Indication	Atezolizumab in combination with paclitaxel albumin bound for the treatment of previously untreated PD-L1-positive, triple negative, unresectable, locally advanced or metastatic breast cancer with a PD L1 expression >/=1%. No previous anti-PD-1/PD-L1 treatment can have been received, **unless** it was for neoadjuvant or adjuvant therapy, as long as there was no disease progression during such treatment and for at least 12 months after completion of anti-PD-1/PD-L1 therapy.
Treatment Intent	Palliative
Frequency and number of cycles	Every 28 days Continue until disease progression or unmanageable toxicity or patient choice. A formal medical review must be scheduled to occur by the end of the first 8 weeks of treatment to assess tolerance and whether to continue with treatment or not.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • **Blood parameters:** • Monitor FBC, U&Es, LFTs and random blood glucose at each cycle. • **Day 1** If neutrophils >/=1.5 and PLT >/=100 continue with treatment. Otherwise d/w consultant. • **DAY 8 and 15:** If neutrophils >/=1 and PLT >/=100 continue with treatment. Otherwise d/w consultant. • **ECG** at first cycle. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure. • Monitor for signs and symptoms of myocarditis. Carry out ECG as clinically indicated. • **Thyroid function** must be assessed at baseline then every 6-8 weeks or as clinically indicated. • Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24hours of the last steroid dose. • Confirm the patient has no symptomatically active brain metastases or leptomeningeal metastases. • **<u>Renal Impairment</u>** o Atezolizumab and paclitaxel albumin bound: no dose adjustment is required in patients with mild or moderate renal impairment (30-89ml/min). No recommendation for patients with severe (<30ml/min) renal impairment as data is too limited. • **<u>Hepatic impairment</u>** (prior to treatment, for immune related hepatitis see below) – o Atezolizumab: no dose adjustment is required for patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 -1.5 × ULN and any AST) or moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST). No data is available in patients with severe hepatic impairment (bilirubin >3 X ULN and any AST). o Paclitaxel albumin bound: For patients with mild **hepatic impairment** (total bilirubin > 1 to ≤ 1.5 x ULN and AST ≤ 10 x ULN), no dose adjustments are required. Moderate to severe hepatic impairment, d/w consultant. • **<u>Infusion-related reactions</u>** o Atezolizumab: reduce infusion rate or interrupt treatment if Grade 1 or 2 infusion-related reaction. Treatment may be resumed when the event is resolved. Premedication with antipyretic and antihistamines should be considered with close monitoring. Permanently discontinue in patients with Grade 3 or 4 infusion related reactions.

- **Adverse Reactions**
  Atezolizumab
  Immune- related reactions: (for comprehensive guidance refer to SPC):
  - Reactions include myositis, nephritis, myocarditis, pneumonitis, colitis, hepatitis, pancreatitis, adrenal insufficiency, meningoencephalitis, hyperthyroidism, hypothyroidism, hypophysitis, diabetes, rash, arthralgia, musculoskeletal pain, neuropathies, myasthenic syndrome and Guillain-Barre syndrome. For details on treatment modification for immune related reactions see table 1.
  - Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported. For signs or symptoms of SJS or TEN, atezolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, atezolizumab should be permanently discontinued.
  - Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some with fatal outcomes, have been observed. Patients should be monitored for clinical signs and symptoms of pericardial disorders.
  - Atezolizumab should be discontinued in the event of any grade Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis
  - If corticosteroids are used to treat an immune related reaction they should be tapered over at least 1 month upon improvement of immune related toxicity to </= grade 1. Treatment should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids (>10mg prednisone) or other immunosuppressive therapy. Prophylactic antibiotics should be used where appropriate to prevent opportunistic infections in patients receiving immunosuppressive therapy.
  - See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/
- Patients should be monitored for signs and symptoms of pneumonitis. After ruling out infectious etiology, d/w consultant and permanently discontinue paclitaxel albumin bound when a diagnosis of pneumonitis is made and initiate appropriate treatment (see SPC for guidance on atezolizumab induced immune related pneumonitis).
- Atezolizumab may be continued as a single agent if paclitaxel albumin bound has to be discontinued due to toxicity in which case atezolizumab may be given either **subcutaneously** at a dose of 1875mg every 3 weeks or **intravenously** at a dose of 1680 mg every 4 weeks.
  Please prescribe using KMCC protocol MULTI-004 atezolizumab.
  In addition, paclitaxel albumin bound may be continued in the event that atezolizumab is discontinued due to toxicity.
- **Driving:** Patients should be advised not to drive and use machines if they feel tired or dizzy.
- **Dose reductions**
  - Atezolizumab: Dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
    Paclitaxel albumin bound:
  - Day 1: Neuts <1.5 and /or PLT <100, delay until recovery. If recovery >7 days on 1st occurrence reduce to 75mg/m^2, 2nd occurrence reduce to 50mg/m^2, if there is a 3rd occurrence discontinue.
  - Day 8 & 15 If neuts <0.5 for >7 days and / or any episode of platelet count <50, once recovered, on 1st occurrence reduce to 75mg/m^2, if recurrence then discontinue.
  - Febrile neutropenia (neuts <0.5 and temp >38°) - 1st occurrence reduce to 75mg/m^2, 2nd occurrence reduce to 50mg/m^2, if there is a 3rd occurrence discontinue.
  - Grade 3-4 peripheral neuropathy; 1st occurrence withhold until </= grade 1 then reduce to 75mg/m^2, 2nd occurrence withhold until </= grade 1 then reduce to 50mg/m^2, 3rd occurrence discontinue.

	• **<u>Drug interactions (for comprehensive list refer to BNF/SPC)</u>:** o The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab. o Patients should not receive the flu vaccine unless the benefit outweighs the risk and after discussion between consultant and patient. o Use paclitaxel albumin bound with caution in patients receiving concomitant inhibitors (e.g. ketoconazole, erythromycin, fluoxetine, cimetidine, clopidogrel) or inducers (e.g. rifampicin, carbamazepine, phenytoin) of CYP2C8 or CYP3A4. • **Delayed or missed doses:** • If a planned dose of atezolizumab is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain the appropriate interval between doses. • The patient should be provided with the Tecentriq® Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment).
References	SPC accessed online 19.06.2023 KMCC protocol BRE-067 V4 BlueTeq form accessed online 21.09.2023

NB For funding information, refer to the refer to CDF and NICE Drugs Funding List

TABLE 1: Dose modification advice for immune related reactions

Immune related reaction	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue
Hepatitis in patients without hepatocellular carcinoma	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] *or* blood bilirubin > 1.5 to 3 x ULN)	Withhold Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)	Permanently discontinue
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) ***or*** Symptomatic Colitis	Withhold Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Permanently discontinue
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold ***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 anti-thyroid medicinal product and thyroid function is improving
Adrenal insufficiency	Symptomatic	Withhold Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	Withhold Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue

Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) regardless of severity	Withhold Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) regardless of severity	Permanently discontinue
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Treatment may be resumed when 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 ≤ 10 mg prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue
Myocarditis	Grade 2 or above	Permanently discontinue
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	Withhold Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
Myositis	Grade 2 or 3	Withhold
	Grade 4 or Grade 3 recurrent myositis	Permanently discontinue
Pericardial disorders	Grade 1 pericarditis	Withhold and conduct a detailed cardiac evaluation to determine the etiology and manage appropriately
	Grade 2 or above	Permanently discontinue
Other immune-related reactions	Grade 2 or Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.
	Grade 4 or recurrent Grade 3	Permanently discontinue (except endocrinopathies controlled with replacement hormones)

Repeat every 28 days

NB It is important to note that this dose and schedule of paclitaxel albumin bound is not currently the licensed dose and schedule in metastatic breast cancer.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO	Stat	
	ATEZOLIZUMAB	**840mg**	IV	1st dose over 60 min. If tolerated, all subsequent infusions over 30 min.	diluted in 250ml 0.9% sodium chloride
	PACLITAXEL ALBUMIN BOUND (Abraxane ®/ Pazenir®)	**100mg/m²**	IV	30 mins	To be administered undiluted in a sterile PVC or non-PVC type intravenous bag. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer infusions.
8	Metoclopramide	20mg	PO	Stat	
	PACLITAXEL ALBUMIN BOUND (Abraxane ®/ Pazenir®)	**100mg/m²**	IV	30 mins	To be administered undiluted in a sterile PVC or non-PVC type intravenous bag. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer infusions.
15	Metoclopramide	20mg	PO	Stat	
	ATEZOLIZUMAB	**840mg**	IV	1st dose over 60 min. If tolerated, all subsequent infusions over 30 min.	diluted in 250ml 0.9% sodium chloride
	PACLITAXEL ALBUMIN BOUND (Abraxane ®/ Pazenir®)	**100mg/m²**	IV	30 mins	To be administered undiluted in a sterile PVC or non-PVC type intravenous bag. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer infusions.

TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required after days 1, 8 and 15 (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.