Chemotherapy Protocol

LUNG CANCER

CARBOPLATIN (AUC6)-PACLITAXEL-PEMBROLIZUMAB

Regimen

- Lung-Carboplatin (AUC6)-Paclitaxel-Pembrolizumab

Indication

- The patient has a histologically- or cytologically-confirmed diagnosis of stage IIIB or stage IIIC or stage IV squamous non-small cell lung cancer.

- PD-L1 testing with an approved and validated test to determine the Tumour Proportion Score (TPS) has been performed prior to treatment. The NICE appraisal committee has made specific comment in those patients with a TPS of 50-100% about the need for a detailed discussion to take place between oncologist and patient as to the relative merits of pembrolizumab monotherapy versus the combination of pembrolizumab, carboplatin and paclitaxel. Hence PD-L1 testing and knowledge of the numeric result remain mandatory in all patients accessing this indication

- Either the patient has a PD-L1 TPS of 0-49% or has a PD-L1 TPS of 50-100% and requires an urgent clinical response (e.g. impending major airway obstruction) so as to justify the use of the combination of pembrolizumab, carboplatin and paclitaxel rather than pembrolizumab monotherapy and this issue has been fully discussed with the patient.

- The patient has not received previous cytotoxic chemotherapy for advanced /metastatic disease. Completion of treatment for earlier stage disease with chemotherapy with or without radiotherapy as part of neoadjuvant/concurrent/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of recurrent locally advanced or metastatic disease.

- The patient will commence treatment with a maximum of four 3-weekly cycles of the combination of pembrolizumab (200mg), carboplatin (AUC 6) and paclitaxel (200mg/m^2). Note: during the combination phase, 3-weekly dosing of pembrolizumab 200mg must be used (not 6-weekly dosing of pembrolizumab 400mg). Note: the use of the combination of pembrolizumab, carboplatin and nab-paclitaxel in this indication was not submitted to NICE for appraisal by MSD and hence nab-paclitaxel is not commissioned in this indication.

- After completion of the combination of pembrolizumab, carboplatin and paclitaxel and in the absence of disease progression, continued treatment with 3-weekly cycles of pembrolizumab monotherapy 200mg (or if the patient is stable and well, 6-weekly cycles of pembrolizumab monotherapy 400mg) will continue until whichever of the following occurs first: loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent or a maximum treatment duration of 2 years (or thirty-five 3-weekly cycles of pembrolizumab including the initial 4 induction cycles of treatment or its equivalent if 6-weekly pembrolizumab monotherapy dosing is used).

- The patient is fit for the combination of pembrolizumab, carboplatin (AUC 6) and paclitaxel (200mg/m²) and has a WHO performance status score of 0 or 1. Note: the chemotherapy doses in this regimen are higher than may be the case in common practice and so careful selection of patients is required to ensure that patients can tolerate these higher doses of chemotherapy.

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

- 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.

- A formal medical review as to whether treatment with the combination of pembrolizumab, carboplatin and paclitaxel should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment.

- Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow any immune toxicities to settle.

Toxicity

Drug	Adverse Effect
Carboplatin	Thrombocytopenia, peripheral neuropathy, nephrotoxicity at high doses, electrolyte disturbances
Paclitaxel	Hypersensitivity, hypotension, bradycardia, peripheral neuropathy, myalgia and back pain on administration
Pembrolizumab	Pneumonitis, nephritis, colitis, thyroid disorders, hypophysitis, infusion related reactions, hepatitis

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

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day each cycle
- EDTA or calculated creatinine clearance prior to each cycle
- Random blood glucose prior to each pembrolizumab dose
- Thyroid function tests at baseline then every 3-6 weeks as clinically indicated
- Random blood cortisol at baseline then every 3-6 weeks

Dose Modifications

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

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for **chemotherapy**

that if a third dose reduction is necessary treatment should be stopped. Generally **immunotherapy** is interrupted to allow toxicities to settle rather than the dose reduced.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

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

The dose of pembrolizumab is rarely reduced in relation to haematological toxicity.

Day 1

Neutrophils ($x10^9$/L)	**Dose Modifications (carboplatin and paclitaxel)**
1 or greater	100%
less than 1	Delay for 7 days. If the counts recover to at least $1x10^9$/L within this time continue with the full dose. If the counts do not recover within 7 days or repeated delays are required then delay until recovery then reduce the dose by 20%
Platelets ($x10^9$/L)	**Dose Modifications (carboplatin and paclitaxel)**
100 or greater	100%
50-99	Delay for 7 days. If the counts recover to at least $100x10^9$/L within this time then continue with the full dose. If counts do not recover within 7 days or repeated delays are required then delay until recovery then reduce dose by 20%
less than 50	Delay until recovery then reduce dose by 50%

Hepatic Impairment

Drug	**Bilirubin (µmol/L)**		**AST/ALT units**	**% of original dose**
Carboplatin	N/A		N/A	No dose adjustment needed
Paclitaxel	less than 21	and	less than 10xULN	100%
	21-26			75%
	27-51			45%
	52-85			30%
	greater than 85	or	greater than 10xULN	Contra indicated
Pembrolizumab	No dose adjustment is required for mild hepatic impairment (see below for hepatic adverse effects)			

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose
Carboplatin*	less than 20	Omit
Paclitaxel	N/A	No dose adjustment needed
Pembrolizumab	No dose adjustment is required for mild to moderate renal impairment (see below for renal adverse effects)	

* Significant changes in GFR of more than 10% may require dose adjustment.

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.

Paclitaxel

NCI-CTC grade 2 peripheral neuropathy withhold paclitaxel only until the neuropathy recovers to NCI-CTC grade 1 then dose reduce to 75% of the original dose. Where the peripheral neuropathy is NCI-CTC grade 3 again withhold the paclitaxel until it resolves to NCI-CTC grade 1 and then reduce the dose of paclitaxel to 50% of the original dose. Paclitaxel should be discontinued if the neuropathy does not resolve to NCI-CTC grade 1.

Pembrolizumab

Pembrolizumab 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 pembrolizumab-related. Early diagnosis and appropriate management are essential to minimise life threatening complications.

For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab should be permanently discontinued for any;

- NCI-CTC grade 3 pneumonitis, nephritis, infusion related reaction, hepatitis, myocarditis, encephalitis or Guillan-Barre Syndrome
- Any NCI-CTC grade 4 or recurrent grade 3 adverse reaction except for endocrinopathies that are controlled with replacement hormones
- Any recurrent grade 2 nephritis

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 at least one month. The pembrolizumab may be re-started when the liver function remains at NCI-CTC grade 1 following corticosteroid taper.

The pembrolizumab 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.

Pembrolizumab should be permanently discontinued in the first instance when hepatitis develops that is associated with an AST / ALT equal to or greater than 5xULN, an increase in AST / ALT of 50% or greater relative to baseline and that lasts at least one week in patients with liver metastasis who begin treatment with moderate (grade 2) elevation of AST / ALT or where the bilirubin is greater than 3xULN.

Renal Impairment

Where NCI-CTC grade 2 nephritis develops withhold treatment and administer corticosteroids. Upon improvement to NCI-CTC grade 1 or less, initiate corticosteroid taper over at least one month. Pembrolizumab may be resumed when the reaction remains at NCI-CTC grade 1 or below following tapering of the corticosteroid.

The pembrolizumab should be permanently discontinued when the nephritis 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.

Endocrine

Pembrolizumab can cause inflammation of the endocrine system organs, specifically hypophysitis, adrenal insufficiency, hyperthyroidism, hypothyroidism and type 1 diabetes mellitus. 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 pembrolizumab 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 pembrolizumab may be resumed and corticosteroid taper initiated 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.

Eye

Uveitis is associated with pembrolizumab. All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). For NCI-CTC grade 1-2 events evaluation by an ophthalmologist is recommended. Treatment with topical corticosteroids eye drops and iridocyclitics can be tried. Discontinue pembrolizumab if symptoms persist despite treatment with topical immunosuppressive therapy. Discontinue pembrolizumab for NCI-CTC grade 3 or above ocular symptoms and consider treatment with systemic corticosteroids. When symptoms improve to NCI-CTC grade 1 taper the corticosteroids over at least four weeks.

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 pembrolizumab 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 pembrolizumab. Symptomatic treatment and close monitoring are advised.

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

The pembrolizumab should be permanently discontinued when the 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 any NCI-CTC grade 4 or recurrent grade 3 reaction.

Lung

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

For NCI-CTC grade 3 or 4 events discontinue pembrolizumab 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, consider treatment 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 consider administration of infliximab**.** The decision to start infliximab should be made by a consultant**.**

Skin

Serious skin reactions include dermatitis exfoliative, erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis. Pembrolizumab can also be associated with pruritus, rash, (generalized and maculo-papular) and vitiligo. All attempts should be made to rule out other causes such as metastatic disease, infection or allergic dermatitis.

For NCI-CTC grade 1-2 skin reactions try symptomatic treatments such as topical corticosteroids or urea-containing creams in combination with oral antipruritics. pembrolizumab can continue.

For NCI-CTC grade 3 or above events withhold the pembrolizumab and consider a dermatology referral. Treatment with systemic corticosteroids such as prednisolone 1mg/kg

each day may be necessary. When symptoms improve to NCI-CTC grade 1 or less then pembrolizumab may be restarted and steroid taper should be started and continued over no less than 4 weeks.

For NCI-CTC grade 4 or recurrent grade 3 reactions pembrolizumab should be permanently discontinued.

Regimen

The starting dose of carboplatin AUC6 is used with calculated GFR. AUC5 may be considered with EDTA clearance, seek advice from the appropriate consultant before prescribing. The recommended maximum dose when using a calculated creatinine clearance at AUC6 is 900mg. This will be set as 890mg in ARIA to comply with national dose bands. If you have an obese patient or an individual with a calculated creatinine clearance above 125ml/min please seek advice from the relevant consultant.

Consider a dose reduction in poor performance patients.

It should be noted that the dose of carboplatin may need to be altered if there is a change (improvement or reduction) in renal function of more than 10% from the previous cycle.

The total duration of pembrolizumab treatment is 2 years i.e. four cycles of combination chemotherapy/ immunotherapy followed by either pembrolizumab 200mg every 3 weeks for 31 cycles or pembrolizumab 400mg every 6 weeks for 16 cycles.

21 day cycle for 4 cycles

Drug	Dose	Days	Administration
Carboplatin	AUC 6 (maximum dose 890mg)	1	Intravenous infusion in 500ml glucose 5% over 60 minutes
Paclitaxel	200mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% over 180 minutes.
Pembrolizumab	200mg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 30minutes

Followed by;

21 day cycle for 31 cycles

Drug	Dose	Days	Route
Pembrolizumab	200mg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 30minutes

Or:

42 day cycle for 16 cycles

Drug	Dose	Days	Route
Pembrolizumab	400mg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 30minutes

Please note that due to the different options for monotherapy the combination therapy will be set up as one regimen in ARIA. This can then be discontinued and the appropriate monotherapy prescribed.

Dose Information

- The recommended maximum dose of carboplatin when using a calculated creatinine clearance at AUC 6 is 900mg. The maximum dose will be set at 890mg to comply with national dose bands. If you have an obese patient or an individual with a calculated creatinine clearance above 125ml/min please seek advice from the relevant consultant.

- It should be noted that the dose of carboplatin may need to be altered if there is a change (improvement or reduction) in renal function of more than 10% from the previous cycle.

- Carboplatin will be dose banded according to the national dose band (10mg/ml)

- The maximum dose will be set at 890mg to comply with national dose bands

- Paclitaxel will be dose banded in accordance with the national dose bands (6mg/ml)

Administration Information

Extravasation

- Pembrolizumab – neutral

- Carboplatin – irritant

- Paclitaxel – vesicant

Other

- Hypersensitivity reactions tend to occur with the first or second infusion of paclitaxel. Paclitaxel infusion should be interrupted for minor symptoms such as flushing or localised rashes. If these resolve promptly (within 5 minutes) the infusion may be restarted at a lower rate with intensive monitoring. Immediately discontinue the infusion for server reactions which include profound hypotension, bronchospasm and generalised erythema.

- Paclitaxel must be administered via a non-PVC administration set containing an in-line 0.22 micron filter.

- Pembrolizumab will be administered before the carboplatin and paclitaxel and administered via a 0.2 to 5 µm in-line low protein binding filter.

Additional Therapy

- Premedication to reduce of risk of hypersensitivity reaction

  30 minutes before paclitaxel
  - chlorphenamine 10mg intravenous

- dexamethasone 20mg oral or intravenous
- H_2 antagonist according to local formulary choice and availability

- Antiemetics

  15-30 minutes prior to chemotherapy (cycles 1-4 only)
  - ondansetron 8mg oral or intravenous

  As take home medication (cycles 1-4 only)

  - dexamethasone 4mg oral twice a day for 3 days
  - metoclopramide 10mg oral three times a day as required

- As required for the treatment of infusion related reactions;

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

- Gastric protection with a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

Additional Information

- Ensure the patient has been given a pembrolizumab Patient Alert Card

References

1. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer. NICE technology appraisal guidance [TA600], 11 September 2019
2. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. Paz-Ares L, Luft A, Vicente D et al. N Engl J Med 2018; 379:2040-2051November 22, 2018

REGIMEN SUMMARY

Carboplatin (AUC6)-Paclitaxel-Pembrolizumab

Cycle 1, 2, 3

1. Pembrolizumab 200mg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
   Administration Instructions
   Administer via a 0.2 to 5 µm in-line low protein binding filter.

2. Chlorphenamine 10mg intravenous
   Administration instructions: To be administered 30 minutes before paclitaxel

3. Dexamethasone 20mg intravenous
   Administration instructions: To be administered 30 minutes before paclitaxel

4. H_2 antagonist according to local formulary choice and availability
   Administration Instructions:
   Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;
   - Ranitidine 50mg intravenous once only
   - Famotidine 20mg oral once only
   - Nizatidine 150mg oral once only
   - Ranitidine 150mg oral once only

   If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

   All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H_2 antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

5. Ondansetron 8mg oral or intravenous
   Administration instructions: Administer 15-30 minutes prior to chemotherapy. This may be given as ondansetron 8mg IV stat if required.

6. Paclitaxel 200mg/m^2 in 500ml sodium chloride 0.9% intravenous infusion over 180 minutes.
   Administration Instructions
   Paclitaxel must be administered via a non-PVC administration set containing an in-line 0.22 micron filter

7. Carboplatin AUC 6 (maximum dose 890mg) intravenous infusion in 500ml glucose 5% over 60 minutes
   Administration Instructions
   This recommended maximum dose is 900mg based on a creatinine clearance of 125ml/min. This will be set at 890mg in ARIA to comply with national dose bands

8. Chlorphenamine 10mg intravenous injection when required for infusion related reactions

9. Hydrocortisone 100mg intravenous injection when required for infusion related reactions

10. Paracetamol 1000mg oral when required for 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.

Take Home Medicines

11. Dexamethasone 4mg oral twice a day for 3 days starting the day after chemotherapy administration (day 2 of the cycle)

12. Metoclopramide 10mg oral three times a day for three days then 10mg three times a day when required for nausea

Cycle 4

13. Warning pembrolizumab maintenance
    Administration Instructions
    The pembrolizumab is continued for a further 31 cycles of the 3 weekly dosage schedule (200mg) or 16 cycles of the six weekly schedule (400mg) after completion of four cycles of carboplatin and paclitaxel. This is not included in this regimen. This needs to be prescribed as a separate regimen after discontinuation of this protocol.

14. Pembrolizumab 200mg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
    Administration Instructions
    Administer via a 0.2 to 5 µm in-line low protein binding filter.

15. Chlorphenamine 10mg intravenous
    Administration instructions: To be administered 30 minutes before paclitaxel

16. Dexamethasone 20mg intravenous
    Administration instructions: To be administered 30 minutes before paclitaxel

17. H_2 antagonist according to local formulary choice and availability
    Administration Instructions:
    Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;
    - Ranitidine 50mg intravenous once only
    - Famotidine 20mg oral once only
    - Nizatidine 150mg oral once only
    - Ranitidine 150mg oral once only

    If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

    All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H_2 antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

18. Ondansetron 8mg oral or intravenous
    Administration instructions: To be administered 15-30 minutes prior to chemotherapy

19. Paclitaxel 200mg/m^2 in 500ml sodium chloride 0.9% intravenous infusion over 180 minutes.
    Administration Instructions
    Paclitaxel must be administered via a non-PVC administration set containing an in-line 0.22 micron filter

20. Carboplatin AUC 6 (maximum dose 890mg) intravenous infusion in 500ml glucose 5% over 60 minutes
    Administration Instructions
    This recommended maximum dose is 900mg based on a creatinine clearance of 125ml/min. This will be set at 890mg in ARIA to comply with national dose bands

21. Chlorphenamine 10mg intravenous injection when required for infusion related reactions

22. Hydrocortisone 100mg intravenous injection when required for infusion related reactions

23. Paracetamol 1000mg oral when required for 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.

Take Home Medicines

24. Dexamethasone 4mg oral twice a day for 3 days starting the day after chemotherapy administration (day 2 of the cycle)

25. Metoclopramide 10mg oral three times a day for three days then 10mg three times a day when required for nausea

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	May 2023	Carboplatin amended to national dose bands and maximum dose changed Added administration instructions Updated regimen summary	Alexandra Pritchard Pharmacist	Tom Hurst Pharmacy Technician
1.1	Nov 2020	Update of premedication due to shortage of IV ranitidine. IV ranitidine changed to H_2 antagonist according to local formulary choice and availability Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	Nov 2019	N/A	Rebecca Wills Pharmacist	Dr Judith Cave Consultant Medical Oncologist Dr Luke Nolan 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 which occur as a result of following these guidelines.