

## Chemotherapy Protocol

### RENAL CANCER

#### IPILIMUMAB (1mg/kg)-NIVOLUMAB(3mg/kg)

##### Regimen

- Renal – Ipilimumab (1mg/kg)-Nivolumab (3mg/kg)

##### Indication

- Ipilimumab in combination with nivolumab is indicated for the first line treatment of unresectable or locally advanced intermediate or poor risk renal cell adenocarcinoma (RCC) which has either a clear cell component or papillary where;
- the patient has intermediate or poor risk advanced renal cell carcinoma as assessed by the International Metastatic RCC Database Consortium (IMDC) system which scores one point for each of the following six factors (a score of 0 indicates good risk disease, a score of 1-2 indicates intermediate risk and a score of 3-6 denotes poor risk). IMDC favourable risk disease (score of 0) did worse with this combination and hence ipilimumab with nivolumab in combination is not licensed in this population. The IMDC factors are;
  - (1) less than one year from time of initial diagnosis of RCC to now
  - (2) a Karnofsky performance status of less than 80%
  - (3) the haemoglobin level is less than the lower limit of normal
  - (4) the corrected calcium level is greater than 2.5mmol/L
  - (5) the platelet count is greater than the upper limit of normal
  - (6) the absolute neutrophil count is greater than the upper limit of normal
- the patient is completely treatment naïve for systemic therapy for locally advanced/metastatic RCC or has only received prior systemic therapy in the context of clinical trials investigating adjuvant therapies in RCC

- the patient has a Karnofsky performance status of at least 70%
- The patient has no symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control.
- The patient is to be treated until loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner. There is no stopping rule as to the maximum treatment duration of nivolumab in this indication.
- A formal medical review to assess the tolerability of treatment with nivolumab and ipilimumab will be scheduled to occur by the start of the 3rd 3-weekly cycle of treatment and thereafter on a regular basis.
- Treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any toxicities to settle.

### 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, LFT's and U&E's prior to day one of each cycle
- Thyroid function tests prior to starting treatment and then before each administration (cycle) or when clinically indicated.

### Dose Modifications

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 ipilimumab 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<sup>(1)</sup>.

### *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.

Immune related hepatic reactions are associated with ipilimumab 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, adrenocorticotrophic 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 eyedrops should be considered as medically indicated.

### Regimen

#### 21 day cycle for 4 cycles

Drug	Dose	Days	Route
Ipilimumab	1 mg/kg	1	Intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
Nivolumab	3mg/kg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Followed by either;

**14 day cycle until intolerance or disease progression (24 cycles will be set in ARIA) starting three weeks after the completion of the combination therapy;**

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

Or

**28 day cycle until intolerance or disease progression (12 cycles will be set in ARIA) starting six weeks after the completion of the combination therapy;**

Drug	Dose	Days	Route
Nivolumab	480mg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 60 minutes

Please note that due to the different cycle lengths the combination treatment will be set up as one regimen. This can then be discontinued and single agent nivolumab started.

#### [Dose Information](#)

- Ipilimumab will be dose banded in accordance with the national dose bands (5mg/ml)
- Nivolumab will be dose banded in accordance with the national dose bands (10NS)

#### [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<sub>2</sub> 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.

### Coding

- Procurement – X70.8
- Delivery – X72.9

### References

1. Haanen J, Carbone 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.
2. Motzer RJ, Tannir NM, McDermott DF et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma. N Engl J Med 2018; 378: 1277-1290.



## REGIMEN SUMMARY

### **Ipilimumab (1mg/kg)-Nivolumab(3mg/kg)**

#### **Cycle 1, 2, 3**

1. Nivolumab 3mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes  
Administration Instructions  
Ensure the patient has been given a nivolumab patient alert card. Administer before the ipilimumab infusion.  
Please leave 30 minutes between the administration of both agents
2. Ipilimumab 1mg/kg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
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

#### **Cycle 4**

6. Warning – Consider single agent nivolumab  
Administration Instructions  
Consider prescribing single agent nivolumab until disease progression or intolerance from cycle five onwards
7. Nivolumab 3mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes  
Administration Instructions  
Ensure the patient has been given a nivolumab patient alert card. Administer before the ipilimumab infusion.  
Please leave 30 minutes between the administration of both agents
8. Ipilimumab 1mg/kg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
9. Chlorphenamine 10mg intravenous when required for the treatment of infusion related reactions
10. Hydrocortisone sodium succinate 100mg intravenous when required for the treatment of infusion related reactions
11. 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 2019	None	Dr Deborah Wright Pharmacist	Dr M Wheeler 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 that occur as a result of following these guidelines.