DURVALUMAB (Imfinzi) GEMCITABINE CISPLATIN

INDICATION (ICD10) C67

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/ (DUR8)

1. Durvalumab with gemcitabine and cisplatin for neoadjuvant treatment then alone for adjuvant treatment of previously untreated (no prior chemotherapy or immunotherapy) muscle-invasive bladder cancer. Has a histologically or cytologically determined diagnosis of resectable muscle-invasive (T2-T4a and N0 or N1 and M0) bladder cancer, and the intent is to treat the patient with a radical cystectomy following systemic neo-adjuvant treatment. PS 0 or 1. (TA1138)

REGIMEN

Cycles 1 to 4 (neoadjuvant)

Day 1	DURVALUMAB	1500mg in #ml sodium chloride 0.9% IV infusion over 60 minutes
	GEMCITABINE	1000mg/m^2 in #ml sodium chloride 0.9%) IV infusion over 30 minutes
	Prehydration	
	CISPLATIN	70mg/m^2* in #ml sodium chloride 0.9% IV infusion over 2 hours
	Posthydration	
Day 8	GEMCITABINE	1000mg/m^2 in #ml sodium chloride 0.9% IV infusion over 30 minutes

Cycles 5 to 12 (adjuvant)

Day 1	DURVALUMAB	1500mg in #ml sodium chloride 0.9% IV infusion over 60 minutes

*or split cisplatin dose (35mg/m^2 on days 1 and 8) for patients with lower GFR
diluent volume for dose prescribed as per national standardised product specification or licensed dose

CYCLE FREQUENCY AND NUMBER OF CYCLES

Neoadjuvant - every 21 days for up to 4 cycles (then prescribe separate cycles 5-12 adjuvant regimen)
Adjuvant – every 28 days for up to 8 cycles

ANTI-EMETICS

High risk day 1 cycles 1 to 4
Low risk day 8 cycles 1 to 4
Minimal risk cycles 5 to 12

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.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cisplatin – exfoliant
Durvalumab - neutral
Gemcitabine – neutral

Durvalumab – Use low protein binding 0.2 or 0.22micron in-line or add-on filter
Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC every dose, U&E including Mg^{++}(>0.4), LFTs and creatinine every cycle
Neutrophils x 10^9/L ≥1.5 on day 1 or ≥1.0 on day 8
Platelets x 10^9/L ≥100
GFR assessed using EDTA result or calculated creatinine clearance at the Consultant's discretion.
TSH at baseline then every 8 weeks or as clinically indicated
Baseline HbA1c then every 3 months
Random blood glucose,
Baseline random cortisol then every cycle
Virology before cycle 1 if not previously checked
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.
Durvalumab	Immune related toxicities
Gemcitabine	Diarrhoea – see dose modifications, treat with loperamide or codeine Mucositis – see dose modifications, use routine mouthcare

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.

DOSE MODIFICATIONS

Haematological

Gemcitabine

Neutrophils >1.5x10^9/L and platelets >100x10^9/L	give 100% dose
Day 1 Neutrophils <1.5x10^9/L or platelets <100x10^9/L	delay treatment (day 1)
Day 8 Neutrophils <1.0x10^9/L or platelets <100x10^9/L	omit treatment (day 8)

Non-haematological

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

Durvalumab
Immune-related adverse reactions - refer to Acute Oncology Initial Management guidelines

Gemcitabine

Diarrhoea and/or mucositis grade 2	omit until toxicity resolved then restart at 100% dose
Diarrhoea and/or mucositis grade 3	omit until toxicity resolved then restart at 75% dose
Diarrhoea and/or mucositis grade 4	omit until toxicity resolved then restart at 50% dose

Hepatic impairment

Cisplatin

No need for dose adjustment is expected

Durvalumab

No dose adjustment is needed for patients with hepatic impairment.

Gemcitabine

Bilirubin >27µmol/L	initiate treatment with 80% dose

Renal impairment

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

Durvalumab

No dose adjustment is needed for patients with hepatic impairment.

Gemcitabine

No need for dose adjustment

REFERENCES

1. CDF