Atezolizumab and Nab-paclitaxel (Breast)

Indication

First line systemic treatment of unresectable locally advanced or metastatic, triple negative breast cancer where the tumour PDL-1 expression is ≥ 1%. Where possible, PDL-1 should be measured on a biopsy from a metastasis.

(NICE TA639)

ICD-10 codes

Codes pre-fixed with C50.

Regimen details

Cycles 1-6:

Days	Drug	Dose	Route
1 ***or*** 1 and 15	Atezolizumab	1680mg ***or*** 840mg	IV infusion IV infusion
1, 8, 15	Nab-Paclitaxel	100mg/m²	IV infusion

Cycles 7 onwards:

Intravenous atezolizumab

Days	Drug	Dose	Route
1	Atezolizumab	1680mg every 4 weeks or 1200mg every 3 weeks	IV infusion

Subcutaneous atezolizumab

Day	Drug	Dose	Route
1	Atezolizumab	1875mg every 3 weeks	SC injection

Cycle frequency

Cycles 1-6: 28 days

Cycle 7 onwards: as above, depending on route and dose

Number of cycles

Nab-paclitaxel is usually given for a maximum of 6 cycles.

Atezolizumab is continued until disease progression or unacceptable toxicity.

Administration

Intravenous atezolizumab

Atezolizumab is administered in 250mL sodium chloride 0.9% over 60 minutes. If the initial infusion is well tolerated, subsequent infusions may be administered over 30 minutes.

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For grade 1-2 infusion related reactions, decrease the infusion rate and closely monitor or temporarily interrupt treatment. Premedication with paracetamol and chlorphenamine should be used for

further doses and patient should be closely monitored. For grade 3-4 infusion related reactions discontinue treatment.

Subcutaneous atezolizumab
Remove from refrigerator and allow to reach room temperature prior to administration. Administer via subcutaneous injection into the thigh over approximately 7 minutes. Use of a SC infusion set (e.g. winged/butterfly) is recommended. DO NOT administer the remaining residual hold-up volume in the tubing to the patient. The injection site should be alternated between the right and left thigh only. New injections should be given at least 2.5cm from the old site and never into areas where the skin is red, bruised, tender or hard.

Nab-Paclitaxel is administered as a 5mg/mL infusion over 30 minutes.

It should be administered using an infusion set incorporating a 15µm filter.

Pre-medication
Nil routinely required.

Emetogenicity
This regimen has moderate emetic potential.

Additional supportive medication
Mouthwashes as per local policy
Antiemetics as per local policy
H_2 antagonist or PPI, if required, as per local policy

Extravasation
Atezolizumab is neutral (Group 1)
Nab-Paclitaxel is vesicant (Group 5)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Thyroid function	14 days
Calcium	14 days
Glucose	14 days
Cortisol	14 days

Baseline echocardiogram and ECG if significant cardiac history. Monitor as clinically indicated.

Investigations – pre cycles #2 - 6

Investigation	Validity period
FBC*	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Thyroid function	7 days
Calcium	7 days
Glucose	7 days
Cortisol	7 days

* FBC is also required within 48 hours of days 8 and 15.

Investigations – pre atezolizumab maintenance cycles

Investigation	Validity period
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Thyroid function	Every other cycle
Calcium	As clinically indicated
Glucose	Every other cycle
Cortisol	Every other cycle

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
CrCl	≥ 30mL/min
Bilirubin	< 1.5 x ULN
AST/ALT	< 2 x ULN

Dose modifications

Dose reductions for atezolizumab are not recommended. Doses should be delayed until an adverse reaction resolves to ≤ grade 1.

- ### Haematological toxicity

Day 1:

If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay nab-paclitaxel dose then resume with next planned dose at 100% if counts recovered. If delayed for > 1 week discuss with consultant, consider dose reduction.

If neutrophils <0.5 x 10^9/L delay nab-paclitaxel until neutrophils >1.0 x 10^9/L and reduce dose to 75mg/m^2.

If second occurrence delay until neutrophils >1.0 x 10^9/L and reduce dose further to 50mg/m^2.

Day 8 and 15:

If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L omit nab-paclitaxel and the next dose should be given as planned if counts have recovered.

- ### Renal impairment

Nab-paclitaxel: If CrCl < 30mL/min discuss with consultant, no need for dose adjustment is expected given minimal renal excretion.

Atezolizumab: No modifications required in mild to moderate renal impairment. There are no recommendations for patients with severe renal impairment.

- ### Hepatic impairment

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Nab-paclitaxel dose**
< 1.5	and	< 2	100%
1.5 – 5	and/or	2 - 10	80%
> 5	and/or	> 10	Discontinue

Atezolizumab: No modifications required for mild or moderate hepatic impairment. Atezolizumab has not been studied in severe hepatic impairment.

- **Other toxicities**

Paclitaxel albumin:

Toxicity	Definition	Nab-paclitaxel dose
Neuropathy	Grade 1-2	No dose reduction usually required.
	Grade 3	Withhold until recovery to ≤ grade 1, resume with 80% of dose. If 2nd occurrence: Withhold until recovery to ≤ grade 1, resume with 60% of dose.
	Grade ≥ 4	Discontinue or continue with dose reduction as above – consultant decision.

For all other grade ≥ 2 toxicities (except alopecia) withhold until grade ≤ 1 and continue with 80% of dose. If delayed for > 1 week, discuss with consultant.

For any grade 4 toxicity (except alopecia) withhold and discuss with consultant.

Post-marketing experience has identified rare reports of reduced visual acuity due to cystoid macular oedema. Treatment should be discontinued.

Rare reports of congestive heart failure and left ventricular dysfunction have been observed in patients with underlying cardiac history or previous exposure to cardiotoxic products such as anthracyclines. Patients should be monitored for the occurrence of cardiac events.

If hypersensitivity reaction occurs, treatment should be discontinued immediately and symptomatic treatment should be initiated. The patient should not be re-challenged.

Atezolizumab:

For suspected immune related adverse events, atezolizumab should be withheld and corticosteroids administered. Once symptoms resolved to ≤ Grade 1 the corticosteroid dose should be tapered over 1 month.

Toxicity	Definition	Dose adjustment
Pneumonitis	Grade 2	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 3-4	Permanently discontinue
Hepatitis	Grade 2 Bilirubin 1.5-3 x ULN and/or AST/ALT 3-5 x ULN	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 3-4 Bilirubin > 3 x ULN and/or AST/ALT > 5 x ULN	Permanently discontinue
Colitis	Grade 2-3 diarrhoea or Symptomatic colitis	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 4 diarrhoea or colitis	Permanently discontinue
Toxicity	**Definition**	**Dose adjustment**

Hypo or hyperthyroidism	Symptomatic	Hypothyroidism: Withhold treatment Treatment may resume once symptoms controlled with thyroid replacement and TSH levels reducing.
		Hyperthyroidism: Withhold treatment Treatment may resume once symptoms controlled with anti-thyroid medication and thyroid function is improving.
Adrenal insufficiency	Symptomatic	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
Hypophysitis	Grade 2-3	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids ≤ 10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
	Grade 4	Permanently discontinue
Insulin dependent diabetes mellitus	Grade 3-4 hyperglycaemia	Withhold treatment Resume once metabolic control achieved with insulin.
Rash	Grade 3 or suspected Stevens-Johnson syndrome (SJS or toxic epidermal necrolysis (TEN)	Withhold treatment Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 4 or confirmed SJS/TEN	Permanently discontinue
Myasthenic syndrome/ myasthenia gravis/Guillain-Barre	Any grade	Permanently discontinue
Pancreatitis	Grade 2-3 (or Grade 3-4 increase in amylase or lipase)	Withhold treatment Resume once amylase and lipase levels ≤ Grade 1 (within 12 weeks) or where symptoms have resolved and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
	Grade 4 or recurrent pancreatitis	Permanently discontinue
Myocarditis/Pericardial disorders	Grade 2 or above	Permanently discontinue
Nephritis	Grade 2 (creatinine 1.5 -3 x baseline or ULN)	Withhold treatment. Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 3 or 4 (creatinine > 3 x baseline or ULN)	Permanently discontinue
Other immune mediated adverse reactions	Grade 2 or 3	Withhold treatment Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 4 or recurrent Grade 3	Permanently discontinue

Permanently discontinue treatment in patients with the following symptoms:

- Any grade 4 toxicity, except endocrinopathies that are controlled with replacement hormones.
- Any recurrent Grade 3 toxicity.
- Any treatment related toxicity that does not resolve to ≤ Grade 1 within 12 weeks after onset.
- If a corticosteroid dose ≥ 10mg/day prednisolone (or equivalent) is required for toxicity beyond 12 weeks after onset.

Adverse effects - for full details consult product literature/ reference texts

- **Rare or serious side effects**

Myelosuppression
Infertility
Teratogenicity
Hypersensitivity reactions
Pneumonitis
Hepatic impairment
Cardiotoxicity
Immune related adverse events
Interstitial lung disease, pneumonitis
Pancreatitis
Hepatitis
Colitis
Neuropathies
Endocrinopathies
Myocarditis
Nephritis

- **Frequently occurring side effects**

Myelosuppression
Thrombocytopenia
Hypothyroidism, hyperthyroidism
Hypotension
Nausea and vomiting
Mucositis, stomatitis
Diarrhoea, constipation
Peripheral neuropathy
Neuropathy
Myalgia, arthralgia
Alopecia
Fatigue
Rash, pruritis

- **Other side effects**

Insomnia, depression, anxiety
Headache, dizziness
Skin reactions
Nail changes
Eye problems
Decreased appetite
Altered electrolytes
Raised transaminases
Guillain-Barre syndrome

Significant drug interactions – for full details consult product literature/ reference texts

Nab-paclitaxel:

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Clozapine: increased risk of agranulocytosis.

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel concomitantly with medicines known to:
inhibit (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir)
or
induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

Atezolizumab:

No formal drug interaction studies have been carried out with atezolizumab.

Corticosteroids: the use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab.

Additional comments

Patients should be issued with the Atezolizumab Patient Alert Card and advised to carry the card at all times.

References

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- Schmid, P et al (2018) Atezolizumab and Nab-Paclitaxel in Advanced Triple Negative Breast Cancer. NEJM 379, pp2108-2121.
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