Chemotherapy Protocol

SKIN CANCER

Cemiplimab (350mg)

Regimen

- Skin – Cemiplimab (350mg)

Indication

- Metastatic or locally advanced cutaneous squamous cell carcinoma in patients who are not candidates for curative surgery or curative radiation.

Toxicity

Drug	Adverse Effect
Cemiplimab	Immune-related reactions including pneumonitis, colitis, hepatitis, hypothyroidism and hyperthyroidism. Fatigue, rash, pruritis, muscular skeletal pain, arthralgia, central nervous system disorders and infusion related reactions

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 each cycle for 8 cycles then every 12 weeks or as clinically indicated
- Thyroid function tests at baseline then every 6 weeks or as clinically indicated
- Blood glucose monitoring every 6 weeks or as clinically indicated

Dose Modifications

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

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

Cemiplimub 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 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

There is no requirement for dose modification or treatment interruption due to haematological toxicity.

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

Hepatic Impairment

There is no requirement for dose modification of cemiplimab in patients with mild hepatic impairment prior to starting therapy.

Cemiplimab has not been studied in patients with moderate or severe hepatic impairment prior to starting therapy. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations.

For patients on cemiplimab who develop immune related hepatitis see below for the treatment of immune-related adverse reactions

Renal Impairment

No dose adjustment of cemiplimab is recommended for patients with renal impairment prior to starting therapy.

There are limited data for cemiplimab in patients with severe renal impairment (creatinine clearance less than <30 ml/min) prior to starting therapy.

For patients on cemiplimab who develop immune related nephritis see below for the treatment of immune-related adverse reactions

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.

Cemiplimab 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 cemiplimab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Cemiplimab 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.

Cemiplimab 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.

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

Treatment with cemiplimab 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 10mg prednisolone, or equivalent, cannot be achieved.

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis (see text below)	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 (see text below)	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 (see text below)	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. Cemiplimab 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

Endocrine

Cemiplimab 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 cemiplimab 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 cemiplimab 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 1mg/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 cemiplimab 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 cemiplimab. Symptomatic treatment and close monitoring are advised.

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

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

Lung

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

For NCI-CTC grade 3 or 4 events discontinue cemiplimab 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

21 day cycle continued until disease progression or development of unacceptable toxicity or for up to 24 months, whichever is sooner.

(35 cycles will be set in ARIA)

Drug	Dose	Days	Route
Cemiplimab	350mg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Administration Information

- Cemiplimab must be administered via a 0.2 to 5 micron an in-line or add-on filter.
- The final concentration of cemiplimab should be between 1 and 20mg/ml.

Other

Additional Therapy

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

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

Additional Information

- Patients receiving cemiplimab must be issued with a Patient Alert Card
- No pharmacokinetic drug-drug interaction studies have been conducted with cemiplimab.
- The use of systemic corticosteroids or immunosuppressants before starting cemiplimab, except for physiological doses of systemic corticosteroid (less than or equal to 10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of cemiplimab. However, systemic corticosteroids or other immunosuppressants can be used after starting cemiplimab to treat immune-related adverse reactions.

Coding

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

References
1. 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.
2.Midgen MR, Rischin D, Schmults CD et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med 2018; 379:341-351

REGIMEN SUMMARY

Cemiplimab (350mg)

Day One

1. Cemiplimab 350mg in 100ml sodium chloride 0.9% over 30minutes
   Administration Instructions
   Administer using a 0.2-5micron in-lineor add on filter

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

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

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2019	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Sarah Ellis 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.