Chemotherapy Protocol

LUNG CANCER – NON-SMALL CELL (NSCLC)

Durvalumab

(28 day – 1500mg)

Regimen

- NSCLC - Durvalumab (28 day – 1500mg)

Indication

- Durvalumab is indicated where;

  - the patient has a histologically or cytologically confirmed diagnosis of non-small cell lung cancer that is locally advanced and unresectable and stage IIIA, B or C at the time of commencing concurrent chemotherapy
  - PD-L1 testing with an approved and validated test to determine the PD-L1 status tumour proportion score (TPS) has been done and the results demonstrate either a PD-L1 score of greater than or equal to 1% or the PDL1 status cannot be ascertained despite a clear intent and reasonable attempt to do so
  - the patient has recently completed treatment with two or more cycles of platinum based combination chemotherapy given concurrently with definitive radical radiotherapy which must have been at a dose of 55-64Gy or biologically equivalent dose (durvalumab is not approved after sequential chemotherapy and radiotherapy)
  - the patient has been re-staged since chemoradiotherapy was completed and does not have any evidence of progressive disease progression or metastatic spread
  - the patient will start the first treatment with durvalumab within 42 days of the last active treatment date of the concurrent chemoradiotherapy treatment program.
  - the maximum treatment duration will be 12 months, this being measured from the date of the first durvalumab infusion (13 four weekly cycles if there are delays to allow toxicity to settle)
  - treatment will continue until loss of clinical benefit, toxicity or the patient chooses to stop treatment or the maximum treatment duration of 13 four weekly cycles is completed. Re-treatment with durvaluamb is not permitted
  - the patient has not received previous treatment with anti-PDL1, anti-PD1, anti-PDL2, anti-CD137, anti-CTLA4 unless durvalumab has been received as part of a patient access programme after concurrent chemoradiotherapy
  - a medical review will be scheduled by the end of three cycles of treatment
  - treatment breaks up to 12 weeks beyond the expected cycle length are allowed solely to allow immune toxicities to settle
  - this dose of 1500mg every four weeks is unlicensed and can only be used to reduce the risk during the COVID-19 pandemoic
  - WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Durvalumab	Immune-mediated reactions (such as pneumonitis, hepatitis, colitis, nephritis, endocrinopathies), pneumonia, diarrhoea, rash

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

Monitoring

- FBC, LFTs and U&Es prior to day one of treatment

Dose Modifications

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

Durvalumab belongs to the immunotherapy class of cancer treatments. Autoimmune toxicities are most frequently noted and can be life threatening. If autoimmune toxicities occur delaying treatment should be considered while investigations or treatments are organised. Some, but not all, toxicities mandate cessation of treatment. Please seek guidance from relevant site-specific specialist teams or oncologists / haematologists with experience of prescribing these agents.

Haematological

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

There is little need to adjust the dose of durvalumab for haematological toxicity.

Dose escalation or reduction is not recommended. Treatment delays are preferred.

Hepatic impairment

Drug	Bilirubin µmol/L		ALT/AST units/L	Dose (% of original dose)
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. The

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	Dose (% of original dose)
Durvalumab	1.5-3xULN	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 NCI-CTC 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.

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 NCI-CTC 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.

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 follicle-stimulating 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 constitutes 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

28 day cycle for 13 cycles

Drug	Dose	Days	Administration
Durvalumab	1500mg	1	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

Extravasation

- Durvalumab - neutral

Additional Therapy

- No antiemetics are required
- 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

- Loperamide 4mg oral initially followed by 2mg after each loose stool when required for the relief of diarrhoea (maximum 16mg/24 hours).
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

Additional Information

- The use of systemic corticosteroids, before starting treatment with durvalumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids can be used after starting durvalumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of durvalumab.
- This is an unlicensed dose of durvalumab

References
1. Antonia SJ, Villegas A, Daniel D et al. Durvalumab after chemoradiotherapy in stage III non-small cell lung cancer. N Engl J Med 2017; 377 (20): 1919-1929.

REGIMEN SUMMARY

Durvalumab (28 day 1500mg)

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Nov 2020	None	Dr Deborah Wright Pharmacist	Dr Andrew Bates Consultant Clinical Oncologist Dr Judith Cave 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 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 that occur as a result of following these guidelines.