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/) (PEMB15) (PEMB29)

1. Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for previously untreated locally advanced or metastatic oesophageal or HER-2 negative gastrooesophageal adenocarcinoma either of which expresses PD-L1 with a combined positive score of ≥10. Has no symptomatically active brain metastases or leptomeningeal metastases. PS 0 or 1. (TA737)
2. Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for previously untreated locally advanced unresectable or metastatic disease HER-2 negative gastric or gastrooesophageal junction adenocarcinoma either of which expresses PD-L1 with a combined positive score of 1 or more. Has no symptomatically active brain metastases or leptomeningeal metastases. PS 0 or 1 (TA997)

REGIMEN (SC) (pembrolizumab before chemotherapy)

Cycles 1 and 4

Day 1 PEMBROLIZUMAB 395mg subcutaneous* (2.4ml) over 1 minute
OXALIPLATIN 85mg/m^2 in #ml glucose 5% IV infusion over 2 hours
CALCIUM FOLINATE 350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
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 #ml glucose 5% IV infusion over 2 hours
CALCIUM FOLINATE 350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
FLUOROURACIL 400mg/m^2 IV bolus
FLUOROURACIL 2400mg/m^2 continuous IV infusion over 46 hours
Day 8 PEMBROLIZUMAB 395mg subcutaneous* (2.4ml) over 1 minute

Cycles 3, 6, 8, 9, 11 and 12

Day 1 OXALIPLATIN 85mg/m^2 in #ml glucose 5% IV infusion over 2 hours
CALCIUM FOLINATE 350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
FLUOROURACIL 400mg/m^2 IV bolus
FLUOROURACIL 2400mg/m^2 continuous IV infusion over 46 hours

Cycles 7 and 10

Day 1 PEMBROLIZUMAB 790mg subcutaneous* (4.8ml) over 2 minutes
OXALIPLATIN 85mg/m^2 in #ml glucose 5% IV infusion over 2 hours
CALCIUM FOLINATE 350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
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 790mg subcutaneous* (4.8ml) over 2 minutes

*Into the thigh or abdomen, avoiding the 5cm area around the navel

REGIMEN (IV) (pembrolizumab before chemotherapy)

Cycles 1 and 4

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
OXALIPLATIN 85mg/m^2 in #ml glucose 5% IV infusion over 2 hours
CALCIUM FOLINATE 350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
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 #ml glucose 5% IV infusion over 2 hours
CALCIUM FOLINATE 350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
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 3, 6, 8, 9, 11 and 12

Day 1 OXALIPLATIN 85mg/m^2 in #ml glucose 5% IV infusion over 2 hours
CALCIUM FOLINATE 350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
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 #ml glucose 5% IV infusion over 2 hours
CALCIUM FOLINATE 350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
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

diluent and diluent volume for dose prescribed as per national standardised product specification

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

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 (once pembrolizumab is stopped after 2 years of treatment, it cannot be re-started).
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.

ADMINISTRATION

Pembrolizumab SC - withdraw the required volume using a transfer needle (18-21G recommended). To avoid needle clogging, change the needle to a 25-30G, 13 mm hypodermic injection needle immediately prior to SC injection.

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

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 (or as specified in Trust guideline)
Random glucose every cycle
Hba1c baseline
DPYD (dihydropyrimidine dehydrogenase) 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 - pneumonitis, colitis or hepatitis etc Pembrolizumab SC skin reactions at site of administration route

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 4 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.	
If hepatic function is impaired, the recommended dose can be reduced to give 50% to 70% dose, but no need for dose adjustment is expected in mild and moderate (without renal impairment).	
Bilirubin >85micromol/L	not recommended

Oxaliplatin
No dose adjustment is needed.

Pembrolizumab
No dose adjustment is needed.

Renal impairment

Fluorouracil

If renal function is impaired, the recommended dose can be reduced to give 50% to 70% dose, but no need for dose adjustment is expected.

Oxaliplatin

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

Pembrolizumab
No dose adjustment is needed.

REFERENCES

1. CDF list