Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	Durvalumab with gemcitabine and cisplatin for first line **neo-adjuvant treatment** of resectable muscle-invasive bladder cancer, with the intent to treat with a radical cystectomy followed by **adjuvant** durvalumab monotherapy.
Treatment Intent	Neo-adjuvant followed by adjuvant
Frequency and number of cycles	**Neo-adjuvant combination therapy:** Durvalumab in combination with gemcitabine and cisplatin Repeat every 21 days for a maximum of 4 cycles. NB there are 2 dosing schedules depending on patient's creatinine clearance (CrCl). Schedule 1 CrCl >/= 60ml/min. Schedule 2 CrCl 40 to 59ml/min. **Adjuvant monotherapy:** Durvalumab Repeat every 28 days Continue until disease progression or unacceptable toxicity or patient choice to stop treatment or for a maximum of EIGHT doses post-surgery, whichever occurs first.

Monitoring Parameters	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.
	• Consider **audiology** test for hearing impaired patients and monitor all patients for ototoxicity through-out treatment.
	• **Pre-treatment cardiac assessment:**
	  ○ **ECG** baseline and as clinically indicated.
	  ○ Check **BNP**, and **Troponin T** prior to treatment.
	• Monitor **FBC, LFTs** and **U&Es** day 1 and day 8 of cycles 1 to 4, then day 1 from cycle 5 onwards.
	• C+G should be used to measure CrCl prior to cycle 1. If CrCl <60ml/min then obtain EDTA.
	• If baseline CrCl >/=60ml/min use schedule 1 combination treatment, if CrCl 40-59ml/min use schedule 2 combination treatment. If CrCl <40ml/min discuss with consultant and consider cisplatin dose reduction.
	• Blood pressure (**BP**) and random blood glucose (**BM**) at each cycle.
	• **Haematological toxicity:**
	  ○ **Cycle 1 – 4**
	  ○ Day 1: If neuts >/=1 x 10^9/l and PLT >/=100 x 10^9/l proceed with treatment. If neuts <1.0 x 10^9/l or PLT <100 x 10^9/l defer treatment 1 week and consider dose reduction.
	  ○ Day 8: If neuts >/= 1 x 10^9/l and platelets >/=75 x 10^9/l proceed with treatment, if parameters not met defer 1 week
	  ○ **Cycle 5 onwards:** Durvalumab monotherapy, if neuts <0.5 x 10^9/l and or PLT <50 x 10^9/l d/w consultant.
	• **Thyroid function** must be assessed at baseline then every 6 to 8 weeks or as indicated based on clinical evaluation.
	• **Cortisol monitoring** should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24hours of the last steroid dose.
	• **Hepatic impairment:**
	  ○ **Durvalumab** - No dose adjustment is necessary.
	  ○ **Cisplatin -** no dose reduction required.

- **Gemcitabine -** If total bilirubin < 27µmol/L: no dose adjustment is needed. Total bilirubin >/= 27µmol/L: either start at 80% of the original dose and increase the dose if tolerated or start with full dose with active monitoring.

- **Renal impairment:**
  - Regimen contraindicated if CrCl <30ml/min
  - **Durvalumab** - No dose adjustment is necessary in mild or moderate renal impairment. No data in severe impairment (<30ml/min).
  - **Cisplatin** – If CrCl >/= 60ml/min use schedule 1, if CrCl 40 to 59ml/min use schedule 2. If CrCl 30-39ml/min discuss with consultant and consider dose reduction.
  - **Gemcitabine** - CrCl >/= 30ml/min no dose adjustment.
- **Infusion-related reactions:**
- **Durvalumab:** In the event of grade 3 to 4 infusion-related reactions, discontinue durvalumab and administer appropriate treatment. In the event of a mild or moderate reaction, interrupt or slow the rate of the infusion. Pre-medication for prophylaxis of subsequent infusion reactions should be considered.
- **Management of adverse reactions and dose adjustments:**
  - **Posterior Reversible Encephalopathy Syndrome (PRES)** has been rarely reported with gemcitabine. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of gemcitabine.
  - **Haemolytic uraemic syndrome.** Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH.
  - **Capillary leak syndrome.** Gemcitabine should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.
  - **Durvalumab Immune-related reactions:** Most common reactions are pneumonitis, colitis, nephritis, hepatitis, hyperthyroidism, hypothyroidism, hypophysitis / hypopituitarism, diabetes, immune-related rash. See table 1 for SPC Recommended treatment modifications and management recommendations for immune related reactions.
  - Treatment with corticosteroids or endocrine therapy should be initiated as appropriate. For events requiring corticosteroid therapy, and upon improvement to </= Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement. After withholding treatment, durvalumab can be resumed within 12 weeks if the adverse reactions improved to </= Grade 1 and the corticosteroid dose has been reduced to </=10 mg prednisone or equivalent per day.
  - Permanently discontinue for recurrent Grade 3 (severe) immune-mediated adverse reactions and for any Grade 4 (life-threatening) immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones.
  - For guidance on managing immune-related adverse reactions, refer to SPC and guidelines available on KMCC website https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/
  - **Durvalumab non-immune-mediated adverse reactions**, withhold treatment for Grade 2 and 3 adverse reactions until </= Grade 1 or baseline.
  - Discontinue in the event of Grade 4 adverse reactions (with the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgment).
  - Patients must be advised to contact the oncology team if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment.

	• **Dose Modification:**
	  ○ **Gemcitabine and Cisplatin:** d/w consultant if chemotherapy is delayed due to haematological toxicity.
	  Dose reduction of cytotoxic chemotherapy should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1.
	  ○ **Durvalumab:** Dose escalation or reduction of durvalumab is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability.
	• *Patients with a body weight of 30 kg or less must receive weight-based dosing of durvalumab at 20 mg/kg.
	• **Common drug interactions (for comprehensive list refer to BNF/SPC):**
	  ○ **Durvalumab -** No interaction studies have been performed.
	  ○ The use of systemic corticosteroids or immunosuppressants before starting durvalumab should be avoided. Systemic corticosteroids or other immunosuppressants can be used after starting durvalumab to treat immune-related adverse reactions.
	  ○ **Cisplatin -** Caution when used concurrently with other nephrotoxic or ototoxic drugs.
	  ○ Caution in patients receiving phenytoin, levels may be affected.
	  ○ **Gemcitabine -** No specific interaction studies have been performed.
	• **Driving and machinery:** gemcitabine may cause drowsiness, patients should be advised to avoid driving or operating machinery until they establish if they are affected.
	• **Pregnancy and contraception:**
	• **Durvalumab:** Women of childbearing potential should use effective contraception during treatment and for at least 3 months after the last dose of durvalumab.
	• **Gemcitabine and Cisplatin:** Women of childbearing potential should use effective contraception and not consider pregnancy during treatment and men should be advised to use effective contraception and not to conceive children during treatment, please refer to the brand specific SPC for further guidance.

References	CDF list V1.386 accessed online 17.02.2026 SPC accessed online durvalumab 17.02.2026 KMCC proforma URO-006 and URO-007 SPC gemcitabine accessed online 20.02.2026 SPC cisplatin accessed online 20.02.2026 https://www.nejm.org/doi/full/10.1056/NEJMoa2408154?logout=true

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 SPC Recommended treatment modifications and management recommendations for immune related reactions.

Adverse reactions	**Severity**[a]	**Treatment modification**
Immune-mediated pneumonitis/ interstitial lung disease	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Immune-mediated hepatitis	ALT or AST > 3 - ≤ 5 x ULN or total bilirubin > 1.5 - ≤ 3 x ULN	Withhold dose
	ALT or AST > 5 - ≤ 10 x ULN	Withhold dose
	Concurrent ALT or AST >3 x ULN and total bilirubin > 2 x ULN[b]	Permanently discontinue
	ALT or AST > 10 x ULN or total bilirubin > 3 x ULN	
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose
	Grade 3 for durvalumab monotherapy	Withhold dose
	Grade 4	Permanently discontinue
Immune-mediated hyperthyroidism, Thyroiditis	Grade 2-4	Withhold dose until clinically stable
Immune-mediated hypothyroidism	Grade 2-4	No changes
Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Immune-mediated type 1 diabetes mellitus	Grade 2-4	No changes
Immune-mediated nephritis	Grade 2 with serum creatinine >1.5 - 3 x (ULN or baseline)	Withhold dose
	Grade 3 with serum creatinine >3 x baseline or >3-6 x ULN; Grade 4 with serum creatinine > 6 x ULN	Permanently discontinue
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for > 1 week	Withhold dose
	Grade 3	
	Grade 4	Permanently discontinue
Immune-mediated myocarditis	Grade 2-4	Permanently discontinue
Immune-mediated myositis/ polymyositis/rhabdomyolysis	Grade 2 or 3	Withhold dose[f]
	Grade 4	Permanently discontinue
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Infection	Grade 3 or 4	Withhold dose until clinically stable
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue
Immune-mediated Myelitis transverse	Any Grade	Permanently discontinue
Immune-mediated meningitis	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue

Immune-mediated Guillain-Barré syndrome	Grade 2-4	Permanently discontinue
Other immune-mediated adverse reactions[g]	Grade 2 or 3	Withhold dose
	Grade 4	Permanently discontinue

a Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; BLV: baseline value.
b For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.
f Permanently discontinue IMFINZI if adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.
g Includes immune thrombocytopenia, pancreatitis, immune-mediated arthritis, uveitis, cystitis noninfective, and polymyalgia rhematca.

Schedule 1 Neo-adjuvant: CrCl >/=60ml/min
Cycle 1 to 4: Repeat every 21 days.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	DURVALUMAB	**1500mg *(see notes above)**	IV	60 minutes	In 100ml sodium chloride 0.9% (final concentration 1-15 mg/mL) via in-line low-protein binding 0.22micron filter.
	Sodium chloride 0.9%	1000ml	IV	2 hrs	+ 20mmol KCl + 10mmol Mg^{2++}
	Sodium chloride 0.9%	1000ml	IV	2 hrs	+ 20mmol KCl
	Aprepitant	125mg	PO		Take one 125mg capsule **one hour prior to chemo** on Day 1
	Mannitol 10%	200mls	IV	15 min	
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium Chloride 0.9% 50ml
	Dexamethasone	8mg	PO		
	CISPLATIN	**70mg/m²**	IV	2 hr	In 1000ml Sodium chloride 0.9%
	Furosemide	40mg	IV/PO	Bolus	Only if urine output <100ml/hour or weight gain >2kg
	Sodium Chloride 0.9%	1000ml	IV	2 hr	+ 20mmol KCl + 10mmol Mg^{2}++
	*Furosemide	40mg	IV/po	*** ONLY IF REQ'D**	If patient remains in a 2L positive balance
	GEMCITABINE	**1000mg/m²**	IV	30 min	Diluted in 0.9% sodium chloride to a final concentration of 0.1mg/ml – 10mg/ml. Consider extending infusion duration if final volume >500ml
8	Metoclopramide	10mg	IV		
	GEMCITABINE	**1000mg/m²**	IV	30 min	Diluted in 0.9% sodium chloride to a final concentration of 0.1mg/ml – 10mg/ml. Consider extending infusion duration if final volume >500ml

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	6mg	PO	OM for 3 days.
	Aprepitant	80mg	PO	Take one 80mg capsule each morning on day 2 and day 3 only
Day 1 and Day 8	Metoclopramide	10mg	PO	10mg three times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously. (max. 30mg per day including 20mg pre-chemo dose)

Schedule 2 Neoadjuvant: CrCl 40 to 59ml/min
Cycle 1 to 4: Repeat every 21 days.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	DURVALUMAB	**1500mg *(see notes above)**	IV	60 minutes	In 100ml sodium chloride 0.9% (final concentration 1-15 mg/mL) via in-line low-protein binding 0.22micron filter.
	Sodium chloride 0.9%	1000ml	IV	2 hrs	+ 20mmol KCl + 10mmol Mg^{2++}
	Mannitol 10%	200mls	IV	15 min	
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium Chloride 0.9% 50ml
	Dexamethasone	8mg	PO		
	CISPLATIN	**35mg/m^2**	IV	2 hr	In 1000ml Sodium chloride 0.9%
	Furosemide	40mg	IV/PO	Bolus	Only if urine output <100ml/hour or weight gain >1kg
	Sodium Chloride 0.9%	500ml	IV	1 hr	
	GEMCITABINE	**1000mg/m^2**	IV	30 min	Diluted in 0.9% sodium chloride to a final concentration of 0.1mg/ml – 10mg/ml. Consider extending infusion duration if final volume >500ml
8	Sodium chloride 0.9%	1000ml	IV	2 hrs	+ 20mmol KCl + 10mmol Mg^{2++}
	Mannitol 10%	200mls	IV	15 min	
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium Chloride 0.9% 50ml
	Dexamethasone	8mg	PO		
	CISPLATIN	**35mg/m^2**	IV	2 hr	In 1000ml Sodium chloride 0.9%
	Furosemide	40mg	IV/PO	Bolus	Only if urine output <100ml/hour or weight gain >1kg
	Sodium Chloride 0.9%	500ml	IV	1 hr	
	GEMCITABINE	**1000mg/m^2**	IV	30 min	Diluted in 0.9% sodium chloride to a final concentration of 0.1mg/ml – 10mg/ml. Consider extending infusion duration if final volume >500ml

Schedule 2 Neo-adjuvant TTO cycles 1 to 4 only

TTO	Drug	Dose	Route	Directions
Day 1 and Day 8	Dexamethasone	6mg	PO	OM for 3 days.
	Metoclopramide	10mg	PO	10mg three times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously. (max. 30mg per day including 20mg pre-chemo dose)

Cycle 5 to 12 Adjuvant: Monotherapy repeat every 28 days.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	DURVALUMAB	**1500mg *(see notes above)**	IV	60 minutes	In 100ml sodium chloride 0.9% (final concentration 1-15 mg/mL) via in-line low-protein binding 0.22micron filter.

TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.