Chemotherapy Protocol

LUNG CANCER

ATEZOLIZUMAB-BEVACIZUMAB-CARBOPlatin (AUC6)-PACLITAXEL

Regimen

- Lung-Atezolizumab-Bevacizumab-Carboplatin (AUC6)-Paclitaxel

Indication

- The treatment of adult patient with locally advanced or metastatic non-squamous non-small cell lung cancer with a PD-L1 tumour proportion score of 0-49% and without EGFR activating mutations/ALK mutation/ROS1 mutation where the following criteria are met:
  - the patient has a histologically- or cytologically-confirmed diagnosis of stage IIIIB or IIIC or IV non-squamous non-small cell lung cancer.
  - the patient’s lung cancer has not been shown to have an EGFR activating mutation(s) or a positive ALK mutation or a positive ROS1 mutation
  - PD-L1 testing with an approved and validated test to determine the Tumour Proportion Score (TPS) has been performed. The combination of atezolizumab, bevacizumab, carboplatin and paclitaxel is not approved or funded if the TPS is 50-100%.
  - 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 does not have a contra-indication to being treated with bevacizumab
  - the patient will be treated with a maximum of four 3-weekly cycles of the combination of atezolizumab (1200mg), bevacizumab (15mg/kg), carboplatin (AUC 6) and paclitaxel (200mg/m²). Note: a lower starting dose of paclitaxel 175mg/m² should be used in patients of Asian origin as per the SPC. The doses in this regimen are higher than may be the case in common practice and so careful selection of patients is required to ensure patients can tolerate the treatment.
  - after completion of the combination of atezolizumab, bevacizumab, carboplatin and paclitaxel and in the absence of disease progression, maintenance treatment with 3-weekly cycles of atezolizumab (1200mg) plus bevacizumab (15mg/kg) will continue until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent or for a maximum treatment duration of 2 years (or 35, 3-weekly cycles of atezolizumab and bevacizumab including the initial 4 induction cycles of treatment), whichever occurs first.
  - the patient has no symptomatically active brain metastases or leptomeningeal metastases
  - the patient has nor received prior treatment with an anti-PD1, antiPDL1, anti-PDL2, anti-CD137 or anti-cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) antibody
  - a formal medical review as to whether treatment with this combination should continue or not will be scheduled to occur at least by the end of the first six 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.
- WHO performance status 0, 1

### Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>Fatigue, rash, pruritis, pneumonitis, colitis, pancreatitis, diarrhoea, diabetes mellitus, adrenal insufficiency, thyroid disorders, nausea, electrolyte disturbances, hepatitis, myasthenic syndrome, Guillain Barre syndrome</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Haemorrhage, hypertension, proteinuria, impaired wound healing, gastrointestinal perforations, fistulae, arterial thrombosis</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Thrombocytopenia, peripheral neuropathy, nephrotoxicity at high doses, electrolyte disturbances</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Hypersensitivity, hypotension, bradycardia, peripheral neuropathy, myalgia and back pain on administration</td>
</tr>
</tbody>
</table>

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
- Blood pressure and dipstick urinalysis for proteinuria prior to treatment with bevacizumab
- Thyroid function tests prior to starting atezolizumab treatment and then every 6 weeks or when clinically indicated

### 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.

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.
### Day 1

<table>
<thead>
<tr>
<th>Neutrophils (x10⁹/L)</th>
<th>Dose Modifications (carboplatin and paclitaxel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or greater</td>
<td>100%</td>
</tr>
<tr>
<td>less than 1</td>
<td>Delay for 7 days. If the counts recover to at least 1x10⁹/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%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelets (x10⁹/L)</th>
<th>Dose Modifications (carboplatin and paclitaxel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 or greater</td>
<td>100%</td>
</tr>
<tr>
<td>50-99</td>
<td>Delay for 7 days. If the counts recover to at least 100x10⁹/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%</td>
</tr>
<tr>
<td>less than 50</td>
<td>Delay until recovery then reduce dose by 50%</td>
</tr>
</tbody>
</table>

There is little need to adjust the dose of atezolizumab or bevacizumab for haematological toxicity.

### Hepatic Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin (µmol/L)</th>
<th>AST/ALT units</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>1.5-3xULN OR 3-5xULN</td>
<td>Delay – see notes below</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Greater than 3xULN OR Greater than 3xULN</td>
<td>Discontinue – see notes below</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>N/A</td>
<td>N/A</td>
<td>No information available</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>N/A</td>
<td>N/A</td>
<td>No dose adjustment needed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paclitaxel</th>
<th>less than 21 and less than 10xULN</th>
<th>175mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21-26</td>
<td>135mg/m²</td>
</tr>
<tr>
<td></td>
<td>27-51</td>
<td>75mg/m²</td>
</tr>
<tr>
<td></td>
<td>52-85</td>
<td>50mg/m²</td>
</tr>
<tr>
<td></td>
<td>greater than 85 or greater than 10xULN</td>
<td>Contra indicated</td>
</tr>
</tbody>
</table>

For patients with pre-existing mild hepatic impairment no dose adjustment is recommended. Atezolizumab has not been studied in patients with moderate or severe hepatic impairment.
For a NCI-CTC grade 2 hepatitis (ALT or AST between 3-5xULN or bilirubin between 1.5-3xULN) that persists for between 5-7 days then withhold the atezolizumab and consider treatment with a corticosteroid. The corticosteroid may be resumed when the event improves to grade 1 or below within 12 weeks and the corticosteroid dose has been reduced to the equivalent of oral prednisolone 10mg per day or less.

For a grade 3 or above hepatitis (ALT or AST greater than 5xULN or bilirubin greater than 3xULN) permanently discontinue atezolizumab

**Renal Impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>N/A</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>N/A</td>
<td>No information available</td>
</tr>
<tr>
<td>Carboplatin*</td>
<td>less than 20</td>
<td>Omit</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>N/A</td>
<td>No dose adjustment needed</td>
</tr>
</tbody>
</table>

* 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.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced to 75% of the original dose or discontinued as appropriate.

**Atezolizumab**

Atezolizumab 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\(^3\).

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

Atezolizumab 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.

<table>
<thead>
<tr>
<th>Immune-related adverse reaction</th>
<th>Severity</th>
<th>Treatment modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-related pneumonitis</td>
<td>Grade 2 pneumonitis</td>
<td>Withhold until symptoms resolve and radiographic abnormalities improve. Consider treatment with oral prednisolone 1-2mg/kg or equivalent per day. Treatment may be resumed if the event improves to grade 0 or grade 1 within 12 weeks, and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 pneumonitis</td>
<td>Permanently discontinue atezolizumab. Consider treatment with corticosteroids.</td>
</tr>
<tr>
<td>Immune-related colitis</td>
<td>Grade 2 or 3 diarrhoea or symptomatic colitis</td>
<td>Withhold the atezolizumab initially. For a grade 2 diarrhoea or colitis, if the symptoms persist for more than 5 days or recur, start treatment with 1-2mg/kg oral prednisolone or equivalent per day. For a grade 3 diarrhoea or colitis treatment with intravenous corticosteroids should be started, this may be converted to oral treatment as symptoms improve. If the symptoms improve to grade 1 or less taper the corticosteroids over one month. Treatment may be resumed if the event improves to grade 0 or grade 1 within 12 weeks, and</td>
</tr>
</tbody>
</table>
**Immune-related pancreatitis**

<table>
<thead>
<tr>
<th>Grade 3 or 4 serum amylase or lipase levels increased (more than 2xULN) or grade 2 or 3 pancreatitis</th>
<th>Withhold atezolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment with atezolizumab may be resumed if serum amylase and lipase levels improve to grade 0 or grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to 10mg or less oral prednisone or equivalent per day</td>
</tr>
</tbody>
</table>

| Grade 4 or any grade of recurrent pancreatitis | Permanently discontinue atezolizumab. Consider treatment with corticosteroids. |

**Immune-related thyroid disorders**

<table>
<thead>
<tr>
<th>Grade 4 or any grade of recurrent pancreatitis</th>
<th>Permanently discontinue atezolizumab. Consider treatment with corticosteroids.</th>
</tr>
</thead>
</table>

**Immune-related adrenal insufficiency**

<table>
<thead>
<tr>
<th>Grade 4 or any grade of recurrent pancreatitis</th>
<th>Permanently discontinue atezolizumab. Consider treatment with corticosteroids.</th>
</tr>
</thead>
</table>

**Immune-related diabetes mellitus**

<table>
<thead>
<tr>
<th>Grade 4 or any grade of recurrent pancreatitis</th>
<th>Permanently discontinue atezolizumab. Consider treatment with corticosteroids.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>Grade</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>Immune-related myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome and meningoencephalitis</td>
<td>All grades</td>
</tr>
<tr>
<td>Myositis</td>
<td>Grade 2-3</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Infusion related reactions</td>
<td>Grade 1</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
</tr>
<tr>
<td>Immune-related rash</td>
<td>Grade 3 rash</td>
</tr>
<tr>
<td></td>
<td>Grade 4 rash</td>
</tr>
</tbody>
</table>

**Bevacizumab**

Bevacizumab doses should be omitted and not reduced for adverse reactions. If more than two doses are missed due to adverse events treatment should be stopped. It should be noted that the half life of bevacizumab is approximately twenty days. Discontinuation of treatment in response to adverse effects is not expected to influence the short term clinical evolution of the event, symptomatic treatment is often necessary.
Bevacizumab should be stopped if the individual develops:

- Gastrointestinal perforation
- Arterial thromboembolic events
- NCI-CTC grade 3 and above haemorrhagic events (requiring a blood transfusion or a major non-elective intervention)
- NCI-CTC grade 3 and above congestive heart failure or left ventricular function
- NCI-CTC grade 4 fistula

If a NCI-CTC symptomatic grade 4 venous thromboembolic event occurs bevacizumab should be stopped. However, if this is a pulmonary embolism bevacizumab may be re-started once a full recovery has been made and the individual is anti-coagulated with a subcutaneous low molecular weight heparin. An oral anticoagulant must not be used.

Hypertension is a common consequence of bevacizumab therapy. For a NCI-CTC grade 1 hypertension no treatment is necessary. NCI-CTC grade 2 hypertension, consider anti-hypertensive therapy. For a NCI-CTC grade 3 and above hypertension that is persistent consider stopping treatment.

Bevacizumab may be continued for a NCI-CTC grade 1 proteinuria or the first occurrence of a grade 2 proteinuria. For the second occurrence of a NCI-CTC grade 2 proteinuria or any NCI-CTC grade 3 proteinuria give the bevacizumab as scheduled. A 24 hour urine collection or UPCR should be conducted at most three days before the next dose. If there is less than 2g protein per 24 hours or a UPCR 0-1 administer the bevacizumab and return to dipstick monitoring. If there is more than 2g protein per 24 hours omit the bevacizumab. Repeat the 24 hour urine collection prior to the next scheduled dose. If this is less than 2g per 24 hours administer the bevacizumab and continue 24 hour urine collection until the protein is 1g per 24 hours or less.

Regimen

**Induction - 21 day cycle for 4 cycles**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>1200mg</td>
<td>1</td>
<td>Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>15mg/kg</td>
<td>1</td>
<td>Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes (see administration information)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 6 (maximum dose 900mg)</td>
<td>1</td>
<td>Intravenous infusion in 500ml glucose 5% over 60 minutes</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>200mg/m²</td>
<td>1</td>
<td>Intravenous infusion in 500ml sodium chloride 0.9% over 180 minutes.</td>
</tr>
</tbody>
</table>

Followed by:

**Maintenance – 21 day cycle for a further 31 cycles (35 cycles in total)**

Atezolizumab is continued until loss of clinical benefit or unmanageable toxicity

Bevacizumab is continued until disease progression or unacceptable toxicity.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
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<tr>
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<td>1</td>
<td>Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>15mg/kg</td>
<td>1</td>
<td>Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes (see administration information)</td>
</tr>
</tbody>
</table>

### Dose Information

- Bevacizumab will be dose banded in accordance with the national dose bands (bevacizumab)
- The recommended maximum dose when using a calculated creatinine clearance at AUC 6 is 900mg. 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 dose will be rounded to the nearest 50mg (up if halfway).
- Paclitaxel will be dose banded in accordance with the national dose bands (6mg/ml)
- A lower starting dose of paclitaxel 175mg/m² should be used in patients of Asian origin as per the SPC

### Administration Information

#### Extravasation

- Atezolizumab – neutral
- Bevacizumab – neutral
- Carboplatin – irritant
- Paclitaxel - vesicant

#### Other

- The first infusion of atezolizumab should be administered over 60 minutes. If this is well tolerated subsequent infusions can be administered over 30 minutes.
- The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes
- 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 severe 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.

**Additional Therapy**

- Premedication to reduce risk of hypersensitivity reaction
  
  30 minutes before paclitaxel
  
  - chlorphenamine 10mg intravenous
  - dexamethasone 20mg oral or intravenous
  - H₂ antagonist according to local formulary choice and availability

- Antiemetics
  
  15-30 minutes prior to chemotherapy (cycles 1-6 only)
  
  - ondansetron 8mg oral or intravenous

  As take home medication (cycles 1-6 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

- 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 H₂ 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 atezolizumab 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 atezolizumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of atezolizumab.

- Patients must be given an atezolizumab Patient Alert Card.
References
REGIMEN SUMMARY

Atezolizumab-Bevacizumab-Carboplatin (AUC6)-Paclitaxel

Cycle 1, 2, 3, 4

1. **Atezolizumab 1200mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes**
   
   **Administration Instructions**
   
   The first infusion of atezolizumab should be administered over 60 minutes. If this is well tolerated subsequent infusions can be administered over 30 minutes.

   Ensure the patient has been an atezolizumab patient alert card.

2. **Bevacizumab 15mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes**
   
   **Administration Instructions**
   
   The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes.

3. **Chlorphenamine 10mg intravenous**

4. **Dexamethasone 20mg intravenous**

5. **H₂ 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 H₂ antagonist provided there is no instruction in the ARIA journal indicating the patient must have H₂ 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 H₂ 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.

6. **Ondansetron 8mg oral or intravenous**

7. **Warning - Check paclitaxel dose**
   
   **Administration Instructions**
   
   A lower starting dose of paclitaxel 175mg/m² should be used in patients of Asian origin as per the SPC

8. **Paclitaxel 200mg/m² in 500ml sodium chloride 0.9% intravenous infusion over 180 minutes.**
   
   **Administration Instructions**
   
   A lower starting dose of paclitaxel 175mg/m² should be used in patients of Asian origin as per the SPC

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

9. **Carboplatin AUC 6 (maximum dose 900mg) intravenous infusion in 500ml glucose 5% over 60 minutes**

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

11. **Hydrocortisone 100mg intravenous injection when required for infusion related reactions**
12. 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**

13. Dexamethasone 4mg oral twice a day for 3 days starting the day after chemotherapy

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

15. Loperamide as directed (cycle 1 only)

**Cycle 5-35**

16. Atezolizumab 1200mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes  
**Administration Instructions**  
The first infusion of atezolizumab should be administered over 60 minutes. If this is well tolerated subsequent infusions can be administered over 30 minutes. 
Ensure the patient has been an atezolizumab patient alert card.

17. Bevacizumab 15mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes  
**Administration Instructions**  
The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes.

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

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

20. 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.
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.