Durvalumab 1500mg, Gemcitabine (1000mg/m^2) and CISplatin (25mg/m^2) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Durvalumab in combination with gemcitabine and CISplatin for the first line treatment of adults with unresectable or metastatic biliary tract cancer (BTC).	C24	00897	N/A

* This applies to post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Durvalumab is administered on Day 1, gemcitabine and CISplatin are administered on Day 1 and Day 8 of a 21 day cycle for up to 8 cycles or until disease progression or unacceptable toxicity, whichever occurs first.

Durvalumab is then continued as monotherapy every 28 days from cycle 9 onwards until disease progression or unacceptable toxicity.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Table 1: Treatment schedule for Cycles 1 to 8

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Durvalumab[a]	1500mg	IV infusion	250mL NaCl 0.9% over 60 minutes using a low-protein binding 0.2-0.22 micron in-line filter.	Every 21 days for cycles 1-8
2	1 and 8	Gemcitabine	1000mg/m^2	IV infusion	250mL NaCl 0.9% over 30 minutes	Every 21 days for cycles 1-8
3	1 and 8	CISplatin[b]	25mg/m^2	IV infusion	1000mL NaCl 0.9% over 60 minutes	Every 21 days for cycles 1-8
[a] 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, a dose of 20mg/kg should be given every 21 days, followed by 20 mg/kg every 28 days as monotherapy until weight increases to greater than 36kg. The final concentration of the diluted solution should be between 1mg/mL and 15mg/mL. Do not co-administer other medicinal products through the same infusion line.						
[b]**Prehydration therapy required for CISplatin** See local hospital policy recommendations. Suggested prehydration for CISplatin therapy: 1. Administer 10mmol magnesium sulphate (MgSO4) (+/-KCl 10-20mmol/L if indicated) in 1000mL NaCl 0.9% over 60 – 120 minutes. (Refer to relevant local hospital policy for advice on administration of electrolyte infusions). Administer CISplatin as described above						

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Table 2: Treatment schedule for Cycles 9 onwards (28 day cycle)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Durvalumab[a]	1500mg	IV infusion	250mL NaCl 0.9% over 60 minutes using a low-protein binding 0.2-0.22 micron in-line filter.	Every 28 days from cycle 9 onwards
[a]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, a dose of 20mg/kg should be given every 21 days, followed by 20 mg/kg every 28 days as monotherapy until weight increases to greater than 36kg. The final concentration of the diluted solution should be between 1mg/mL and 15mg/mL. Do not co-administer other medicinal products through the same infusion line.						

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indication as above
- ECOG 0-2
- Adequate haematological, hepatic and renal function

CAUTIONS:

- Patients with clinically significant autoimmune disease
- Brain metastases or spinal cord compression
- Immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids
- Any active clinically significant infection requiring therapy
- Patients with biliary tract cancer (especially those with biliary stents) should be closely monitored for development of cholangitis or biliary tract infections before initiation of treatment and, regularly, thereafter

EXCLUSIONS:

- Hypersensitivity to durvalumab, gemcitabine, CISplatin or to any of the excipients
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is Available on NCCP website
- Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1
- Pre-existing renal impairment
- Significant hearing impairment/tinnitus
- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- Thyroid function tests

- Virology Screen: Hepatitis B (HBsAg, HBcoreAb), and Hepatitis C
- PD-L1 expression using a validated test method
- Audiology and creatinine clearance as clinically indicated

Regular tests:

- Day 1: FBC, renal and liver profile
- Day 8: FBC, creatinine
- Glucose
- Thyroid function tests

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Durvalumab:
  - Dose escalation or reduction is not recommended
  - Treatment withholding or discontinuation may be required based on individual safety and tolerability (Refer to Table 5)
  - Gemcitabine and CISplatin:
    - For dose modifications relating to gemcitabine and CISplatin, refer to Tables 3 and 4

Haematological:

Table 3: Dose modification of Gemcitabine and CISplatin in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Gemcitabine Dose	CISplatin Dose
≥1.0	and	>100	100% Dose	100% Dose
0.5 to 0.99	or	50-100	75%	100% Dose
<0.5	or	<50	Omit	Omit

Renal and Hepatic Impairment:

Table 4: Dose modification of durvalumab, CISplatin and gemcitabine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Durvalumab	**CrCl (mL/min)**	**Dose**	**Impairment**	**Dose**
	≥30	No dose adjustment is needed	Mild	No dose adjustment is needed
	<30	No need for dose adjustment is expected	Moderate and severe	No need for dose adjustment is expected
	Haemodialysis	No need for dose adjustment is expected. Start haemodialysis 6-12 hours after administration.		
CISplatin	**CrCl (mL/min)**	**Dose**	No need for dose adjustment is expected	
	50-59	75% of the original dose		
	<40-49	50% of the original dose		
	<40	Not recommended		
	Haemodialysis	50% of the original dose may be considered		
Gemcitabine	≥30	100%*	**Total bilirubin (µmol/L)**	**Dose**
	<30	Consider dose reduction. Clinical decision.	<27	No dose adjustment is needed
	Haemodialysis		≥27	Either start at 80% of the original dose and increase the dose if tolerated or start with full dose with active monitoring
Durvalumab: Renal and hepatic from Giraud et al. CISplatin: Renal (palliative) and hepatic from Giraud et al. Gemcitabine: Renal and hepatic from Giraud et al.				

Management of adverse events:

Table 5: Dose modification of Durvalumab for adverse events

Adverse reactions	Severity[a]	Durvalumab treatment modification	Corticosteroid treatment unless otherwise specified
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose	Initiate 1-2mg/kg/day prednisone or equivalent followed by a taper

	Grade 3 or 4	Permanently discontinue	2-4mg/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 1-2mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST > 5 - ≤ 10 x ULN		
	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 or 3	Withhold dose	Initiate 1-2mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic treatment.
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 1-2mg/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 1-2mg/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 1-2mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis	Grade 2-4	Permanently discontinue	Initiate 2-4mg/kg/day prednisone or equivalent followed by a taper[c]
Immune-mediated myositis/polymyositis/rhabdomyolysis	Grade 2 or 3	Withhold dose[d]	Initiate 1-2mg/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 - 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated Myelitis transverse	Any grade	Permanently discontinue	Initiate 1 - 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated meningitis	Grade 2	Withhold dose	Initiate 1 - 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3-4	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[e]	Grade 2 or 3	Withhold dose	Consider initial dose of 1-2mg/kg/day prednisone or equivalent followed by taper
	Grade 4	Permanently discontinue	
Non-immune-mediated adverse reactions	Grade 2 and 3	Withhold dose until ≤ Grade 1 or return to baseline	
	Grade 4	Permanently discontinue[f]	

[a] Common Terminology Criteria for Adverse Events, version 4.03.
[b] For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.
[c] 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.
[d] Permanently discontinue durvalumab if adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.
[e] Includes immune thrombocytopenia, pancreatitis, immune-mediated arthritis, uveitis and cystitis non-infective.
[f] 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.

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm etiology or exclude alternate etiologies. Based on the severity of the adverse reaction, durvalumab should be withheld or permanently discontinued. Treatment with corticosteroids or endocrine therapy should be initiated. 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 withhold, durvalumab can be resumed within 12 weeks if the adverse reactions improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤10mg prednisone or equivalent per day. Durvalumab should be permanently discontinued 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.

Table 6: Dose modification of CISplatin and gemcitabine for adverse events

Adverse reactions	Recommended dose modification
Grade ≥ 3 non-haematological toxicity (except nausea/vomiting)	Therapy with gemcitabine and CISplatin should be withheld (until toxicity has resolved to grade ≤ 1) and may be resumed with dose reduction at discretion of prescribing consultant.
Grade ≥ 2 peripheral neuropathy	Omit CISplatin or consider substituting CISplatin with CARBOplatin 100% dose of gemcitabine
Grade ≥ 2 pneumonitis	Discontinue gemcitabine

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

Durvalumab: Minimal **(Refer to local policy)**
CISplatin: High **(Refer to local policy)**
Gemcitabine: Low **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists. Information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

- Durvalumab: None specified
- Hydration prior to CISplatin administration (Refer to local policy or see recommendations above)

OTHER SUPPORTIVE CARE:

- Durvalumab: Women of childbearing potential should use effective contraception during treatment with durvalumab and for at least 3 months after the last dose of durvalumab.

- Patient should be encouraged to drink large quantities of liquids for 24 hours after the CISplatin infusion to ensure adequate urine secretion.

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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Version	Date	Amendment	Approved By
1	20/02/2025		Prof. Maccon Keane

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