Atezolizumab and nab-PACLitaxel Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease	C50	00688a	Atezolizumab ODMS 01/03/2022 nab-PACLitaxel: Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Atezolizumab is administered on days 1 and 15, and nab-PACLitaxel is administered on days 1, 8, and 15 of a 28 day cycle. Treatment with atezolizumab should continue until disease progression or unacceptable toxicity occurs. Treatment with nab-PACLitaxel should continue for up to 6 cycles and may continue beyond that at the discretion of the prescribing Consultant.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 15	Atezolizumab	840mg[a, b]	IV infusion	100ml 0.9% NaCl over 60 mins	Every 28 days
2	1, 8, 15	nab-PACLitaxel[c]	100mg/m^2	IV infusion	Over 30 mins	Every 28 days
[a]The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.						
[b]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						
[c]The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer nab-PACLitaxel may result in the formation of proteinaceous strands. Administer nab-PACLitaxel 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. If strands are present and a filter is not available, the product must be discarded.						

ELIGIBILITY:

- Indication as above
- ECOG 0-1
- Metastatic or locally advanced, histologically documented TNBC (absence of HER2, ER, and PR expression)
- No prior chemotherapy or targeted systemic therapy for inoperable locally advanced or metastatic TNBC
    - Radiation therapy or endocrine therapy for metastatic disease is permitted.
    - Prior chemotherapy (including taxanes) in the neoadjuvant or adjuvant setting is allowable if treatment was completed ≥ 12 months prior to treatment.

- Adequate haematological, hepatic and renal function

Use with caution in:

- Patients with clinically significant autoimmune disease

EXCLUSIONS:

- Hypersensitivity to atezolizumab, PACLitaxel, albumin or any of the excipients.
- Symptomatic central nervous system (CNS) metastases
- Any active clinically significant infection requiring therapy
- Prior treatment with anti−PD-1, or anti−PD-L1 therapeutic antibody or pathway-targeting agents
- Symptomatic interstitial lung disease
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids
- Severe hepatic impairment
- Grade ≥ 2 sensory or motor neuropathy
- Pregnancy or lactation

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, liver and renal profile
- Glucose
- Thyroid function (C1D1 & every 2nd cycle)
- Virology Screen: Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- Serum cortisol (ideally a morning sample)
- PD-L1 testing with the Ventana platform using the SP142 antibody to score PD-L1 expression in tumour-infiltrating immune cells on the request of a Consultant Medical Oncologist where there is an intention to treat with atezolizumab in line with this licensed indication
- Assessment of cardiac function, e.g. ECHO/MUGA scan if significant cardiac history or previous anthracycline therapy

Regular tests:

- FBC, liver, renal and glucose profile prior to each cycle
- Thyroid function (every 2nd cycle)
- Cardiac function if clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- **Atezolizumab:**
  - Dose reduction not recommended.
  - Atezolizumab treatment may be interrupted or discontinued due to toxicity. Please refer to table 4 below for treatment modification
- **nab-PACLitaxel:**
  - ANC must be ≥1.5x10^9/L and platelets must be ≥100x10^9/L on day one of each cycle
  - Nab-PACLitaxel should not be administered on Days 8 or 15 of the cycle until counts recover to an ANC ≥0.5x10^9/L and platelets ≥50 x10^9/L
  - If nab-PACLitaxel cannot be administered on Day 15 of the cycle, the next dose of nab-PACLitaxel should be administered on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels. When dosing resumes, the nab-PACLitaxel doses should be permanently reduced as outlined in table 1

Haematological toxicity

Table 1: Dose modifications of nab-PACLitaxel haematological toxicity

Haematological toxicity	Occurrence	Dose Modification
Neutropenic fever (nadir ANC <0.5 x10^9/L with fever >38°C Or Delay of first administration of nab-PACLitaxel in a cycle by >7 days for nadir ANC<1.5 x10^9/L Or Nadir ANC <0.5 x10^9/L for >7 days	First	Reduce dose to 75mg/m^2
	Second	Reduce dose to 50mg/m^2
	Third	Discontinue treatment
Nadir platelet count <50 x10^9/L	First	Reduce dose to 75mg/m^2
	Second	Discontinue treatment

Renal and Hepatic Impairment:

Table 2: Dose Modification of Atezolizumab and nab-PACLitaxel in renal impairment

Drug	Renal Impairment	
Atezolizumab	Mild/Moderate	No dose adjustment required
	Severe	Data too limited to draw conclusions
nab-paclitaxel	**CrCl (ml/min)**	**Dose**
	≥30 to <90	No dose adjustment necessary
	<30	Insufficient data available to make recommendation

Table 3: Dose Modification of Atezolizumab and Nab-PACLitaxel in hepatic impairment

Drug	Hepatic impairment			
Atezolizumab	Mild/Moderate		No dose adjustment required	
	Severe		Has not been studied	
Nab-PACLitaxel	AST		Bilirubin	Dose
	≤10×ULN	**And**	>1 to 1.5×ULN	No dose modification; proceed with 100 mg/m^2
	≤10× ULN	**And**	>1.5 to ≤5 ×ULN	Interrupt treatment until resolved to AST <10 x ULN and Bilirubin ≤1.5x ULN, then reduce to *75mg/m^2. If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment.
	>10× ULN	**Or**	>5 ×ULN	Discontinue treatment.
	*A dose increase to 100 mg/m^2 in subsequent courses should be considered if the patient tolerates the reduced dose for two cycles			

Management of adverse events:

Table 4: Guidelines for withholding or discontinuation of atezolizumab

Immune related adverse reaction	Treatment modification
Pneumonitis Grade 2 Grade 3 or 4	 Withhold atezolizumab. 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 prednisolone or equivalent per day. Permanently discontinue atezolizumab
Hepatitis Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] or blood bilirubin > 1.5 to 3 x ULN) Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)	 Withhold atezolizumab. 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 prednisolone or equivalent per day. Permanently discontinue atezolizumab

Immune related adverse reaction	Treatment modification
Colitis Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic Colitis Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Withhold atezolizumab. 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 prednisolone equivalent per day. Permanently discontinue atezolizumab
Hypothyroidism or hyperthyroidism 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 anti-thyroid medicinal product and thyroid function is improving.
Adrenal insufficiency Symptomatic	Withhold atezolizumab. 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 prednisolone or equivalent per day and patient is stable on replacement therapy.
Hypophysitis Grade 2 or 3 Grade 4	Withhold atezolizumab. 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 prednisolone or equivalent per day and patient is stable on replacement therapy. Permanently discontinue atezolizumab
Type 1 diabetes mellitus Grade 3 or 4 hyperglycaemia (fasting glucose >250 mg/dL or 13.9 mmol/L)	Withhold atezolizumab. Treatment may be resumed when metabolic control is achieved on insulin replacement therapy.
Infusion-related reactions Grade 1 or 2 Grade 3 or 4	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved. Permanently discontinue atezolizumab
Rash/Severe cutaneous adverse reaction Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1] Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Withhold atezolizumab. 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 prednisolone or equivalent per day Permanently discontinue atezolizumab
Myasthenic syndrome/ myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis All grades	Permanently discontinue atezolizumab

Immune related adverse reaction	Treatment modification
Pancreatitis Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold Atezolizumab. 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 prednisolone or equivalent per day.
Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab
Myocarditis Grade 2 or above	Permanently discontinue atezolizumab
Nephritis Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	Withhold atezolizumab. 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: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue atezolizumab
Myositis Grade 2 or 3	Withhold atezolizumab
Grade 4 or recurrent Grade 3	Permanently discontinue atezolizumab
Other immune-related adverse reactions Grade 2 or Grade 3	Withhold until adverse reaction recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10mg prednisolone or equivalent per day.
Grade 4 or recurrent Grade 3	Permanently discontinue atezolizumab (except endocrinopathies controlled with replacement hormones)
Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4).	
[1]Regardless of severity	

Table 5: Dose Modifications of nab-PACLitaxel for neurological toxicity

Adverse reactions	Recommended dose modification
Grade 3 or 4 peripheral neuropathy First occurrence	Hold treatment until resolved to grade ≤1 then reduce dose to 75mg/m^2
Second occurrence	Hold treatment until peripheral neuropathy resolves to Grade ≤1, then resume treatment at 50 mg/m^2
Third occurrence	Discontinue treatment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:
Atezolizumab Minimal (**Refer to local policy).**
nab-PACLitaxel Low (**Refer to local policy).**

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE: Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover can be considered

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Atezolizumab

- **Atezolizumab is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**
- **Immune-mediated adverse reactions:** Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more than one body system have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab. For suspected immune-related adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered. Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones.
- **Infusion related reactions:** These have been observed in clinical trials with atezolizumab. The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion-related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion- related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.
- **Immune-related severe cutaneous adverse reactions (SCARs):** Immune-related severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. In case a SCAR is suspected, atezolizumab should be withheld and patients should be referred to a specialist in SCARs for diagnosis and treatment. If SJS or TEN is confirmed, and for any grade 4 rash/SCAR, treatment with atezolizumab should be permanently discontinued. Caution is recommended when considering the use

of atezolizumab in patients with previous history of a severe or life-threatening SCAR with other immune-stimulatory cancer medicines.

nab-PACLitaxel

- **Formulation:** nab-PACLitaxel is an albumin-bound nanoparticle formulation of PACLitaxel, which may have substantially different pharmacological properties compared to other formulations of PACLitaxel. It should not be substituted for or with other paclitaxel formulations.
- **Hypersensitivity:** Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. If a hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be re-challenged with paclitaxel.
- **Extravasation:** Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during administration of the medicinal product **(Refer to local policy)**.
- **Neutropenia:** Bone marrow suppression (primarily neutropenia) occurs frequently with nab-PACLitaxel. Neutropenia is dose-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during nab-PACLitaxel therapy. Patients should not be retreated with subsequent cycles of nab-PACLitaxel until neutrophils recover to >1.5x 10^9/L and platelets recover to >100x10^9/L. Neutropenia and peripheral neuropathies occurring during treatment with atezolizumab and nab-paclitaxel may be reversible with interruptions of nab-paclitaxel.
- **Hepatic impairment:** Because the toxicity of PACLitaxel can be increased with hepatic impairment, administration of nab-paclitaxel in patients with hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression; such patients should be closely monitored for development of profound myelosuppression. nab-PACLitaxel is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN.
- **Cardiotoxicity:** Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving nab-paclitaxel. Most of the individuals were previously exposed to cardiotoxic medicinal products such as anthracyclines, or had underlying cardiac history. Thus patients receiving nab-PACLitaxel should be vigilantly monitored by physicians for the occurrence of cardiac events.
- **Neuropathy Sensory:** neuropathy occurs frequently with nab-PACLitaxel, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction
- **Pneumonitis:** Even though the incidence is low, patients should be closely monitored for signs and symptoms of pneumonitis. During the conduct of a trial in metastatic pancreatic cancer, a higher rate of pneumonitis events was observed in patients receiving nab-PACLitaxel in combination with gemcitabine.

DRUG INTERACTIONS:

- 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.
- The use of systemic corticosteroids or immunosuppressant's before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressant's can be used to treat

immune-related adverse reactions after starting atezolizumab.
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP
Patient Alert Card
https://www.hpra.ie/img/uploaded/swedocuments/53ca611d-f634-4438-83db-4da11cebd0c6.pdf

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Version	Date	Amendment	Approved By
1	20/01/2022		Prof Maccon Keane
2	16/12/2022	Reviewed. Amended management of adverse events section.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.