Chemotherapy Protocol

LUNG CANCER – NON-SMALL CELL (NSCLC)

Nivolumab (240mg-14 days)

Regimen

- NSCLC – Nivolumab (240mg-14days)

Indication

- Nivolumab monotherapy is recommended for the treatment of metastatic non-squamous or squamous non-small cell lung cancer with progressing after prior treatment with chemotherapy where;

  - the patient has a confirmed diagnosis of stage IIIB or IV non-squamous or squamous non-small cell lung cancer

  - the patient has progressed after previously receiving at least two cycles of platinum- containing chemotherapy for stage IIIB or IV non-small cell lung cancer and also a targeted treatment if the tumour is EGFR positive or ALK positive

  - the patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD- L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless it was received as part of the nivolumab EAMS programme for this indication

  - The patient's tumour expresses PD-L1 (that is, with a tumour proportion score (TPS) greater than or equal to 1%) by an approved and validated test.

  - the patient has no symptomatically active brain metastases or leptomeningeal metastases.

  - Nivolumab will be stopped at two years of treatment or on disease progression* or unacceptable toxicity, whichever occurs first.

    *Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until further disease progression is confirmed

    - WHO performance status 0, 1 and would otherwise be potentially fit for docetaxel based therapy

Toxicity

Drug	Adverse Effect
Nivolumab	Fatigue, rash, pruritis, pneumonitis, diarrhoea, nausea, electrolyte disturbances, endocrine disorders such as thyroid disorders, diabetes and adrenal insufficiency hepatitis and other immune-related adverse reactions.

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

Monitoring

Regimen

- FBC, LFTs and U&Es prior to day one of each cycle
- Thyroid function tests prior to starting treatment and then every 6 weeks or when clinically indicated.

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.

Nivolumab 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. Clinicians should be aware that the current funding approval for nivolumab precludes further treatment after an interruption of 12 weeks or longer; this situation may change.

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 nivolumab for haematological toxicity.

Dose escalation or reduction is not recommended. Doses should be delayed for toxicity.

Hepatic Impairment

For patients with pre-existing mild hepatic impairment no dose adjustment is recommended. Nivolumab has not been studied in patients with moderate or severe hepatic impairment.

For a hepatitis associated with an AST / ALT of 3-5xULN and / or a total bilirubin of 1.5-3xULN 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 nivolumab may be re-started when the liver function remains at NCI-CTC grade 1 following corticosteroid taper.

The nivolumab 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.

Nivolumab should be permanently discontinued in the first instance when hepatitis develops that is associated with an AST / ALT equal to or greater than 5xULN or where the bilirubin is greater than 3xULN.

Renal Impairment

No dose adjustment is required in patients with pre-existing mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Severe nephritis or renal dysfunction has been observed with nivolumab 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, nivolumab should be withheld and corticosteroids initiated. Upon improvement to NCI-CTC grade 1 initiate corticosteroid taper over at least one month. Nivolumab may be resumed when the reaction remains at NCI-CTC grade 1 or below following tapering of the corticosteroid.

The nivolumab 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, nivolumab 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.

Nivolumab 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 have 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 nivolumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Nivolumab 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.

Nivolumab 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 nivolumab if the patient is still receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy.

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

Endocrine

Nivolumab 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 nivolumab 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 nivolumab 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 (ACTH), cortisol, luteinising hormone (LH), and follicle-stimulating hormone (FSH) 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. Cases should be jointly managed with an endocrinologist. 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 nivolumab 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 nivolumab. Symptomatic treatment and close monitoring are advised.

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

The nivolumab 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, nivolumab must be permanently discontinued, and corticosteroid treatment initiated.

Lung

Interstitial lung disease including pneumonitis and acute interstitial pneumonitis are associated with nivolumab. For NCI-CTC grade 1 events (asymptomatic with radiographic findings only) then the nivolumab 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 nivolumab 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 2 mg/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 nivolumab 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 nivolumab.

For NCI-CTC grade 3 or 4 events discontinue nivolumab 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.

Regimen

14 day cycle (12 cycles will be set in Aria)

Drug	Dose	Days	Route
Nivolumab	240mg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Dose Information

- Nivolumab is a flat dose. Doses are delayed, not reduced, for toxicity.

Administration Information

Extravasation

- Nivolumab – neutral

Other

- Nivolumab should be administered via a 0.2-1.2 micron a low protein binding filter. The polyethylene lined giving sets used for paclitaxel with a 0.22 micron filter are appropriate.

Additional Therapy

- No antiemetics are required
- As required for the treatment of infusion related reactions;

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg oral

- 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 nivolumab 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 nivolumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of nivolumab.

- Patients must be given a nivolumab Patient Alert Card.

Coding

- Procurement – X71.5
- Delivery – X72.3

References

1. Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus docetaxel in advanced squamous cell non-small cell lung cancer. N Engl J Med 2015; 373 (2): 123-135
2. OPDIVO prescribing information March 2015, Bristol Myers Squibb.
3. Early access to medicines scheme (EAMS) scientific opinion: Nivolumab (for lung cancer) 29/06/15

REGIMEN SUMMARY

Nivolumab (240mg-14days)

Day One

1. Nivolumab 240mg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
   Administration Instructions
   Ensure the patient has been a nivolumab patient alert card.

2. Chlorphenamine 10mg intravenous when required for the treatment of infusion related reactions

3. Hydrocortisone sodium succinate 100mg intravenous when required for the treatment of infusion related reactions

4. Paracetamol 1000mg oral when required for the relief of infusion related reactions

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2018	None	Dr Deborah Wright Pharmacist	Dr Luke Nolan Consultant Medical Oncologist Dr Andrew Bates Consultant Clinical 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 that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.