Indication	For the 1st line treatment of locally advanced or unresectable or recurrent or metastatic biliary tract cancer. The patient has NOT received prior treatment with an anti-PD-1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless the patient is transferring from a durvalumab compassionate access scheme for this indication NB patients who have received prior adjuvant or neoadjuvant chemotherapy are eligible for durvalumab plus gemcitabine and cisplatin provided that the adjuvant or neoadjuvant chemotherapy did not contain the combination of gemcitabine and cisplatin.
Treatment Intent	Palliative
Frequency and number of cycles	**Combination therapy:** Durvalumab in combination with gemcitabine and cisplatin Repeat every 21 days for a maximum of 8 cycles. **Monotherapy:** Durvalumab Repeat every 28 days Continue until disease progression or unacceptable toxicity or patient choice to stop treatment. A formal medical review as to whether treatment should continue or not will be scheduled to occur at least by the end of the 2nd cycle of treatment.

Monitoring Parameters pre-treatment	• **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.
	• Monitor FBC day 1 and day 8 of cycles 1 to 8, then day 1 from cycle 9 onwards.
	• C+G should be used to measure CrCl prior to cycle 1. If CrCl <60ml/min then obtain EDTA.
	• LFTs, U&Es, blood pressure and random blood glucose (BM) at each cycle.
	• **Haematological toxicity:**
	  • Cycles 1-8 (day 1 and 8): If neuts >/= 1 and platelets >/=75 proceed with treatment, if parameters not met defer 1 week.
	  • Cycle 9 onwards: Durvalumab monotherapy, if neuts <0.5 and or PLT <50 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.
	• *Patients with a body weight of 36 kg or less must receive weight-based dosing of durvalumab at 20 mg/kg. In combination with chemotherapy dose every 3 weeks (21 days), followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 36 kg.
	• **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** - Impaired renal function d/w consultant. If CrCl 30-59ml/min consider dose reduction of cisplatin
- **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:**
  - 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.
  - **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:** Dose escalation or reduction of durvalumab is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability.
  - **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.
  - For suspected immune-mediated adverse reactions, consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement. Upon improvement to </= Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. 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.
  - 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.
- **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:**
  - **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:** gemcitabine may cause drowsiness, patients should be advised to avoid driving or operating machinery until they establish if they are affected.
References	https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200015 Prot_003.pdf (storage.googleapis.com) CDF list V1.281 accessed online 29.11.2023 SPC accessed online 29.11.2023 KMCC protocol UGI-022 V5

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**	**Corticosteroid treatment unless otherwise specified**
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated hepatitis	ALT or AST > 3 - ≤ 5 x ULN or total bilirubin > 1.5 - ≤ 3 x ULN	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST > 5 - ≤ 10 x ULN	Withhold	
	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 hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values)[c]	ALT or AST > 2.5 - ≤ 5 x BLV and ≤ 20 x ULN	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST > 5 – 7 x BLV and ≤ 20 x ULN or concurrent ALT or AST 2.5 – 5 x BLV and ≤ 20 x ULN and total bilirubin > 1.5 - < 2 x ULN[b]	Withhold	
	ALT or AST > 7 x BLV or > 20 ULN whichever occurs first or bilirubin > 3 X ULN	Permanently discontinue	
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 monotherapy	Withhold dose	
	Grade 4	Permanently discontinue	
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic treatment, see section 4.8
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5 - 3 x (ULN or baseline)	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	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	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis	Grade 2	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper[e]
	Grade 3 or 4, or any Grade with positive biopsy	Permanently discontinue	
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[f]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion reactions
	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	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated Myelitis transverse	Any Grade	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated meningitis	Grade 2	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated Guillain-Barré syndrome	Grade 2-4	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-mediated adverse reactions	Grade 2 or 3	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by taper
	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.
c If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement.
e If no improvement within 2 to 3 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month, after which IMFINZI can be resumed based on clinical judgment.
f Permanently discontinue IMFINZI if adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.

Cycles 1-8: Combination therapy 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	**25mg/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	**25mg/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

TTO cycles 1 to 8 only

TTO	Drug	Dose	Route	Directions
Day 1 and Day 8	Dexamethasone	6mg	PO	OM for 2 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 9 onwards: 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.	