**Chemotherapy Protocol**

## GENITOURINARY CANCER

**Atezolizumab (1680mg-28 days)**

### Regimen

- Urothelial– Atezolizumab (1680mg-28 days)

### Indication

- This protocol was developed in response to the COVID-19 pandemic and covers patients;

  - with inoperable locally advanced or metastatic urothelial cancer who would normally be treated with 1st line platinum-based chemotherapy
  - whose disease is either locally advanced (i.e. T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease)
  - who have not received any previous chemotherapy for inoperable locally advanced or metastatic urothelial cancer
  - who have either not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy, or if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy, has relapsed = 12 months since completing the platinum-based chemotherapy
  - who have an WHO performance status (PS) of 0, 1 or 2. The treatment of patients of performance status 2 should only proceed with caution as there is limited safety data on PS 2 patients with urothelial cancer treated with atezolizumab
  - who do not have any symptomatically active brain metastases or leptomeningeal metastases.
  - who have not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PDL2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless it was received as part of the atezolizumab compassionate use programme
  - urothelial tumour has undergone PD-L1 testing. It is important for clinicians to be aware that based on an IMvigor130 trial Data Monitoring Committee recommendation following an early review of survival data, accrual of patients on the atezolizumab monotherapy arm with tumours staining positive for PD-L1 at the <5% level was stopped in the trial after an observation of decreased overall survival in this subgroup. As a consequence the atezolizumab marketing authorisation was changed such that 1st line use of atezolizumab for patients ineligible for cisplatin was restricted to patients with urothelial tumours having a PD-L1 expression of equal to 5%. Clinicians should consider this information in patients with tumours staining less than 5% for PD-L1 at the same time as being aware that the trial randomised against cisplatin- or carboplatin-based chemotherapy-containing arms and such chemotherapy may not be in the best interests of patients during the COVID19 pandemic.
  - formal medical review as to whether treatment with atezolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment
  - is to be treated until disease progression and loss of clinical benefit or

excessive toxicity or patient choice, whichever is the sooner.
- the patient will receive a maximum treatment duration of 2 years (i.e. a maximum of 35 administrations if given every 3 weeks or 26 administrations if given every 4 weeks)

## Toxicity

| Drug | Adverse Effect |
|---|---|
| Atezolizumab | Fatigue, rash, pruritis, pneumonitis, colitis, pancreatitis, diarrhoea, diabetes mellitus, adrenal insufficiency, thyroid disorders, nausea, electrolyte disturbances, hepatitis, myasthenic syndrome, Guillain Barre syndrome |

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

## Monitoring

### *Regimen*

- FBC, LFTs and U&Es prior to day one of each cycle
- Thyroid function tests prior to starting treatment and then every 6 weeks or when clinically indicated.

## Dose Modifications

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

In principle no dose reductions are recommended for atezolizumab. The preference is to delay the dose or discontinue treatment.

Please discuss all treatment delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

### *Haematological*

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

There are no standard dose adjustments for haematological toxicity with atezolizumab treatment.

*Hepatic Impairment*

| Drug | Bilirubin (µmol/L) | | AST/ALT units | Dose |
|---|---|---|---|---|
| Atezolizumab | 1.5-3xULN | OR | 3-5xULN | Delay – see notes below |
| | Greater than 3xULN | OR | Greater than 5xULN | Discontinue – see notes below |

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 a 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 tapered over at least one month if the LFTs improve. Treatment with atezolizumab 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*

No dose adjustment is required in patients with pre-existing renal impairment.

*Other*

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[(2)].

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 month's 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.

| Immune-related adverse reaction | Severity | Treatment modification |
|---|---|---|
| Immune-related pneumonitis | Grade 2 pneumonitis | Withhold until symptoms resolve and radiographic abnormalities improve. Consider treatment with oral prednisolone 1-2mg/kg or equivalent per day<br><br>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. |
| | Grade 3 or 4 pneumonitis | Permanently discontinue atezolizumab. Consider treatment with corticosteroids. |
| Immune-related colitis | Grade 2 or 3 diarrhoea or symptomatic colitis | Withhold the atezolizumab initially.<br><br>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<br><br>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<br><br>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 |
| | Grade 4 diarrhoea or colitis | Permanently discontinue |

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|---|---|---|
| | | atezolizumab. Consider treatment with corticosteroids. |
| Immune-related pancreatitis | Grade 3 or 4 serum amylase or lipase levels increased (more than 2xULN) or grade 2 or 3 pancreatitis | Withhold atezolizumab<br><br>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 |
| | Grade 4 or any grade of recurrent pancreatitis | Permanently discontinue atezolizumab. Consider treatment with corticosteroids. |
| Immune-related thyroid disorders | Symptomatic | Withhold atezolizumab<br><br>*Hypothyroidism*<br><br>Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing<br><br>*Hyperthyroidism*<br><br>Treatment may be resumed when symptoms are controlled by cabimazole or equivalent and thyroid function is improving |
| Immune-related adrenal insufficiency | Symptomatic | Withhold atezolizumab<br><br>Treatment may be resumed if the symptoms improve to grade 0 or grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10mg or less of oral prednisone or equivalent per day and patient is stable on replacement therapy |
| Immune-related diabetes mellitus | Grade 3 or 4 hyperglycaemia (fasting glucose more than 250-500mg/dL or 13.9mmol/L) | Withhold atezolizumab<br><br>Treatment may be resumed if metabolic control is achieved on insulin replacement therapy |
| Immune-related myasthenic | All grades | Permanently discontinue |

| | | |
|---|---|---|
| syndrome / myasthenia gravis, Guillain-Barre syndrome and meningoencephalitis | | atezolizumab |
| Myositis | Grade 2-3 | Withhold for a moderate to severe myositis and discontinue |
| | Grade 3-4 | Permanently discontine |
| Infusion related reactions | Grade 1 | Reduce the infusion rate to half<br><br>Once the event has resolved, wait for 30minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to original rate |
| | Grade 2 | Withhold atezolizumab<br><br>Restart at half of the infusion rate only after the symptoms have resolved |
| | Grade 4 | Permanently discontinue atezolizumab |
| Immune-related rash | Grade 3 rash | Withhold atezolizumab<br><br>Treatment may be resumed if the rash is resolved and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day |
| | Grade 4 rash | Permanently discontinue atezolizumab. Consider treatment with corticosteroids |

## Regimen

**28 day cycle until loss of clinical benefit or unmanageable toxicity or two years of treatment has been given (26 cycles will be set in Aria)**

| Drug | Dose | Days | Route |
|---|---|---|---|
| Atezolizumab | 1680mg | 1 | Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes |

## Dose Information

- If a planned dose of atezolizumab is missed, it should be administered as soon as possible. Do not wait until the next planned dose. The schedule of administration must be adjusted to maintain a 28 day period between doses.

## Administration Information

### *Extravasation*

- Atezolizumab – neutral

### *Other*

- The first infusion of atezolizumab should be administered over 60 minutes. If this is well tolerated subsequent infusions can be administered over 30minutes.

- Please refer to the toxicity table above for the actions to be taken in relation to infusion related reactions.

## Additional Therapy

- No antiemetics are 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 proton pump inhibitor or a $H_2$ 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

1. Balar AV, Galsky MD, Rosenberg JE et al. Atezolizumab as a first line treatment in cisplatin ineligible patients with locally advanced and metastatic urothelial carcinoma; a single arm multicentre phase two trial. Lancer 2017; 389 (10064): 67-76.
2. Haanen J, Carbonnel F, Robert C, Kerr K.M , Peters S, Larkin J, Jordan J on behalf of the ESMO Guidelines Committee. Management of toxicities from immunotherapy. ESMO clinical practice guidelines for diagnosis, treatment and follow up. Ann Oncol 2017; 28 (suppl 4): 119-142.

## REGIMEN SUMMARY

## Atezolizumab (1680mg-28 days)

### Day One

1. Atezolizumab 1680mg 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 30minutes.

   Ensure the patient has been an atezolizumab patient alert card.

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

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

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

## DOCUMENT CONTROL

| Version | Date | Amendment | Written By | Approved By |
|---|---|---|---|---|
| 1 | Sept 2020 | None | Dr Deborah Wright<br>Pharmacist | Dr Mathew Wheater<br>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.