PEMBROLIZUMAB (Keytruda) CISPLATIN 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/) (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.

REGIMEN (SC) (recommended regimen)

Cycles 1 to 4 **(pembrolizumab before chemotherapy)**

Day 1	PEMBROLIZUMAB	395mg subcutaneous* (2.4ml) over 1 minute
	Prehydration	
	CISPLATIN	80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
	Posthydration	
Days 1 to 21	CAPECITABINE	625mg/m^2 twice daily (1250mg/m^2/day) oral continuously

Cycle 5

Day 1	PEMBROLIZUMAB	790mg subcutaneous* (4.8ml) over 2 minutes
	Prehydration	
	CISPLATIN	80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
	Posthydration	
Days 1 to 21	CAPECITABINE	625mg/m^2 twice daily (1250mg/m^2/day) oral continuously

Cycle 6

Day 1	Prehydration	
	CISPLATIN	80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
	Posthydration	
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 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)

Cycles 1 to 4 **(pembrolizumab before chemotherapy)**

Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride 0.9% IV infusion over 30 minutes
Prehydration
CISPLATIN 80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
Posthydration
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
Prehydration
CISPLATIN 80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
Posthydration
Days 1 to 21 CAPECITABINE 625mg/m^2 twice daily (1250mg/m^2/day) oral continuously

Cycle 6

Day 1 Prehydration
CISPLATIN 80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
Posthydration
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 and 35

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

CYCLE FREQUENCY AND NUMBER OF CYCLES

Cisplatin Capecitabine every 21 days for 6 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

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

Highly emetogenic day 1 cycles 1 to 6
Low emetogenic risk days 2 to 14 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
Cisplatin	Ensure adequate pre and post hydration. If urine output is <100ml/hour or if patient gains >2kg in weight during IV administration post cisplatin give 20-40mg furosemide PO/IV.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cisplatin – exfoliant
Pembrolizumab IV – 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 (or as specified in Trust guideline)
Hba1c baseline
Random glucose every cycle
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
Cisplatin	Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities.
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
Cisplatin	Aminoglycosides increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests as required. Cisplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

DOSE MODIFICATIONS

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

Haematological

ANC ≥1x10^9/L and/or platelets ≥75x10^9/L give 100% dose
ANC 0.5-0.99x10^9/L and/or platelets 50-74x10^9/L OR any episode of neutropenic sepsis during the previous cycle. Stop chemotherapy until recovery. Restart with 75% dose cisplatin and capecitabine.
ANC <0.5x10^9/L and/or platelets <50x10^9L. Stop chemotherapy until recovery. Restart with 50% dose cisplatin and capecitabine.

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

Cisplatin
If patient complains of tinnitus, tingling of fingers and/or toes, discuss with SpR or Consultant before administration.
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.

Cisplatin
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

Cisplatin

CrCl >60ml/min	give 100% dose
CrCl 50-59ml/min	give 75% dose
CrCl 40-49ml/min	give 50% dose (curative intent) not recommended (palliative intent)
CrCl <40ml/min	not recommended

Pembrolizumab
No dose adjustment is needed.

REFERENCES
1. CDF list