative gastrooesophageal adenocarcinoma either of which expresses PD-L1 with a combined positive score of ≥10 where the following criteria have been met:

2. The prescribing clinician is fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to anti-PD-1 or anti-PD-L1 treatments including pneumonitis, colitis, nephritis, endocrinopathies, hepatitis and skin toxicity.
3. Has a histologically- or cytologically-confirmed diagnosis of oesophageal cancer (squamous or adenocarcinoma) or HER-2 negative adenocarcinoma of the gastro-oesophageal junction.
4. Has locally advanced unresectable or metastatic disease.
5. An approved and validated test has demonstrated that the tumour has a PD-L1 expression with a combined positive score (CPS) of ≥10.
6. Has not received any previous systemic therapy for locally advanced unresectable or metastatic disease i.e. that pembrolizumab plus chemotherapy will be 1st line systemic therapy for locally advanced unresectable or metastatic disease.
- has not received any previous systemic therapy for oesophageal cancer or adenocarcinoma of the gastro-oesophageal junction.
- was previously treated with neoadjuvant chemotherapy for oesophageal cancer or HER-2 negative adenocarcinoma of the gastro-oesophageal junction and underwent surgery and has since had disease progression.
- was previously treated with concurrent chemo-radiotherapy for oesophageal cancer or HER-2 negative adenocarcinoma of the gastro-oesophageal junction and has since had disease progression.
7. Has not received prior treatment with any antibody which targets PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4).
8. ECOG performance status (PS) of 0 or 1 and is fit for platinum and fluoropyrimidine-based chemotherapy in combination with pembrolizumab.
9. Has no symptomatically active brain metastases or leptomeningeal metastases.
10. Pembrolizumab will be administered at a dose of either 200mg 3-weekly or 400mg 6-weekly initially in combination with platinum and fluoropyrimidine-based chemotherapy and subsequently as monotherapy.
11. The chemotherapy used in combination with pembrolizumab will be both platinum and fluoropyrimidine-based - oxaliplatin plus capecitabine, - oxaliplatin plus modified de Gramont regimen, - cisplatin plus capecitabine, - cisplatin plus infused 5-fluorouracil, - another regimen
12. Pembrolizumab will be stopped at whichever of the following events occurs first: disease progression or unacceptable toxicity or withdrawal of patient consent or after 2 years of treatment (or after 35 x 3-weekly cycles or its equivalent if 6-weekly dosing is used).
Note: the 2 year stopping rule for pembrolizumab in this indication was a key part of the company submission to NICE of the clinical and cost effectiveness of pembrolizumab in this indication.
Note: once pembrolizumab is stopped after 2 years of treatment, it cannot be re-started.
13. A formal medical review as to how pembrolizumab plus chemotherapy is being tolerated and whether pembrolizumab should continue or not will be scheduled to occur at least by the end of the second 3-weekly cycle of treatment.
14. When a treatment break of more than 3 months beyond the expected 3- or 6-weekly cycle length is needed, I will complete a treatment break approval form to restart treatment, including indicating as appropriate if the patient had an extended break because of Covid-19.
15. Pembrolizumab will otherwise be used as set out in its Summary of Product Characteristics (SPC) with the exception of criterion 12.

REGIMEN

Cycles 1 to 4

Day 1	PEMBROLIZUMAB	200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
	OXALIPLATIN	130mg/m^2 in 500ml* glucose 5% IV infusion over 2 hours
Days 1 to 21	CAPECITABINE	625mg/m^2 twice daily (1250mg/m^2/day) oral continuously

Cycle 5

Day 1	PEMBROLIZUMAB	400mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
	OXALIPLATIN	130mg/m^2 in 500ml* glucose 5% IV infusion over 2 hours
Days 1 to 21	CAPECITABINE	625mg/m^2 twice daily (1250mg/m^2/day) oral continuously

Cycle 6

Day 1	OXALIPLATIN	130mg/m^2 in 500ml* glucose 5% IV infusion over 2 hours
Days 1 to 21	CAPECITABINE	625mg/m^2 twice daily (1250mg/m^2/day) oral continuously

Cycles 7, 9, 11, 13,15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35

Day 1	PEMBROLIZUMAB	400mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes

*oxaliplatin doses 55mg to 200mg in 250ml glucose 5%

CYCLE FREQUENCY AND NUMBER OF CYCLES

Oxaliplatin Capecitabine every 21 days for 6 cycles
Pembrolizumab every 21 days for 4 cycles then every 42 days for up to 2 years

ADMINISTRATION

Tablets should be taken 12 hours apart.
Swallowed with water within 30 minutes after a meal, or dissolve in 200ml luke warm water, stir thoroughly (squash may be added if unpalatable).

ANTI-EMETICS

Moderately emetogenic day 1 cycles 1 to 6
Low emetogenic risk days 2 to 21 cycles 1 to 6
Minimal emetogenic risk day 1, 7, 9, 11, 13,15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35

CONCURRENT MEDICATION REQUIRED

Capecitabine	Mouth and bowel support eg Loperamide, benzydamine mouthwash
Oxaliplatin	Flush with glucose 5% after infusion

EXTRAVASATION AND TYPE OF LINE / FILTERS

Oxaliplatin – exfoliant
Pembrolizumab – neutral
Use low protein binding 0.2 to 5micron in-line or add-on filter for pembrolizumab

Peripheral or central line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs and creatinine every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Serum creatinine
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
ECG (possible ECHO) required if patient has preexisting cardiac disease
DPYD test
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Capecitabine	Palmar plantar (handfoot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds Diarrhoea – treat with loperamide or codeine Cardiotoxicity – monitor cardiac function. To minimise risk of anthracycline induced cardiac failure signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue. All patients should be told to report any cardiac symptoms immediately and should be told to stop the medication immediately if any suspicion of cardiac problems. Stomatitis
Oxaliplatin	Peripheral sensory neuropathy and laryngeal spasm – avoid cold drinks and touching cold items
Pembrolizumab	Immune related toxicities

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Capecitabine	Brivudine and analogues should be avoided Warfarin Phenytoin Allopurinol

DOSE MODIFICATIONS

Haematological

Platelets ≥100x10^9/L neutrophils ≥1.5x10^9/L	Give 100% dose
Platelets 50-100x10^9/L neutrophils 0.5-1.5x10^9/L	Stop capecitabine, delay oxaliplatin until recovery. Restart capecitabine at 100% dose give 75% oxaliplatin doses on subsequent cycles
Platelets 25-49x10^9/L neutrophils <0.5x10^9/L	Stop capecitabine, delay oxaliplatin until recovery. Restart capecitabine at 100% dose, give 50% 75% oxaliplatin doses on subsequent cycles
Platelets <25x10^9/L	Stop capecitabine, delay oxaliplatin until recovery. Restart capecitabine at 100% dose and oxaliplatin 75%

Non-haematological

Capecitabine

Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and handfoot syndrome.

Toxicity can 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.

When capecitabine is stopped for toxicity, the doses are omitted and not delayed.

Toxicity Grades	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 2 - 1st appearance	Interrupt until resolved to grade 0-1	100%
Grade 2 - 2nd appearance	Interrupt until resolved to grade 0-1	75%
Grade 2 - 3rd appearance	Interrupt until resolved to grade 0-1	50%
Grade 2 - 4th appearance	Discontinue treatment permanently	Not applicable
Grade 3 - 1st appearance	Interrupt until resolved to grade 0-1	75%
Grade 3 - 2nd appearance	Interrupt until resolved to grade 0-1	50%
Grade 3 - 3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4 - 1st appearance	Discontinue permanently OR if physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
Grade 4 - 2nd appearance	Discontinue treatment permanently	Not applicable

Oxaliplatin

If patients develop acute laryngopharyngeal dysaesthesia infuse the next cycle over 6 hours.

If symptoms persist give 80% dose.

If persistent sensory symptoms occur, withdraw treatment

Pembrolizumab

Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline.

If the drug-related toxicity does not resolve to grade 0-1 within 12 weeks after onset of toxicity, discontinuation is recommended.

Hepatic impairment

Capecitabine

Bilirubin of >3xULN or ALT/AST >2.5xULN	Interrupt Capecitabine Treatment may be resumed when bilirubin decreases to <3xULN or hepatic aminotransferases decrease to <2.5xULN.

Renal impairment

Capecitabine

CrCl (ml/min) >50	give 100% dose
CrCl (ml/min) 30-50	give 75% dose
CrCl (ml/min) <30	contraindicated

REFERENCES

Blueteq