

Chemotherapy Protocol

LUNG CANCER

Atezolizumab (1680mg 28 days)

Regimen

- Lung – Atezolizumab

Indication

- Atezolizumab is indicated for treating previously platinum-treated locally advanced/ metastatic non-small cell lung cancer where all the following criteria are met;
 - the patient has a histologically- or cytologically-confirmed diagnosis of stage IIIB or IV non-small cell lung cancer and is either non-squamous or squamous in type.
 - the patient has either progressed after previously receiving at least 2 cycles of platinum-containing chemotherapy for stage IIIB or IV non-small cell lung cancer and also a targeted treatment if the tumour is EGFR positive or ALK positive or progressed within 6 months of completing platinum-based chemotherapy given as adjuvant or neoadjuvant therapy or concurrent with radiotherapy.
 - PD-L1 testing with an approved and validated test to determine the Tumour Proportion Score (TPS) has been attempted prior to this application. Either; the TPS score will be documented or the TPS score cannot be documented as the TPS result was unquantifiable or PD-L1 testing was not possible as the pathologist has documented that there is insufficient tissue for PD-L1 analysis.
 - the patient has no symptomatically active brain metastases or leptomeningeal metastases.
 - atezolizumab will be administered as monotherapy
 - 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
 - atezolizumab will be stopped at 2 years of treatment or on loss of clinical benefit or unacceptable toxicity, whichever occurs first.
 - a 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 first 9 weeks of treatment
 - treatment breaks of up to 12 weeks beyond the expected cycle length of atezolizumab are allowed solely to allow immune toxicities to settle

- WHO performance status 0, 1 and be otherwise fit for second line docetaxel therapy

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

		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 <i>Hypothyroidism</i> Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing <i>Hyperthyroidism</i> Treatment may be resumed when symptoms are controlled by cabimazole or equivalent and thyroid function is improving
Immune-related adrenal insufficiency	Symptomatic	Withhold atezolizumab 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 13.9 mmol/L)	Withhold atezolizumab Treatment may be resumed if metabolic control is achieved on insulin replacement therapy
Immune-related myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome and meningoencephalitis	All grades	Permanently discontinue atezolizumab
Myositis	Grade 2-3	Withhold for a moderate to severe myositis and discontinue
	Grade 3-4	Permanently discontinue

Infusion related reactions	Grade 1	Reduce the infusion rate to half 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 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 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 to a maximum of 26 cycles (two years)

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 for reasons other than toxicity, 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 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

1. National Institute for Health and Clinical Excellence (2018). Technology Appraisal 520. Atezolizumab for treating locally advanced or metastatic non-small cell lung cancer after chemotherapy. NICE:DOH.
2. 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.

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	Nanda Basker Haematology Pharmacist	Dr Judith Cave 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. These protocols are only one source of information. They should be read in conjunction with the latest Summary of Product Characteristics and published information.