Indication	**UROLOGY** The first line treatment of locally advanced or metastatic transitional cell urothelial cancer which has PD-L1 expression at a level of >/= 5% in patients who are ineligible for cisplatin-based chemotherapy and meet commissioning criteria. For locally advanced or metastatic transitional cell urothelial cancer previously treated with platinum-based chemotherapy and meeting commissioning criteria. **NSCLC** For previously platinum-treated locally advanced/ metastatic non squamous or squamous non-small cell lung cancer which has been prospectively determined to be PD-L1 positive or PD-L1 negative or PD-L1 unquantifiable at PD-L1 assay or one in which PD-L1 status cannot be determined on account of insufficient lung cancer tissue being available for PD-L1 assay. If the tumour is EGFR positive, ALK positive, ROS1, MET exon 14, KRAS G12C, RET or BRAF V600 positive the patient should also, where appropriate, have received a targeted treatment. For untreated metastatic squamous or non-squamous NSCLC which has PD-L1 expression on at least 50% of tumour cells or in at least 10% of tumour-infiltrating immune cells and does not have an epidermal growth factor receptor (EGFR) 19 or 21 mutation or anaplastic lymphoma kinase (ALK) gene rearrangement. In squamous NSCLC disease a clinical decision can be made to treat without EGFR or ALK mutation testing. Adjuvant treatment of completely resected stage IIB or IIIA or N2 only IIIB NSCLC which has PD-L1 expression at a level of >/= 50% which has not progressed on adjuvant platinum-based chemotherapy (maximum 4 cycles). Patients must not have received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody. NB: Patient must have commenced adjuvant platinum-based chemotherapy within 12 weeks of resection of the NSCLC and no more than 12 weeks must have elapsed since the start of the last cycle of adjuvant platinum-based chemotherapy.
Treatment Intent	Palliative Adjuvant (NSCLC only)
Frequency and number of cycles	Schedule 1: Every 21 days SC Schedule 2: Every 28 days IV **1st line treatment of locally advanced or metastatic transitional cell urothelial cancer & untreated metastatic NSCLC:** Continue until disease progression or excessive toxicity or patient choice to discontinue. **Locally advanced or metastatic transitional cell urothelial cancer previously treated with platinum-based chemotherapy & previously treated NSCLC:** Continue until progressive disease or unacceptable toxicity up to a maximum treatment duration of 2 years of uninterrupted treatment or 35 administrations with Atezolizumab if given 3 weekly, or a maximum of 26 administrations if given 4 weekly, whichever is later. Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle.

	Adjuvant treatment of NSCLC: Continue until progressive disease, unacceptable toxicity or patient choice or up to a maximum treatment duration of 1 year (maximum of 13 x 4-weekly cycles or 18 x 3-weekly). NB patients can be switched between atezolizumab SC and IV therapy if the clinical need arises.
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. • Monitor FBC, U&Es, and LFTs at each cycle. • Thyroid function must be assessed at baseline then at least every 6-8 weeks. • 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 24 hours of the last steroid dose. • Monitor for signs and symptoms of myocarditis. Carry out ECG as clinically indicated. • Dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. • **Renal Impairment:** 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. • **Hepatic impairment**: (prior to treatment, for immune related hepatitis see below) - no dose adjustment is required for patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 × to 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). • **Atezolizumab Sub Cutaneous administration and injection-related reactions** o Remove from fridge and allow to reach room temperature before administration. o Inject into the subcutaneous tissue of the thigh only, over 7 minutes. o Injection site should be alternated between left and right thigh. o New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. o During the treatment other medicinal products for subcutaneous administration should preferably be injected at different sites. o If a grade 1 or 2 injection-related reaction occurs, the injection should be slowed down or paused and appropriate medical therapies should be administered. Treatment may be resumed once the event has resolved. o Permanently discontinue atezolizumab SC in the event of grade 3 or 4 hypersensitivity reaction. • **Intravenous Infusion-related reactions**: o Reduce infusion rate or interrupt treatment if Grade 1 or 2 infusion-related reaction. Atezolizumab may be continued with close monitoring; premedication with antipyretic and antihistamines should be considered. o Permanently discontinue in patients with Grade 3 or 4 infusion related reactions. • **Immune- related reactions:** o Patients must be advised to contact the oncology team if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment.

	○ Reactions include 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 ○ 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. ○ If corticosteroids are used to treat an immune related reaction they should be tapered over at least 1 month. 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/ ○ **Drug interactions:** ○ 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. • Patients experiencing fatigue should be advised not to drive and use machinery. • Use with caution in patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression, after careful consideration of the potential risk-benefit. • The patient should be provided with the appropriate Tecentriq® Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment).
Reference(s)	KMCC protocol MULTI-004 V11 SPC accessed online 18.09.2023

NB For funding information, 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 HCC	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
Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to > 3x to ≤ 10x ULN ***or*** If AST/ALT is >1 to ≤ 3x ULN at baseline and increases to >5x to ≤10x ULN ***or*** If AST/ALT is > 3x to ≤ 5x ULN at baseline and increases to > 8x to ≤ 10x 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
	If AST/ALT increases to >10x ULN ***or*** total bilirubin increases to > 3x 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, Meningoencephalitis and Facial paresis	Facial paresis Grade 1 or 2	Withhold Treatment may be resumed if the event fully resolves. If the event does not fully resolve while withholding, permanently discontinue
	All Grades Myasthenic syndrome/myasthenia gravis, Guillain Barré syndrome and Meningoencephalitis or Facial paresis Grade 3 or 4	Permanently discontinue
Myelitis	Grade 2, 3, or 4	Permanently discontinue
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold 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
	Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue
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
Haemophagocytic lymphohistiocytosis	Suspected haemophagocytic lymphohistiocytosis[1]	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)

Schedule 1 Sub cutaneous: Repeat every 21 days

Day	Drug	Dose	Route	Infusion Time	Administration Details
Day 1	Metoclopramide	20mg	PO		
	ATEZOLIZUMAB	**1875mg**	SC	7 mins	Inject 15ml into the subcutaneous tissue of the left or right thigh over 7 minutes. Do not inject at other sites of the body. Injection sites should be rotated for successive injections.
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	

Schedule 2 intravenous: Repeat every 28 days

Day	Drug	Dose	Route	Infusion Time	Administration Details
Day 1	Metoclopramide	20mg	PO		
	ATEZOLIZUMAB	**1680mg**	IV	1st dose over 60 mins. If tolerated, all subsequent infusions over 30 mins	diluted in 250ml 0.9% sodium chloride
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	