Systemic Anti Cancer Treatment Protocol

Atezolizumab/Paclitaxel Albumin (Abraxane)
Triple Negative Breast Cancer, PDL1 positive

PROTOCOL REF: MPHAAPAABR
(Version No: 1.0)

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

Initial funding via MHRA EAM Scheme

Each prescribing physician will be required to complete the initial application and drug supply request form to confirm eligibility within the scheme, once the patient has signed the informed consent form. These forms can be requested by sending an email to welwyn.atezolizumabeams@roche.com

A Physician Agreement and Safety Data Exchange agreement will be signed by the prescribing physician. Once the signed documents are returned, Roche will arrange safety training and each prescribing oncologist will also be provided with a physician pack containing all the relevant documents, including adverse events reporting form, needed to manage patients receiving atezolizumab under EAMS.

Dosage:

Drug	Dosage	Route	Frequency	Duration of Treatment
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	Minimum 6 cycles

Discontinuation of atezolizumab or paclitaxel albumin due to toxicity can occur independently, please refer to the 'Dose Modifications and Toxicity Management' section for further details.

Supportive treatments:

Domperidone 10mg oral tablets 3 times a day or as required

Extravasation risk:

Monoclonal antibody – treat symptomatically, no specific recommendations.

Paclitaxel albumin (Abraxane) and paclitaxel are both **VESICANTs**.

Refer to the network guidance for the prevention and management of extravasation

Interactions:

Atezolizumab
No formal pharmacokinetic drug interaction studies. Cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected. Use of systemic corticosteroids or immunosuppressants prior to starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab
Paclitaxel albumin (Abraxane)/Paclitaxel
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.

Refer to the SmPC for each agent for full details on:

https://www.medicines.org.uk/emc

Administration:

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

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

Cycle is repeated every 28 days

Hypersensitivity: routine prophylaxis against infusion related reactions is not required with Paclitaxel Albumin (Abraxane).

Note: Paclitaxel albumin (Abraxane) is time consuming to prepare, therefore patients must be booked for a go ahead appointment the day before treatment to prevent delays.

Main Toxicities

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 Paclitaxel- risk of bradycardia and hypotension is 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

*****The infusion should be stopped and the hypersensitivity protocol implemented as per the Trusts Hypersensitivity- Management Prevention Policy**. It should be strongly noted that patients who have severe reactions should not be re-challenged.**

Atezolizumab Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions. Refer to trust immunotherapy toxicity management guidelines for further advice.	
Immune related adverse reaction	**Actions**
Pneumonitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Hepatitis/ hepatotoxicity	Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Colitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Other toxicities: Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Myositis **Less frequently:** Exfoliative dermatitis, uveitis, arthritis, pancreatitis, haemolytic anaemia, myocarditis	Monitor LFTs, biochemistry, cortisol and TFTs regularly Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite, pruritus, rash Constipation, diarrhoea Arthralgia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia, raised serum amylase and lipase levels	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Motor or sensory neuropathy	Monitor symptoms. Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	Permanently discontinue atezolizumab Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Incidence of Adverse Effects (AEs) in combined regimen

All grades (most common)	Alopecia, nausea, cough, neutropenia, pyrexia, hypothyroidism.
Grade 3-4 AEs (≥ 5%)	Decreased neutrophil count, neutropenia, thrombocytopenia, peripheral neuropathy, anaemia, decreased WBC count, diarrhoea, pneumonia
Other- All grades (≥ 1%)	Rash, infusion-related reactions

Immune-related AEs

All grades	Hypothyroidism, Hepatitis, deranged LFTs, hyperthyroidism, pneumonitis, meningoencephalitis, colitis, adrenal insufficiency.
Most common 3-4 AEs	Diarrhoea and colitis, increased AST and colitis, diabetes, Type I, drug reaction with eosinophilia and systemic symptoms, increased ALT, and pneumonitis

The safety of atezolizumab given in combination with nab-paclitaxel is based on data in 452 patients with unresectable locally advanced or metastatic TNBC. The most common (≥ 20%) AEs were:

- Alopecia (56.4%),
- Fatigue (46.7%),
- Nausea (46%),
- Peripheral neuropathies (42.5%),
- Rash (34%)
- Diarrhoea (32.5%)
- Neutropenia (32.1%)
- Anaemia (27.7%)
- Constipation (25%)

- Headache (23.2%)
- Cough (24.8%)
- Decreased appetite (20.1%)

Investigations and treatment plan:

	Pre	C1	C2	Pre C3	C3	C4	Pre C5	C5	C6	Ongoing
Oncology Team Assessment	X			X			X			Every 8 weeks for 12 months then every 12 weeks thereafter or as clinically indicated
Informed Consent	X									
Nursing Assessment Including toxicity assessment		X	X		X	X		X	X	Every cycle*
FBC, U&E, LFTs and LDH *Local hospital/GP surgery 48 hours before due dose*	X		X		X	X		X	X	Every cycle*
TFTs and cortisol *Local hospital/GP surgery 48 hours before due dose*	X	X	X		X	X		X	X	Every cycle (Day 1 and 15 ONLY)
Blood glucose	X	X	X		X	X		X	X	Every cycle (Day 1 and 15 ONLY)
Lipid profile (cholesterol)	X				X			X		Every 6 weeks
CT scan	X			X			X			Every 8 weeks for 12 months then every 12 weeks thereafter or as clinically indicated
Blood pressure	X	X	X		X	X		X	X	Every cycle*
ECOG PS	X	X	X		X	X		X	X	Every cycle*
Weight recorded	X	X	X		X	X		X	X	Every cycle

*** Day 1, 8 and 15 for Cycles 1 to 6 then Day 1 and 15 thereafter.**

Dose Modifications and Toxicity 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 rules* for day 1 of each cycle (cycles 1-6):

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

*Based on IMpassion130 clinical trial criteria.

Proceed rules on days 8 or 15 of each cycle (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	

Proceed rules cycle 7 onwards

Monitor for immunotherapy- induced toxicities. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

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 < 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 < 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

Atezolizumab
Atezolizumab has not been studied in patients with moderate or severe hepatic or renal impairment No dose reductions are recommended, toxicity should be managed with a dose delay or discontinuation of treatment. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions. Refer to trust immunotherapy toxicity management guidelines for further advice.

Hepatic impairment

Hepatic Toxicity	Paclitaxel Albumin (Abraxane) dose modification
AST < 10 x ULN or BIL ≤ 1.25 x ULN	Full dose
AST < 10 x ULN and BIL ≤ 2 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 and BIL ≤ 5 x ULN	
AST > 10 x ULN or BIL > 5 x ULN	Discontinue Treatment

Renal impairment

Atezolizumab
Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Paclitaxel Albumin (Abraxane)
No formal guidance. CrCl ≥ 30ml/min (mild to moderate renal impairment) – no dose reduction

Patient Counselling Points

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

References:

https://www.medicines.org.uk/emc

Impassion130 Clinical Trial Protocol v1

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