PEMBROLIZUMAB (Keytruda) OXALIPLATIN Modified de Gramont

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 and 4

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
OXALIPLATIN 85mg/m^2 in 250ml* glucose 5% IV infusion over 2 hours
CALCIUM LEVOFOLINATE 175mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin via a Y site placed immediately before the injection site
FLUOROURACIL 400mg/m^2 IV bolus
FLUOROURACIL 2400mg/m^2 continuous IV infusion over 46 hours

Cycles 2 and 5

Day 1 OXALIPLATIN 85mg/m^2 in 250ml* glucose 5% IV infusion over 2 hours
CALCIUM LEVOFOLINATE 175mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin via a Y site placed immediately before the injection site
FLUOROURACIL 400mg/m^2 IV bolus
FLUOROURACIL 2400mg/m^2 continuous IV infusion over 46 hours
Day 8 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes

Cycles 6, 8, 9, 11 and 12

Day 1 OXALIPLATIN 85mg/m^2 in 250ml* glucose 5% IV infusion over 2 hours
CALCIUM LEVOFOLINATE 175mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin via a Y site placed immediately before the injection site
FLUOROURACIL 400mg/m^2 IV bolus
FLUOROURACIL 2400mg/m^2 continuous IV infusion over 46 hours

Cycles 7 and 10

Day 1 PEMBROLIZUMAB 400mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
OXALIPLATIN 85mg/m^2 in 250ml* glucose 5% IV infusion over 2 hours
CALCIUM LEVOFOLINATE 175mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin via a Y site placed immediately before the injection site
FLUOROURACIL 400mg/m^2 IV bolus
FLUOROURACIL 2400mg/m^2 continuous IV infusion over 46 hours

Cycles 13,16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49 and 52

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

*oxaliplatin doses 225mg to 395mg in 500ml glucose 5%

NB Calcium levofolinate is not the same as calcium folinate (calcium leucovorin).
Calcium levofolinate is a single isomer of folinic acid and the dose is generally half that of calcium folinate. If calcium levofolinate is not available calcium folinate (leucovorin) may be used instead.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Oxaliplatin Fluorouracil every 14 days for 12 cycles
Pembrolizumab every 21 days for 4 doses then every 42 days for up to 2 years

ADMINISTRATION

Tablets should be taken 12 hours apart.

ANTI-EMETICS

Moderately emetogenic risk day 1 cycles 1 to 12
Minimal emetogenic risk day 8 cycles 2 and 5, day 1 cycles 13,16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49 and 52

CONCURRENT MEDICATION REQUIRED

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

EXTRAVASATION AND TYPE OF LINE / FILTERS

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

Central line – Oxaliplatin Fluorouracil
Peripheral line - pembrolizumab

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

Fluorouracil	Palmar plantar (handfoot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds Diarrhoea – treat with loperamide or codeine Cardiotoxicity – monitor cardiac function. Special attention is advisable in treating patients with a history of heart disease, arrhythmias or angina pectoris or those who develop chest pain during treatment with fluorouracil. 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)

Fluorouracil	Cimetidine slightly increases exposure to fluorouracil Metronidazole increased toxicity Phenytoin concentration increased Warfarin

DOSE MODIFICATIONS

Haematological

If neutrophils <1.5x10^9/L or platelets <100x10^9/L delay 1 week, only treat when neutrophils and platelets are above these limits.
If grade 4 neutropenia consider giving 50% oxaliplatin and fluorouracil in palliative disease.
If >1 delay or 1 delay ≥2 weeks reduce all the oxaliplatin and fluorouracil doses to give 80% for future cycles. Dose reductions may be made at the Clinician's discretion.

Non-haematological

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

Fluorouracil
Significantly impaired hepatic function eg bilirubin >50micromol/L may be a sign of disease progression and require cessation of, or change in, treatment. Always discuss deteriorating liver function with consultant.

Bilirubin >85micromol/L	not recommended

Renal impairment

Fluourouracil

CrCl >30ml/min	give 100% dose
CrCl <30ml/min	consider dose reduction

Oxaliplatin

CrCl >30ml/min	give 100% dose
CrCl <30ml/min	Dose reduce (consider 50% of original dose)

REFERENCES

Blueteq criteria