Chemotherapy Protocol

MESOTHELIOMA

IPILIMUMAB-NIVOLUMAB

Regimen

- Mesothelioma – Ipilimumab-Nivolumab

Indication

- Nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.
- WHO Performance status 0, 1.

Toxicity

Drug	Adverse Effect
Ipilimumab	Colitis, diarrhoea, dermatitis, neuropathy, hypothyroidism, hepatotoxicity, infusion related reactions, hypophysitis
Nivolumab	Fatigue, rash, pruritis, pneumonitis, diarrhoea, nausea, electrolyte disturbances, 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 staring treatment and then before each administration (cycle) or when clinically indicated.

Dose Modifications

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

The dose modifications listed are for haematological, liver and renal function and some drug specific toxicities.

Ipilimumab and nivolumab belong 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 ipimumab and

nivolumab precludes further treatment after an interruption of 12 weeks or longer; this situation may change.

Refer to the latest version of the European Society of Medical Oncology guidelines; Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[1].

Haematological

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

There is little need to adjust the dose of ipilimumab or nivolumab for haematological toxicity. Instead dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). Both drugs must be delayed until treatment can resume.

Hepatic Impairment

For patients with pre-existing mild hepatic impairment no dose adjustment is recommended for either ipilimumab or nivolumab.

Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. Nivolumab must be administered with caution in patients with moderate (total bilirubin greater than 1.5 to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin greater than 3×ULN and any AST) hepatic impairment.

Immune related hepatic reactions are associated with ipimumab and nivolumab.

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 combination may be re-started when the liver function remains at NCI-CTC grade 1 following corticosteroid taper.

Both ipilimumab and 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.

The combination 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 ipilimumab and 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, both agents should be withheld and corticosteroids initiated. Upon improvement to NCI-CTC grade 1 initiate corticosteroid taper over at least one month. Treatment may be resumed when the reaction remains at NCI-CTC grade 1 or below following tapering of the corticosteroid.

The combination 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, the ipilimumab and 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.

Ipilimumab and 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 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 ipilimumab-related. Early diagnosis and appropriate management are essential to minimise life threatening complications.

Endocrine

Ipilimumab and 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.

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 ipilimumab and 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 ipilimumab and 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, 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 ipilimumab and 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 or 2 diarrhoea or suspected mild to moderate colitis may continue on the combination. Symptomatic treatment and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days, the scheduled dose of the agents should be omitted and consideration given to prescribing prednisolone 1 mg/kg orally once a day. If resolution to NCI-CTC grades 0-1 or return to baseline occurs, the ipilimumab and nivolumab may be resumed at the next scheduled dose.

Doses omitted due to an adverse reaction must not be replaced. Consider endoscopy to confirm or rule out colitis if there is persistent NCI-CTC grade 2 diarrhoea or NCI-CTC grade 1 - 2 diarrhoea with bleeding.

Ipilimumab and nivolumab must be discontinued if NCI-CTC grade 3 or 4 diarrhoea, colitis, peritoneal signs of bowel perforation, ileus or fever occur. High-dose intravenous corticosteroid therapy should be initiated immediately unless bowel perforation is present. Once diarrhoea and other symptoms are controlled, the initiation of corticosteroid taper should be based on clinical judgment (tapering over 6-8 weeks). In clinical trials, rapid tapering (over periods of less than 1 month) resulted in recurrence of diarrhoea or colitis in some patients. Consider alternative

immunosuppressive therapy (eg single dose of infliximab 5mg/kg) if symptoms do not respond to steroids in 5-7 days.

Neurological

Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 days must be evaluated and other causes excluded.

For patients with NCI-CTC grade 2, neuropathy likely related to be related to ipilimumab or nivolumab omit the scheduled dose. If the neurologic symptoms resolve to baseline, the patient may resume treatment at the next scheduled dose.

Ipilimumab and nivolumab must be permanently discontinued in patients with NCI-CTC grade 3 or 4, sensory neuropathy. Patients must be treated according to local guidelines for management of sensory neuropathy.

Skin

A diffuse, erythematous maculopapular rash that can be intensely pruritic was observed in 47% to 68% of patients, starting an average of 3 to 4 weeks after ipilimumab or nivolumab.

NCI-CTC grade 1 or 2 skin reactions may remain on therapy with symptomatic treatment such as topical corticosteroids and antihistamines. For mild to moderate rash or pruritus that persists for 1 to 2 weeks and does not improve with topical corticosteroids consider oral corticosteroid therapy (e.g. prednisolone 1 mg/kg once a day).

For patients with NCI-CTC grade 3 symptomatic skin reactions, the scheduled dose of ipilimumab and nivolumab should be omitted. If initial symptoms improve to NCI-CTC grade 1 or resolve then the therapy may be resumed at the next scheduled dose. Ipilimumab and nivolumab must be permanently discontinued in patients with a NCI-CTC grade 4 rash or grade 3 pruritus and consideration given to systemic corticosteroid therapy.

Other Immune-Related Adverse Reactions

The following additional adverse reactions, suspected to be immune-related, have been reported and include uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported. If these occur at NCI-CTC grade 3 or above then consider immediate high-dose corticosteroid therapy and discontinuation of ipilimumab and nivolumab.

For ipilimumab and / or nivolumab-related uveitis, iritis, or episcleritis, topical corticosteroid eye drops should be considered as medically indicated.

Regimen

42 day cycle continued for up to 24 months in patients without disease progression* (18 cycles will be set in ARIA)

Drug	Dose	Days	Route
Ipilimumab	1mg/kg	1	Intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
Nivolumab	360mg	1 & 22	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

*Please note that 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 with nivolumab or nivolumab in combination with ipilimumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Dose Information

- Ipilimumab will be dose banded in accordance with the national dose bands (Ipilimumab 5mg/ml).

Administration Information

Extravasation

- Ipilimumab – neutral
- Nivolumab - neutral

Other

- The nivolumab must be administered first during the combination phase of treatment. Thirty minutes should elapse between both agents.
- Ipilimumab should be administered using a low protein binding filter
- The final concentration of ipilimumab should be between 1-4mg/ml
- 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
- When required for infusion related reactions;

  - chlorphenamine 10mg intravenous when required for the treatment of infusion related reactions
  - hydrocortisone sodium succinate 100mg intravenous when required for the treatment of infusion related reactions
  - paracetamol 1000mg oral when required for the relief of infusion related reactions

- Gastric protection with a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed. There is evidence that proton pump inhibitors may reduce the efficacy of the combination of ipilimumab and nivolumab.

Additional Information

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

References

1. Early Access to Medicines Scheme: Nivolumab in combination with ipilimumab for the first line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM) 25th January 2021
2. Haanen J, Carbonnel F, Robert C, Kerr K.M , Peters S, Larkin J, Jordan J on behalf of the ESMO Guidelines Committee. Management of toxicities from immunotherapy. ESMO clinical practice guidelines for diagnosis, treatment and follow up. Ann Oncol 2017; 28 (suppl 4): 119-142.

REGIMEN SUMMARY

Ipilimumab-Nivolumab

Day 1

1. Nivolumab 360mg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
   Administration Instructions
   Administer before ipilimumab on days when both agents are scheduled. Administer via a 0.2-1.2 micron in line filter. Ensure the patient has been given a nivolumab patient alert card.

2. Ipilimumab 1mg/kg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
   Administration Instructions
   Administer 30 minutes after completion of the nivolumab infusion. Administer via a 0.2-1.2 micron in line filter.

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

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

5. Paracetamol 1000mg oral when required for the relief of infusion related reactions
   Administration Instructions
   Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Day 22

6. Nivolumab 360mg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
   Administration Instructions
   Administer before ipilimumab on days when both agents are scheduled. Administer via a 0.2-1.2 micron in line filter. Ensure the patient has been given a nivolumab patient alert card.

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

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

9. Paracetamol 1000mg oral when required for the relief of infusion related reactions
   Administration Instructions
   Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2021	None	Rebecca Wills Pharmacist	

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.