Chemotherapy Protocol

BREAST CANCER

Atezolizumab-Paclitaxel Albumin Bound

Regimen

- Breast – Atezolizumab-Paclitaxel Albumin Bound

Indication

- Atezolizumab in combination with paclitaxel albumin bound is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression greater than or equal to 1% and who have not received prior chemotherapy for metastatic disease according to the following criteria;

  - the patient has a histologically or cytologically-confirmed diagnosis of locally advanced and unresectable breast cancer or metastatic breast cancer
  - the patient's breast cancer has had receptor analysis performed and this is negative for the HER2, oestrogen and progesterone receptors, ie the patient has triple negative disease
  - that the patient's breast cancer has been tested for PD-L1 expression on tumour cells and the test result has demonstrated PD-L1 expression of greater than or equal to 1%
  - that the patient has not been treated with any chemotherapy for locally advanced or metastatic breast cancer
  - the patient is eligible for treatment with chemotherapy for the locally advanced/metastatic breast cancer
  - 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
  - that the patient has no symptomatically active brain metastases or leptomeningeal metastases
  - that the patient has a WHO performance status of 0, 1 or 2
  - that a formal medical review as to whether treatment with the combination of atezolizumab and nab-paclitaxel should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
  - that treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any immune toxicities to settle

Toxicity

Drug	Adverse Effect
Atezolizumab	Fatigue, rash, pruritis, pneumonitis, colitis, pacreatitis, diarrhoea, diabetes mellitus, adrenal insufficiency, thyroid disorders, nausea, electrolyte disturbances, hepatitis, myasthenic syndrome, Guillain Barre syndrome, myositis
Paclitaxel Albumin Bound	Neuropathy, hypersensitivity, arthralgia, alopecia, rash

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 1, 8, 15 of each cycle
- Thyroid function tests prior to starting treatment and then every 6 weeks or if 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. The dose should be delayed or treatment stopped in relation to toxicity. The following applies to paclitaxel albumin bound. Prior to day one the following applies;

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Table Two - Dose modifications for neutropenia and/or thrombocytopenia at the start of a cycle or within a cycle

Cycle Day	Neutrophil ($x10^9$/L)		Platelet ($x10^9$/L)	Paclitaxel Albumin Bound
1	less than 1.5	or	less than 100	Delay until recovery
8	equal to or more than 0.5 but less than 1	or	equal to or more than 50 but less than 75	Reduce one dose level
8	less than 0.5	or	less than 50	Withhold
15	**If the day 8 doses were given without modification**			
15	equal to or more than 0.5 but less than 1	or	equal to or more than 50 but less than 75	Treat with day 8 dose level and follow with growth factors OR reduce doses 1 dose level from day 8 doses
15	less than 0.5	or	less than 50	Withhold
15	**If the day 8 doses were reduced**			
15	equal to or more than 1	and	Equal to or more than 75	Return to the day 1 dose levels and follow with growth factors OR treat with same doses as day 8
15	equal to or more than 0.5 but less than 1	or	equal to or more than 50 but less than 75	Treat with day 8 dose levels and follow with growth factors OR reduce doses 1 dose level from day 8 doses
15	less than 0.5	or	less than 50	Withhold
15	**If the day 8 doses were withheld**			
15	equal to or more than 1	and	more than 75	Return to day 1 dose levels and follow with growth factors OR reduce doses 1 dose level from day 1 doses
15	equal to or more than 0.5 but less than 1	or	Equal to or more than 50 but less than 75	Reduce 1 dose level and follow with growth factors OR reduce doses 2 dose levels from day 1 doses
15	Less than 0.5	or	Less than 50	Withold

Hepatic Impairment

Atezolizumab

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.

Paclitaxel Albumin Bound

For patients with mild hepatic impairment (total bilirubin between 1 to 1.5 x ULN and aspartate aminotransferase [AST] less than or equal to 10 x ULN) no dose adjustments are required. Treat with same doses as patients with normal hepatic function.

For metastatic breast cancer patients with moderate to severe hepatic impairment (total bilirubin between 1.5 to 5 x ULN and AST less than or equal to 10 x ULN), a 20% reduction in dose is recommended. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles.

Renal Impairment

Atezolizumab

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

Paclitaxel Albumin Bound

Adjustment of the starting dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance 30 to 90 ml/min). There are insufficient data available to recommend dose modifications of paclitaxel albumin bound in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance less than 30ml/min).

Other

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[(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 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. 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 corticosteroids have been reduced to 10mg or less oral prednisone

		equivalent per day
	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	Withhold atezolizumab 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 *Hypothyroidism* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism* 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)	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 discontine
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

Paclitaxel Albumin Bound

Adjust the dose of paclitaxel albumin bound according to the following table;

Table One - Dose level reductions for paclitaxel albumin bound

Dose Level	Paclitaxel Albumin Bound (mg/m^2)
Full	100
1st level reduction	75
2nd level reduction	50
If additional dose reduction required	Discontinue

These should be applied for the following adverse effects;

Adverse Reaction	Paclitaxel Albumin Bound
Febrile Neutropenia (NCI-CTC grade 3-4)	Withhold doses until fever resolves and the neutrophil count is $1.5x10^9$/L or above then resume at next lower dose level
Peripheral Neuropathy (NCI-CTC grade 3-4)	Withhold dose until improves to NCI-CTC grade 1 or below then resume at next lower dose level
Cutaneous toxicity (NCI-CTC grade 2-3)	Reduce to next lower dose level, discontinue treatment if the adverse drug reaction persists
Gastrointestinal toxicity (grade 3 mucositis or diarrhoea)	Withhold doses until improves to NCI-CTC grade 1 or below then resume at next lower dose level

Regimen

28 day cycle with a target of at least 6 cycles administered and with no maximum of treatment cycles in the absence of disease progression, unacceptable toxicity or withdrawal of patient consent (12 cycles will be set in ARIA).

It is worthy of note that at the time of writing this is an unlicensed schedule of dosing.

Drug	Dose	Days	Route
Atezolizumab	840mg	1, 15	Intravenous infusion in 100ml sodium chloride 0.9% over 60 minutes
Paclitaxel albumin bound	$100mg/m^2$	1, 8, 15	Intravenous infusion over 30 minutes

Dose Information

- Paclitaxel albumin bound will be dose banded in accordance with the national dose bands (paclitaxel albumin)

Administration Information

Extravasation

- Atezolizumab – neutral
- Paclitaxel albumin bound - exfoliant

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.

- The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer paclitaxel albumin bound may result in the formation of proteinaceous strands. Administer using an infusion set incorporating a 15 µm filter to avoid administration of these strands. Use of a 15 µm filter removes strands and does not change the physical or chemical properties of the reconstituted product. Use of filters with a pore size less than 15 µm may result in blockage of the filter

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy on days 1, 8, 15

  - metoclopramide 10mg oral or intravenous

  As take home medication on **day 1** only;

  - metoclopramide 10mg three times a day when required oral

- As required for the treatment of infusion related reactions on days 1 and 15;

  - 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.

Coding

- Procurement – X70.8
- Delivery – X72.9, X72.4

References
1. Schmid P, Adams S, Rugo HS et al. Atezolizumab and nab-paclitaxel in advanced triple negative breast cancer. N Engl J Med 2018; 379: 2108-2121.
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-Paclitaxel albumin bound

Day 1, 15

1. Atezolizumab 840mg intravenous infusion in 100ml 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. Metoclopramide 10mg oral or intravenous

3. Paclitaxel albumin bound 100mg/m^2 intravenous infusion over 30 minutes
Administration Instructions
The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer paclitaxel albumin bound may result in the formation of proteinaceous strands. Administer using an infusion set incorporating a 15 µm filter to avoid administration of these strands. Use of a 15 µm filter removes strands and does not change the physical or chemical properties of the reconstituted product. Use of filters with a pore size less than 15 µm may result in blockage of the filter

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

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

6. Paracetamol 1000mg oral when required for the relief of 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

Day 8

7. Metoclopramide 10mg oral or intravenous

8. Paclitaxel albumin bound 100mg/m^2 intravenous infusion over 30 minutes
Administration Instructions
The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer paclitaxel albumin bound may result in the formation of proteinaceous strands. Administer using an infusion set incorporating a 15 µm filter to avoid administration of these strands. Use of a 15 µm filter removes strands and does not change the physical or chemical properties of the reconstituted product. Use of filters with a pore size less than 15 µm may result in blockage of the filter

Take Home Medicines (day 1 only)

9. Metoclopramide 10mg three times a day when required oral
Administration Instructions
Please supply 60 tablets or two original packs as appropriate

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	April 2020	Infusion volume changed	Siow Chin Phua Pharmacist	Dr Deborah Wright Pharmacist
1	August 2019	None	Dr Deborah Wright Pharmacist	Dr Chern Lee 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 Hospital 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.