PEMBROLIZUMAB (Keytruda) OXALIPLATIN CAPECITABINE (OX)

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. 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 to 4

Day 1	PEMBROLIZUMAB	395mg subcutaneous* (2.4ml) over 1 minute
	OXALIPLATIN	130mg/m^2 in #ml 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 and 7

Day 1	PEMBROLIZUMAB	790mg subcutaneous* (4.8ml) over 2 minutes
	OXALIPLATIN	130mg/m^2 in #ml 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 and 8

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

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

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 to 4

Day 1	PEMBROLIZUMAB	200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
	OXALIPLATIN	130mg/m^2 in #ml 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 and 7

Day 1	PEMBROLIZUMAB	400mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
	OXALIPLATIN	130mg/m^2 in #ml 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 and 8

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

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

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

CYCLE FREQUENCY AND NUMBER OF CYCLES

Oxaliplatin Capecitabine every 21 days for 6-8 cycles
Pembrolizumab every 21 days for 4 cycles 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

Capecitabine 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).
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 day 1 cycles 1 to 6-8
Low emetogenic risk days 2 to 21 cycles 1 to 6
Minimal emetogenic risk day 1 cycles (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 IV – neutral
Use low protein binding 0.2 to 5micron in-line or add-on filter for pembrolizumab IV

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 (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

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 - 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)

Capecitabine	Brivudine and analogues should be avoided Warfarin Phenytoin Allopurinol

DOSE MODIFICATIONS
DPYD variant identified follow national or local DPD dose modification guidelines.

Haematological

Platelets $\geq 100 \times 10^9$/L neutrophils $\geq 1.5 \times 10^9$/L	Give 100% dose
Platelets $50\text{-}100 \times 10^9$/L neutrophils $0.5\text{-}1.5 \times 10^9$/L	Stop capecitabine, delay oxaliplatin until recovery. Restart capecitabine at 100% dose give 75% oxaliplatin doses on subsequent cycles
Platelets $25\text{-}49 \times 10^9$/L neutrophils $< 0.5 \times 10^9$/L	Stop capecitabine, delay oxaliplatin until recovery. Restart capecitabine at 100% dose, give 75% oxaliplatin doses on subsequent cycles
Platelets $< 25 \times 10^9$/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 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

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.

Oxaliplatin

No dose adjustment is needed.

Pembrolizumab

No dose adjustment is needed.

Renal impairment

Capecitabine

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

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