PEMBROLIZUMAB (Keytruda) CISPLATIN FLUOROURACIL

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 for previously untreated locally advanced unresectable or metastatic oesophageal or HER-2 negative gastro-oesophageal adenocarcinoma either of which expresses PD-L1 with a combined positive score of ≥10. No symptomatically active brain metastases or leptomeningeal metastases. PS 0 or 1 and is fit for platinum and fluoropyrimidine-based chemotherapy in combination with pembrolizumab. (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
	Prehydration	
	CISPLATIN	80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
	Posthydration	
	FLUOROURACIL	4000mg/m^2 over 96 hours via an infusor

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	
	FLUOROURACIL	4000mg/m^2 over 96 hours via an infusor

Cycle 6

Day 1	Prehydration	
	CISPLATIN	80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
	Posthydration	
	FLUOROURACIL	4000mg/m^2 over 96 hours via an infusor

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) (pembrolizumab before chemotherapy)

Cycles 1 to 4

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
FLUOROURACIL 4000mg/m^2 over 96 hours via an infusor

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
FLUOROURACIL 4000mg/m^2 over 96 hours via an infusor

Cycle 6

Day 1 Prehydration
CISPLATIN 80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
Posthydration
FLUOROURACIL 4000mg/m^2 over 96 hours via an infusor

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 Fluorouracil every 21 days for 6 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).
Formal medical review as to how pembrolizumab plus chemotherapy is being tolerated and whether pembrolizumab should continue or not 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

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

CONCURRENT MEDICATION REQUIRED

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.
Fluorouracil	Mouth and bowel support eg Loperamide, benzydamine mouthwash

EXTRAVASATION AND TYPE OF LINE / FILTERS

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

Central line – Cisplatin 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)
Hba1c baseline
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

Cisplatin	Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities.
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
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)

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

DOSE MODIFICATIONS

Haematological

If neutrophils <1.5x10^9/L and/or the platelet count <100x10^9/L delay the second course by one week, recheck blood count.
Then if satisfactory (>1.5x10^9/L and >100x10^9/L) give 75% dose cisplatin and fluorouracil
If not satisfactory delay by a further week and recheck blood count, if satisfactory (>1.5x10^9/L and >100x10^9/L) then give 50% dose cisplatin and fluorouracil.
If still unsatisfactory after 2 week delay chemotherapy should be discontinued.

Non-haematological

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

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

Pembrolizumab
No dose adjustment is needed.

Renal impairment

Cisplatin

CrCl >60ml/min	give 100% dose
CrCl 45-60ml/min	give 75% dose

Fluourouracil

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

Pembrolizumab
No dose adjustment is needed.

REFERENCES

Blueteq criteria