SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Atezolizumab/Paclitaxel Albumin (Abraxane) TRIPLE NEGATIVE BREAST CANCER

PROTOCOL REF: MPHAAPABR
(Version No. 2.0)

Approved for use in:

First line treatment of unresectable locally advanced/metastatic triple negative breast cancer (HR negative, HER2 negative PR negative), inclusion criteria:

- PD-L1 ≥ 1%- PD-L1 expression status in tumour-infiltrating immune cells (IC)
- PS 0-1
- Asymptomatic CNS disease
- Patients who have never had any pior treatment with anti-PDL1/PD-1 treatment or has received prior neoadjuvant and adjuvant treatment with anti-PDL1/PD-1 treatment and there was no disease progression during such treatment and for at least 12 months after completion.

************Blueteq Registration Required************

Dosage:

Drug	Dose	Route	Frequency	
Atezolizumab	840mg (flat dose)	IV infusion	Days 1 and 15 4 weekly	Until progression or unacceptable toxicity
Paclitaxel Albumin (Abraxane)	100mg/m^2	IV infusion	Days 1, 8 and 15 every 4 weeks	Until disease progression or unacceptable toxicity

NHSE recommendation: target of at least 6 cycles of Abraxane, however there is no maximum number of cycles

Administration + Counselling Points:

Women of childbearing potential should use effective contraception throughout treatment and for at least 5 months following the last dose of atezolizumab.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection / sepsis
- Flu like symptoms are common, particularly during cycle 1.
- Pregnancy test if applicable. Women of childbearing potential have to use effective contraception during and for 5 months after treatment with atezolizumab. Serum samples for HIV, Hep C antibody and HBsAg if risk factors

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

Metoclopramide 10mg oral tablets 3 times a day as required

Extravasation risk:

Atezolizumab is a monoclonal antibody – Neutral

Paclitaxel albumin (Abraxane) - Vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	**Atezolizumab**	GFR ≥ 30ml/min- proceed with treatment GFR < 30ml/min- limited data use with caution

	Paclitaxel Albumin (Abraxane)	CrCl ≥ 30ml/min (mild to moderate renal impairmtent) – proceed with treatment

Hepatic	**Atezolizumab**	Administered with caution in patients with: Moderate (total bilirubin > 1.5 -3 × ULN and any AST) or Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment. * Within normal limits or high Refer to 'Dose Modification and Toxicity' section if LFTs become deranged AFTER starting treatment with immunotherapy	
	Paclitaxel Albumin (Abraxane)	AST < 10 x ULN or BIL ≤ 1.25 x ULN	Full dose
		AST < 10 x ULN and BIL ≤ 5 x ULN	Interrupt treatment until AST < 10 x ULN or BIL ≤ 1.25 x ULN (if no resolution within 3 weeks discontinue treatment) Reduce by 1 dose level
		AST > 10 x ULN or BIL > 5 x ULN	Discontinue Treatment

Interactions:

Atezolizumab
No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
Paclitaxel albumin (Abraxane)
Paclitaxel toxicity may be increased with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, ritonavir and nelfinavir)- use with caution

Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended- paclitaxel efficacy may be compromised.

For more detailed interactions please refer to the SmPC for each agent.

Treatment schedule:

Cycles 1 to 6

Day	Drug	Dose	Route	Diluent and rate
1 and 15	Atezolizumab	840mg	IV infusion	250mL sodium chloride 0.9%. Infused over 60 minutes for cycle 1 if well tolerated cycle 2 onwards can be administered over 30minutes in a non-pyrogenic line with a 0.2 micron filter
	Note: change administration line between infusions			
1, 8 and 15	Paclitaxel Albumin (Abraxane)	100mg/m^2	IV infusion	Sodium Chloride 0.9% over 30 minutes via a giving set with a 15 micron filter

Cycle is repeated every 28 days

Cycle 7 onwards: If decision has been made to stop Abraxane due to toxicity, Atezolizumab may be continued as a single agent either 3 or 4 weekly:

Day	Drug	Dose	Route	Frequency	Diluent and rate
1	**Atezolizumab**	**1875mg** (flat dose)	**SC**	3 weekly	Administer over 7 minutes
SUBCUTANEOUS ROUTE IS THE PREFERRED ROUTE UNLESS PATIENT INTOLERANT The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with atezolizumab SC formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.					

OR					
1	Sodium chloride 0.9%	250mL	IV	Prior to each Atezolizumab infusion.	Flush
	Atezolizumab	**1680mg** (flat dose)	**IV**	4 weekly	250mL sodium chloride 0.9%. Infused over 60 minutes for cycle 1 if well tolerated cycle 2 onwards can be administered over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
OR					
1	Sodium chloride 0.9%	250mL	IV	Prior to each Atezolizumab infusion.	Flush
	Atezolizumab	**1200mg** (flat dose)	**IV**	3 weekly	250mL sodium chloride 0.9%. Infused over 60 minutes for cycle 1 if well tolerated cycle 2 onwards can be administered over 30 minutes in a non-pyrogenic line with a 0.2 micron filter

Main toxicities:

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Atezolizumab	
Immune-Mediated Pneumonitis Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%).	Monitor patients for signs and symptoms and evaluate with radiographic imaging and administer corticosteroids for toxicities of grade 2 or above.
Immune-Mediated Colitis	Monitor patients for signs and symptoms and administer corticosteroids for grade 2 or greater.
Other Immune-Mediated Toxicities: Hepatitis Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia, Guillain-Barré syndrome	Monitor LFTs, biochemistry, cortisol, TFTs and blood glucose, consider corticosteroids for grade 2 or greater.
Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Symptomatic management for grade 1 with close monitoring
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Monitor at each cycle and rule out immune-medicated reaction
Injection site reaction (for subcutaneous preparation)	
Injection site pain, erythema, and rash	Symptomatic management for grade 1 with close monitoring. Pre-medication to be added to subsequent cycles.

Paclitaxel Albumin (Abraxane)	
Haematological	Neutropenia, anaemia, thrombocytopenia,
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis
Immune system	Abraxane- hypersensitivity reactions* uncommon Paclitaxel- minor hypersensitivity reactions* (mainly flushing and rash), significant hypersensitivity reactions requiring therapy, anaphylactic reactions
Cardiac and vascular disorders	Abraxane- tachycardia, arrhythmia, supraventricular tachycardia are common
Musculoskeletal	Arthralgia, myalgia
Nervous system	Peripheral neuropathy
Hepatobiliary	Elevation of liver transaminases, alkaline phosphatase and bilirubin.
Skin and subcutaneous tissue disorders	Alopecia Allergic skin rash frequently associated with pruritus
General disorders and administration site conditions	Fatigue Infertility, early menopause

Investigations and treatment plan:

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 1 D8	Cycle 1 Day 15	Cycle 2 D1	Cycle 2 D8	Cycle 2 D15	Cycle 3	Ongoing
Informed Consent	x								
Clinical Assessment	x							x	Then every 12 weeks or as clinically indicated
On treatment review / Go ahead	x	x	x	x	x	x	x	x	Day before treatment for abraxane only
SACT Assessment (to include PS and toxicities)	x	x	x	x	x	x	x	x	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (ALT, AST and Bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x	x	x	x	x	x	x	Every cycle
Lipid profile (cholesterol)	x								At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x								At baseline then if clinically indicated

Full set of observations (*BP, heart rate, temperature, respiratory rate and O_2 sats*)		x							At baseline then if clinically indicated
CrCl (Cockcroft and Gault)	x	x	x	x	x	x	x	x	<u>With chemotherapy (abraxane)</u> Every cycle <u>Atezolizumab ONLY (no chemotherapy)</u> With every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline
CT scan	X								Every 12 weeks or as clinically indicated
Trop-T, CK, pro-BNP	X								At baseline (refer to 'Pre-assessment Baseline Cardiac Pathway' guidance) and thereafter as clinically indicated (ECG to be reviewed by ANP or ECG clinic or clinical team)
ECG	X								
Weight recorded	X	X	X	X	X	X	X	X	Every cycle
Height recorded	X								

Pregnancy test if applicable.

Dose Modifications and Toxicity Management:

- Dose modifications due to toxicity are ONLY permitted on chemotherapy agents
- Only dosing delay or discontinuation due to toxicity are permitted for atezolizumab based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of atezolizumab doses are contained in 'Treatment Threshold' section below.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.
- If a toxicity is considered to be due solely to one component of the regimen (i.e. Atezolizumab or Paclitaxel Albumin) and the dose of that component is delayed or modified in accordance with the regimen protocol the other component may be administered **if there is no** contraindication and at the **discretion of the clinical team managing the patient.**
- If it is anticipated that Paclitaxel Albumin will be delayed by ≥ 2 weeks, then the Atezolizumab should be given without the chemotherapy if there is no contraindication.

Haematological toxicity:

Proceed on day 1 of each cycle prior to Paclitaxel Albumin administration (cycles 1-6):

ANC ≥ 1.5 x 10^9/L	Platelets ≥ 100 x 10^9/L

Proceed on day 8 or 15 of each cycle, prior to Paclitaxel Albumin administration (cycles 1-6):

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L
If Paclitaxel Albumin (Abraxane) cannot be administered on day 15 then this dose should be omitted and then next dose be given on day 1 of subsequent cycle if bloods have recovered sufficiently	

Single agent Atezolizumab.

Platelets	Neutrophils	Creatinine Clearance (mL/min)	Bilirubin	AST/ALT
≥ 75x10^9/L	≥ 1.0 x 10^9/L	≥30	<3 x ULN	<3 x ULN

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Dose Level	Paclitaxel Albumin (Abraxane) Dose (mg/m^2)
Starting dose	100
1st dose reduction	75
2nd dose reduction	50

Haematological Toxicity	Occurrence	Weekly Paclitaxel Albumin Dose (mg/m^2)
Neutropenic fever (nadir ANC <1.5 x 10^9/L with fever > 38°C) or Delay of next cycle by > 7 days for nadir ANC <1.5 x 10^9/L or Nadir ANC < 1.5 x 10^9/L for > 7 days	1st	Reduce by 1 dose level
	2nd	
	3rd	Discontinue treatment
Nadir Platelets < 50 x 10^9/L	1st	Reduce by 1 dose level
	2nd	Discontinue Treatment

Neurological Toxicity	Occurrence	Weekly Paclitaxel Albumin Dose modification

Grade 3-4 peripheral neuropathy	1st	Withhold treatment until resolves to grade ≤ 1 Resume dose at next lower dose level.
	2nd	
	3rd	Discontinue treatment

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to ≤ grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold treatment. Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

References:

1. https://www.medicines.org.uk/emc
2. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
3. BNF available via: https://bnf.nice.org.uk/
4. NICE TA 639 (Published date: 01 July 2020) Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer

5. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Diéras V,
6. Hegg R, Shaw G (2018) Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *NEJM* 379, pp2108-2121.

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
Nov 23	2.0	**Gabriella Langton Advanced Pharmacist V2.0**	Updated template, updated renal/hepatic information, change domepridone to metoclopramide, change of formulation of atezolizumab to subcutaneous and other formulation options, indication updated from Blueteq