Lancashire and South Cumbria Cancer Network
Systemic Anticancer Treatment Protocol

Drug regimen
Atezolizumab and Nab-Paclitaxel (Abraxane)

Indications for use
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
(Approved for use by NICE as part of interim COVID guidance)

Regimen

DAY	DRUG	Dose	FLUID	TIME
1 & 15	Atezolizumab	840mg	250ml 0.9% sodium chloride	60 min (30 mins from cy 2 if tolerated)
1,8 & 15	Abraxane	100mg/m^2	N/A	30 min

Cycle should be repeated every 28 days until disease progression or unmanageable toxicity

If Abraxane is stopped (e.g. if not tolerated) then atezolizumab should be continued using a dose of 1680mg every 28 days

Investigation prior to initiating treatment
FBC, U&Es incl bicarbonate
LFTs (do not use Abraxane if bilirubin >5 x ULN or if ALT >10 x ULN)
Ca, glucose
TFTs
Serum samples for HIV, hep C antibody and HBsAg if risk factors.
Pregnancy test (if applicable)
Weight and vital signs
ECG

Cautions
Abraxane - Neuropathy

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, 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
Avoid concomitant use of systemic steroids or immunosuppressants before starting treatment

Impassion 130: Patients with the following conditions were excluded from the clinical trial: age <18 years; a baseline performance status ≥ 2; a history of autoimmune disease, history of pneumonitis, active brain metastasis, HIV, hepatitis B or hepatitis C infection; significant cardiovascular disease and patients with inadequate hematologic and end-organ function.

Investigations and consultations prior to each cycle
Performance status
FBC, U&E and LFTs
TFTs every other cycle
Consultation needed prior to each cycle

Acceptable limits for treatment to proceed
- AST and ALT ≤2.5 X ULN or ≤5 X ULN with liver metastases
- Serum total bilirubin ≤1.5 X ULN or direct bilirubin ≤ULN for patient with total bilirubin level >1.5 ULN
- Serum creatinine ≤1.5 X ULN
- Absolute neutrophil count >1.5
- Platelets >100
- Haemoglobin >9 g/dL

Check with consultant prior to any deferrals

Delay treatment until sensory neuropathy recovers to grade 2 or better

Side effects

Abraxane: Hypersensitivity reactions, Myalgia and arthralgia, Neuropathy, Alopecia, Rash, Nausea and vomiting, Bone marrow suppression, Diarrhoea

Atezolizumab: Pneumonitis, hepatitis, colitis, endocrinopathy (hypo and hyperthyroidism, adrenal insufficiency, diabetes), meningioencephalitis, neuropathy, pancreatitis, Infusion reactions.

Dose Modification Criteria

Abraxane

Dose modifications are recommended for haematological and neurological toxicities as per table below

Nab-paclitaxel dose modification advice		
	Occurrence	**Weekly nab-paclitaxel dose modification**
Neurological toxicity		
Grade 3-4 peripheral neuropathy	First	Withhold treatment until resolves to Grade <= 1, then resume treatment at 75mg/m^2
	Second	Withhold treatment until peripheral neuropathy resolves to Grade <=1, then resume treatment at 50mg/m^2
	Third	Discontinue treatment
Haematologic toxicity		
Neutropenic fever (nadir ANC<0.5 with fever >38°C) or Delay of first administration of nab-paclitaxel in a cycle by >7 days for nadir ANC <1.5	First	Reduce dose to 75mg/m^2
	Second	Reduce dose to 50mg/m^2
	Third	Discontinue treatment
Nadir ANC<0.5 for >7 days Nadir platelet count <50	First	Reduce dose to 75mg/m^2
	Second	Discontinue treatment

Atezolizumab

Dose reductions of atezolizumab are not recommended.

Important: For management of toxicities, consult network Immune Related Toxicity Management Guidelines and see table below

Atezolizumab dose modification advice for specified adverse drug reactions		
Immune related adverse reaction	Severity	Treatment modification
Pneumonitis	Grade 2	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	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)	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: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)	Permanently discontinue atezolizumab
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4	Withhold atezolizumab

	stools/day over baseline) or Symptomatic Colitis	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 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 antithyroid 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 prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	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 prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue atezolizumab
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 13.9etmmol/L)	Withhold atezolizumab Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue atezolizumab
Rash	Grade 3	Withhold atezolizumab Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4	Permanently discontinue atezolizumab
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	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 prednisone or equivalent per day

	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab
Myocarditis	Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue atezolizumab
	Grade 3 and 4	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
Other immune-related adverse 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 atezolizumab (except endocrinopathies controlled with replacement hormones)

Elderly – no dose adjustment of atezolizumab is required in patients >65 yrs
Renal impairment – No dose adjustment in patient with mild or moderate renal impairment. No data with severe renal impairment
Hepatic impairment – no dose adjustment with mild hepatic impairment. No data in moderate or severe hepatic impairment.

Specific Information on Administration
In-line filters should not be used when administering Abraxane

THIS PROTOCOL HAS BEEN DIRECTED BY DR Eaton, CLINICIAN FOR BREAST CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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