Chemotherapy Protocol

Biliary Tract Cancer

Cisplatin-Gemcitabine-Durvalumab

Regimen

- Biliary Tract Cancer- Cisplatin-Gemcitabine-Durvalumab

Indication

- First Line treatment if adults with locally advanced, unresectable or metastatic biliary tract cancer
- Patient has not received previous chemotherapy for the locally advanced or unresectable or recurrent or metastatic biliary tract cancer indication unless the patient is transferring from a durvalumab compassionate access scheme in which case the patient may have previously had gemcitabine plus cisplatin in combination with durvalumab for this indication.
- 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.
- WHO Performance Statis of 0 or 1.

Toxicity

Drug	Adverse Effect
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Gemcitabine	Diarrhoea, constipation, rash, respiratory problems (pneumonitis), influenza like symptoms, radiosensitising, transient elevation of LFTs
Durvalumab	Immune-mediated reactions (such as pneumonitis, hepatitis, colitis, nephritis, endocrinopathies), pneumonia, pyrexia, diarrhoea, rash, anthralgia

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- For Cycle 1-8: FBC, LFTs and U&Es prior to day one and eight of treatment
- From Cycle 9 onwards: FBC, LFTs and U&Es prior to day one of treatment
- TFTs should be measured at baseline and then every 6-8 weeks or as indicated based on clinical evaluation.
- Random cortisol at baseline and then every 6-8 weeks or as indicated based on clinical evaluation.
- Random blood glucose each cycle

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped. But please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. As the approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Prior to prescribing the following criteria must be met:

Criteria	Eligible Level
Neutrophil	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

On Day 8, if the above criteria are not met, but neutrophils are between 0.5-$1x10^9$/L and/or platelets are between 50-$100x10^9$/L. A patient may still be able to proceed with a dose reduction of gemcitabine +/- cisplatin. But this would need to be decided on an individual case by case basis by an appropriate clinician.

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L)

Hepatic Impairment

Drug	Bilirubin (µmol/L)		ALT/AST (units/L)	Dose (% of original dose)
Cisplatin	No dose adjustments needed.			
Gemcitabine	Consider dose reductions when the bilirubin is raised. Especially when bilirubin is over 27µmol/L			
Durvalumab	Greater than1.5xULN	Or	Greater than 3xULN	Withhold dose
	Greater than 5xULN	Or	Greater than 8xULN	Permanently discontinue
	Greater than 2xULN	And	Greater than 3xULN	Permanently discontinue

For a hepatitis associated with an AST / ALT of 3xULN and / or a total bilirubin of 1.5xULN then withhold treatment and administer corticosteroids. Upon improvement to NCI-CTC grade 1 hepatic injury begin to taper the corticosteroid over a period of one month. Durvalumab may be re-started when the liver function remains at NCI-CTC grade 1 following corticosteroid taper.

The durvalumab should be permanently discontinued when the hepatic injury does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or any NCI-CTC grade 3 or above reaction.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cisplatin	More than 60	100
	45-59	75
	Less than 45	Consider alternative
Gemcitabine	Consider dose adjustments when the CrCl is less than 30ml/min	

Drug	Creatinine	Dose (% of original dose)
Durvalumab	1.5-3x ULN	Withhold dose
	Greater than 3xULN	Permanently discontinue

Severe nephritis or renal dysfunction has been observed with durvalumab treatment. Patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.

For NCI-CTC Grade 2 or 3 serum creatinine elevation, durvalumab should be withheld and corticosteroids initiated. Upon improvement to NCI-CTC grade 1 initiate corticosteroid taper over at least one month. Durvalumab may be resumed when the reaction remains at NCICTC grade 1 or below following tapering of the corticosteroid.

The durvalumab should be permanently discontinued when the serum creatinine does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or in the case of a recurrent NCI-CTC grade 3 reaction.

For NCI-CTC Grade 4 serum creatinine elevation, durvalumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

If lethargy occurs at CTC grade 3 – 4 administer gemcitabine at 75% of the original dose. If the lethary continues at this level despite the dose reduction then stop treatment.

For grade CTC 3 – 4 nausea and / or vomiting that does not respond to optimisation of anti-emetic therapy delay treatment until recovery and then omit the cisplatin. If this is insufficient to control the symptoms administer the gemcitabine at 75% of the original dose.

Oedema is a complication of gemcitabine. If this occurs at CTC grade 3 – 4 delay all treatment until recovery to baseline then re-start treatment using gemcitabine at 75% of the original dose. If the oedema fails to respond to this dose modification then stop treatment.

For CTC grade 1 – 2 peripheral neuropathy delay the cisplatin until recovery to baseline then continue treatment at the original dose. There is no need to modify the dose of gemcitabine. For CTC grade 3 – 4 neuropathy or CTC grade 1 -2 that does not recover stop the cisplatin therapy and continue with single agent gemcitabine.

There is no need to modify doses for tinnitus that resolves between cycles. If the tinnitus persists omit the cisplatin and continue with single agent gemcitabine.

In the event of the development of obstructive jaundice due to biliary tract obstruction, appropriate measures will be undertaken to diagnose and relieve the obstruction. Defer chemotherapy until the liver function tests have improved to the pre-treatment eligibility levels (i.e. total bilirubin less than or equal to 1.5xULN; ALT, AST & alkaline phosphatase less than or equal to 5xULN). Chemotherapy may then resume at the start of the next treatment cycle.

Durvalumab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity, likely to be related to its pharmacology.

Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. Most occur during treatment, however, onset months after the last dose has been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and durvalumab related. Early diagnosis and appropriate management are essential to minimise life threatening complications.

Durvalumab should be permanently discontinued for: any NCI-CTC grade 3 or 4 pneumonitis or hepatitis; any other life-threatening NCI-CTC grade 4 reaction (including colitis and renal impairment); any recurrence of a severe or NCI-CTC grade 3 reaction; any persistent NCICTC grade 2 or 3 treatment-related adverse reaction that does not recover to grade 1 or resolve within 12 weeks after the last dose.

Durvalumab should be withheld for any NCI-CTC grade 2 pneumonitis or hepatitis; any grade 2 or 3 colitis or renal impairment; any other severe or grade 3 treatment-related adverse reaction.

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue
Immune- related colitis	Grade 2 or 3 diarrhoea or colitis	Withhold until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue

Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue
Immune-related endocrinopathies	Symptomatic endocrinopathies (including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency and diabetes)	Withhold until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Nivolumab should be continued in the presence of hormone replacement therapy as long as no symptoms are present
Immune-related rash	Grade 3 rash	Withhold dose until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue

Do not resume durvalumab if the patient is still receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy.

Treatment with durvalumab should be permanently discontinued for grade 2 or 3 immune related adverse reactions that persist in spite of treatment modifications or a reduction of corticosteroid dose to 10 mg prednisolone, or equivalent, cannot be achieved.

For all other non-haematological NCI-CTC grade 3 and above toxicities, delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced to 75% of the original dose or discontinued as appropriate.

Endocrine

Durvalumab can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism. This may present with nonspecific symptoms resembling other causes such as brain metastasis or underlying disease.

Isolated hypothyroidism can be managed with replacement therapy, without treatment interruption or corticosteroids.

If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of intravenous corticosteroids with mineralocorticoid activity is recommended, the patient must be evaluated for presence of sepsis or infections. If there are signs of adrenal insufficiency but the patient is not in crisis, further investigations should be considered including laboratory and imaging assessment. Evaluation of laboratory results to assess endocrine function may be performed before corticosteroid therapy is initiated. If pituitary imaging or laboratory tests of endocrine function are abnormal, a short course of high-dose corticosteroid therapy is recommended to treat the gland inflammation. The scheduled dose of durvalumab should be omitted. It is currently unknown if the corticosteroid treatment reverses the gland dysfunction. Appropriate hormone replacement should also be initiated. Long-term hormone replacement therapy may be necessary.

Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with durvalumab may be resumed and initiation of corticosteroid taper should be based on clinical judgment.

Hypophysitis can present as a diffuse, heterogenous enlargement of the pituitary on a brain MRI but can be completely normal. When hypophysitis with pituitary dysfunction is suspected, blood tests including thyroid stimulating hormone (TSH), free T4, adrenocorticotropic stimulating hormone, cortisol, leutinizing hormone, and folliclestimulating hormone should be obtained in women, and the first four plus testosterone in men. Typically the anterior pituitary axis is involved, affecting thyroid, gonadal, and adrenal function, but isolated axis dysfunction can be seen. Hypophysitis will cause low free T4 as well as TSH. Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities such as hyponatremia and hyperkalemia constitute adrenal crisis. Hospitalization and intravenous steroids with mineralocorticoid activity, such as methylprednisolone, should be initiated while waiting for laboratory results. Infection and sepsis should be ruled out with appropriate cultures and imaging. Prednisolone 1 mg/kg by mouth should be administered if patients are clinically stable. Steroids can usually be tapered over 30 days to achieve physiologic replacement levels. Thyroid hormone and/or testosterone replacement therapy may not be permanent, as the need for those hormones may wane over months in some patients. Cortisone replacement may also not be permanent in a modest portion of patients.

Gastrointestinal

Gastro-intestinal immune reactions include diarrhoea, increased frequency of bowel movements, abdominal pain or haematochezia, with or without fever. Diarrhoea or colitis occurring after initiation of durvalumab must be promptly evaluated to exclude infectious or other alternate causes. Immune-related colitis is often associated with evidence of mucosal inflammation, with or without ulcerations and lymphocytic and neutrophilic infiltration.

NCI-CTC grade 1 diarrhoea or suspected mild colitis may continue on durvalumab. Symptomatic treatment and close monitoring are advised.

For a NCI-CTC grade 2 - 3 diarrhoea or colitis withhold the durvalumab and administer corticosteroids. Upon improvement to NCI-CTC grade 1begin to taper the corticosteroid over a period of one month. The durvalumab may be re-started when the diarrhoea or colitis remains at NCI-CTC grade 1 following corticosteroid taper.

The durvalumab should be permanently discontinued when the diarrhoea or colitis does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or in the case of a recurrent NCI-CTC grade 3 reaction.

For Grade 4 diarrhoea or colitis, durvalumab must be permanently discontinued, and corticosteroid treatment initiated.

Lung

Interstitial lung disease including pneumonitis and acute interstitial pneumonitis are associated with durvalumab. For NCI-CTC grade 1 events (asymptomatic with radiographic findings only) then the durvalumab may be continued with close monitoring. Radiologic findings should be followed on serial imaging studies and consideration given to pulmonary consultation and/or bronchoscopy, if clinically indicated. For NCI-CTC grade 2 events withhold the durvalumab and consider

pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL) and pulmonary function tests. Treat with systemic corticosteroids at a dose of 1 to 2mg/kg/day prednisone or equivalent. When symptoms improve to NCI-CTC grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Treatment with durvalumab may be resumed if the event improves to NCI-CTC grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of prednisolone 10 mg oral daily or less. Repeat chest imaging monthly as clinically indicated.

Should a second episode of pneumonitis occur then discontinue the durvalumab.

For NCI-CTC grade 3 or 4 events discontinue durvalumab and consider pulmonary function tests and seek advice from a lung specialist. A bronchoscopy with biopsy and / or BAL should be considered. Treatment involves corticosteroid therapy such as intravenous methylprednisolone 125mg. When symptoms improve to NCI-CTC grade 1 or less, a high dose oral steroid such as prednisone 1 to 2 mg/kg once per day can be considered. A reducing schedule should be considered over a period of at least four weeks. If intravenous corticosteroids followed by high dose oral corticosteroids do not reduce initial symptoms within 48 to 72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose followed by a more prolonged taper and administer infliximab.

Infusion Reactions

Severe infusion-related reactions have been reported in patients receiving durvalumab. Monitor for signs and symptoms of an infusion-related reaction. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions and consider pre-medications prior to subsequent doses. Permanently discontinue durvalumab in patients with NCI-CTC grade 3 or 4 infusion reactions.

Regimen

Combination of Durvalumab with cisplatin and gemcitabine, is a 21-day cycle for a maximum of 8 cycles.

Drug	Dose	Days	Administration
Durvalumab	1500mg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes, using a sterile low protein 0.2 or 0.22 micron in line filter.
Cisplatin	25mg/m^2	1,8	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/minute (minimum time 60 minutes)
Gemcitabine	1000mg/m^2	1,8	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Then monotherapy with durvalumab, as a 28-day cycle that continues until disease progression or unacceptable toxicity.

Drug	Dose	Days	Administration
Durvalumab	1500mg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

Dose Information

- Cisplatin will be dose banded according to the national dose bands.
- Gemcitabine will be dose banded according to the national dose bands.

Administration Information

- Durvalumab should be administered using a sterile low protein 0.2 or 0.22 micron in line filter.

Extravasation Information

- Durvalumab – neutral
- Cisplatin – exfoliant
- Gemcitabine - neutral

Additional Information

- For the treatment of infusion related reactions;
  - chlorphenamine 10mg intravenous once only when required for infusion related reactions
  - hydrocortisone 100mg intravenous once only when required for infusion related reactions
  - salbutamol 2.5mg nebule when required for infusion related bronchospasm

- Antiemetics

  15-30 minutes prior to chemotherapy:
  - dexamethasone 8mg oral or intravenous
  - ondansetron 8mg oral or intravenous

  As take-home medication:
  - dexamethasone 4mg oral twice a day for 3 days
  - metoclopramide 10mg oral three times a day as required (day 1 only)
  - ondansetron 8mg oral twice a day for 3 days

- Cisplatin pre and post hydration as follows:

  Pre
  Furosemide 40mg oral or intravenous
  1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

  Post
  1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

  Patients should be advised to drink at least 3 litres of fluid in the 24 hours after administration of cisplatin.

- Mouthwashes according to local or national policy on the treatment of mucositis
- Gastric protection with a proton pump inhibitor or a H2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

REGIMEN SUMMARY

Cycles 1-8 (21 day cycle)

Day One

1. Durvalumab 1500mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
   Administration Instructions
   Administer using a sterile low protein 0.2 or 0.22 micron in line filter

2. Dexamethasone 8mg oral or intravenous
   Administration Instructions
   Administer 15-30minutes prior to chemotherapy

3. Ondansetron 8mg oral or intravenous
   Administration Instructions
   Administer 15-30minutes prior to chemotherapy

4. Furosemide 40mg when required oral or intravenous

5. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

6. Gemcitabine 1000mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

7. Cisplatin 25mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over a minimum time of 60 minutes
   Administration Instructions
   Administration time should be a minimum of 60 minutes. And at a maximum rate of 1mg cisplatin/minute

8. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

9. Chlorphenamine 10mg intravenous injection once only when required for infusion related reactions.

10. Hydrocortisone 100mg intravenous injection once only when required for infusion related reactions

11. Salbutamol 2.5mg nebule once only when required for infusion related bronchospasm

Take Home Medications (Day One Only)

12. Dexamethasone 4mg twice a day oral for 3 days starting on the day following chemotherapy

13. Metoclopramide 10mg three times a day when required oral

14. Ondansetron 8mg twice a day oral for 3 days starting on the evening of the day of chemotherapy

Day Eight

15. Dexamethasone 8mg oral or intravenous
    Administration Instructions
    Administer 15-30minutes prior to chemotherapy

16. Ondansetron 8mg oral or intravenous
    Administration Instructions
    Administer 15-30minutes prior to chemotherapy

17. Furosemide 40mg when required oral or intravenous

18. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

19. Gemcitabine 1000mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

20. Cisplatin 25mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over a minimum time of 60 minutes
    Administration Instructions
    Administration time should be a minimum of 60 minutes. And at a maximum rate of 1mg cisplatin/minute

21. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Take Home Medications (Day Eight Only)

22. Dexamethasone 4mg twice a day oral for 3 days starting on the day following chemotherapy

23. Ondansetron 8mg twice a day oral for 3 days starting on the evening of the day of chemotherapy

The metoclopramide is not listed as a day eight TTO as the patient is likely to have supplies left from day one. They should be counselled to use the metoclopramide as per day one of the cycle.

Cycle 9 Onwards (28 Day Cycle)

Day One

1. Durvalumab 1500mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
   Administration Instructions
   Administer using a sterile low protein 0.2 or 0.22 micron in line filter.

2. Chlorphenamine 10mg intravenous injection once only when required for infusion related reactions.

3. Hydrocortisone 100mg intravenous injection once only when required for infusion related reactions.

4. Salbutamol 2.5mg nebule once only when required for infusion related bronchospasm.

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DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	1/10/2025	None	Beth Douse Pharmacist	Dr Fangfei Gao Consultant medical oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.