

Teclistamab (Multiple Myeloma)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

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Indication

Treatment of relapsed and refractory multiple myeloma after 3 or more lines of treatment (including an immune-modulatory agent, a proteasome inhibitor and an anti-CD38 antibody) when the myeloma has progressed on the last treatment. It is only recommended if:

- Pomalidomide plus dexamethasone would otherwise be offered

(NCIE TA1015)

Response Rates

Phase I/II MajesTEC-1 trial

- ORR: 63%, (39% CR or greater, 58.8% VGPR or greater), mDOR: 18.4 months
- Median PFS: 11.4 months
- Median OS: 22.2 months

Treatment related mortality

~3%

Regimen details

Week 1 – Step up dosing

Day	Drug	Dose	Route
1	Teclistamab	0.06mg/kg (step-up dose 1)	SC injection
3	Teclistamab	0.3mg/kg (step-up dose 2)	SC injection
5	Teclistamab	1.5mg/kg (first maintenance dose)	SC injection

Patients should be monitored for cytokine release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS) for 48 hours after step-up doses on days 1, 3 and 5. Patients should remain within the proximity of a healthcare facility or be treated as an inpatient during this period. The minimum dose interval between these doses is 2 days.

Ongoing Weekly dosing schedule

Starts one week after week 1 D5 dose

Day	Drug	Dose	Route
1, 8, 15 & 22	Teclistamab	1.5mg/kg	SC injection

Bi-weekly schedule

To be considered in patients who have had a complete response for a minimum of 6 months

Day	Drug	Dose	Route
1 & 15	Teclistamab	1.5mg/kg	SC injection

Cycle frequency

28 days (after initial step-up dosing)

Number of cycles

Until disease progression or unacceptable toxicity

Pre-medication

During step up dosing, 1-3 hours prior to teclistamab:

- Dexamethasone 16mg IV or PO
- Chlorphenamine 10mg IV/4mg PO
- Paracetamol 1g IV or PO

Continue premedication for subsequent doses of teclistamab in patients who:

- Require repeat doses of the step up schedule due to dose delays
- Experience cytokine release syndrome (CRS) with previous doses

Supportive medication

Cycle 1 days 1-8: Omeprazole 20mg od, consider ongoing treatment as indicated.

Cycle 1 only days 1-7: Allopurinol 300 mg OD (100mg OD if CrCl < 20mL/min)

Cycle 1 only days 1-14: Paracetamol 1g qds/prn

Cycles 1-3: Levofloxacin 500mg OD (reduced dose if CrCl < 50ml/min)

All cycles: Antiviral prophylaxis as per local policy and continue until off treatment for > 3 months

All cycles: Prophylactic co-trimoxazole 480mg bd on Mon, Weds, Fri until CD4 count >200/microL

All cycles: metoclopramide 10mg TDS prn

Hep B virus treatment entecavir: screen for virus prior to treatment and start if positive hep B PCR.

Ganciclovir/valganciclovir: if positive CMV PCR with CMV related organ disease. Monitor the viral load.

Bisphosphonates as per [local policy](#)

IVIg monthly when total IgG <4g/L. Recommended dose of IVIg: 0.4-0.6g/kg/month to achieve a trough level of at least the lower limit of the age-specific reference range. Continue when off treatment until IgG >4g/L as per [NHSE policy](#)

Emetogenicity

Low risk

Administration

Inject into the subcutaneous tissue of the abdomen (preferred) or, alternatively, it may be injected into the subcutaneous tissue at other sites (e.g. thigh). Each injection volume should not exceed 2mL, doses greater than 2 mL should be divided equally between multiple syringes. If multiple injections are required, injections should be administered at least 2 cm apart. Do not press or rub the site of injection. Do not inject into areas where the skin is red, bruised, tender, hard or not intact.

A minimum of 2 days should be maintained between step-up dose 1 (0.06mg/kg) and 2 (0.3mg/kg) and step-up dose 2 (0.3mg/kg) and the first maintenance dose (1.5mg/kg). A minimum of 5 days should be maintained between weekly maintenance (1.5mg/kg) doses.

If a dose is delayed, treatment should be restarted according to the table below, based on last dose administered and length of delay:

Last dose administered	Duration of delay from last dose administered	Action
Step-up dose 1 (0.06mg/kg)	> 7 days	Restart step-up dosing schedule at step-up dose 1 (0.06mg/kg)
Step-up dose 2 (0.3mg/kg)	8 - 28 days	Repeat step-up dose 2 (0.3mg/kg) and continue step-up schedule
	> 28 days	Restart step-up dosing schedule at step-up dose 1 (0.06mg/kg)
Any maintenance doses (1.5mg/kg)	8 - 28 days	Continue with maintenance dose (1.5mg/kg) at previous schedule
	> 28 days	Restart step-up dosing schedule at step-up dose 1 (0.06mg/kg)

Mandatory investigations – pre first cycle

Investigation	Validity period
FBC	14 days
Renal profile (U&Es including creatinine)	14 days
Liver profile (ALT/AST, ALP, bilirubin, albumin)	14 days
Clotting screen	14 days
Virology (Hep B/C, HIV, CMV (inc PCR), EBV inc PCR))	3 months
Immunoglobulins	14 days

Additional investigations advised pre-first cycle

- HBA1C
- Serum protein electrophoresis
- Serum free light chains
- β 2 microglobulin
- Bone profile (Calcium, phosphate, magnesium)
- CRP
- LDH
- Serum free light chains (SFLC)/Paraprotein (PP)
- Urine protein/creatinine ratio
- Bone marrow examination for cytogenetic analysis FISH
- Imaging as per local guidelines
- ECG/ECHO (if indicated)
- Blood pressure
- Baseline ICE score
- Annual flu, Covid-19 and pneumococcal vaccination

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	7 days
Renal profile (U&Es including creatinine)	7 days
Liver profile (ALT/AST, ALP, bilirubin)	7 days
Immunoglobulins	7 days

Additional investigations advised pre subsequent cycles

- SFLC, PP – results are not required prior to administration of cycle
- Bone profile (Calcium, phosphate, magnesium)
- Viral PCRs inc EBV, CMV (every 3 months)
- Blood pressure

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	$\geq 0.5 \times 10^9/\text{L}$
Platelets	$\geq 25 \times 10^9/\text{L}$
Haemoglobin (Hb)	$\geq 80\text{g/L}$
Creatinine clearance (CrCl)	$> 30 \text{ ml/min}$
Bilirubin	$< 1.5 \times \text{ULN}$
ALT/AST	$< \text{ULN}$ (see below)

Dose modifications

Dose modifications are not recommended. Dose delays may be required to manage toxicities.

Haematological toxicity

Toxicity	Action
Hb $< 80\text{g/L}$	Withhold dose until Hb $> 80\text{g/L}$ or consider transfusion if disease related
Neutrophils $< 0.5 \times 10^9/\text{L}$ or febrile neutropenia	Withhold dose until count $\geq 0.5 \times 10^9/\text{L}$ (or $> 1.0 \times 10^9/\text{L}$ and resolution of fever if febrile neutropenia). Consider GCSF if disease related.
Platelets $< 25 \times 10^9/\text{L}$ or Platelets $25 - 50 \times 10^9/\text{L}$ with bleeding	Withhold dose until count $\geq 25 \times 10^9/\text{L}$ and no evidence of bleeding

Renal impairment

No dose adjustment is recommended in mild to moderate renal impairment. Emerging data on the use of teclistamab in severe renal impairment ($< 30\text{ml/min}$) suggests it is safe to administer.

Hepatic impairment

No dose adjustment is recommended in mild hepatic impairment (bilirubin $> 1.5 \times \text{ULN}$ with any ALT). No data is available in patients with moderate or severe hepatic impairment.

Other toxicities

Toxicity	Definition	Action/Dose adjustment
Cytokine release syndrome (CRS)	Any grade	If CRS is suspected, treatment should be withheld until adverse reaction resolves. For recurrent or persistent ($> 48 \text{ hrs}$) Grade 3 or any Grade 4 CRS permanently discontinue teclistamab For management of CRS see below .
Immune effector cell-associated neurotoxicity syndrome (ICANS)	Any grade	If ICANS is suspected, treatment should be withheld until adverse reaction resolves. For recurrent Grade 3 or any Grade 4 ICANS permanently discontinue teclistamab For management of ICANS see below .
Infections	Any grades	For patients on step-up dosing schedule, DO NOT administer restart on resolution of active infection
	Grade 3 or 4	Withhold subsequent maintenance doses of teclistamab until infection resolves to \leq Grade 2
Any other non-haematological toxicity	Grade 3 or 4	Withhold teclistamab until adverse reaction resolves to \leq Grade 2

Side Effects

MajesTEC-1 study:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	Neutropenia	70.9	64.2
	Anaemia	52.1	37.0
	Thrombocytopenia	40.0	21.2
	Lymphopenia	34.5	32.7
Non-haematological	Cytokine release syndrome	72.1	0.6
	Diarrhoea	28.5	3.6
	Fatigue	27.9	2.4
	Nausea	27.3	0.6
	Pyrexia	27.3	0.6
	Injection site erythema	26.1	0
	Headache	23.6	0.6
	Arthralgia	21.8	0.6
	Constipation	20.6	0
	Cough	20.0	0
	Pneumonia	18.2	12.7
	COVID-19	17.6	12.1
	Bone pain	17.6	3.6
	Back pain	16.4	2.4
	Hypogammaglobulinaemia	14.5	1.8
	Neurotoxic event	14.5	0.6
	Hypokalaemia	13.9	4.8
	Bronchitis	13.3	0
	Hypomagnesaemia	13.3	0
	Vomiting	12.7	0.6
	Pain in extremity	12.7	0.6
	Hypophosphataemia	12.1	6.1
	Decreased appetite	12.1	0.6
	Hypertension	12.1	5.5
	Hypercalcaemia	11.5	3.0
	Blood alkaline phosphatase increased	10.9	1.8
	Asthenia	10.9	0.6
	Upper respiratory tract infection	10.9	0
	Peripheral oedema	10.9	0
	Musculoskeletal chest pain	10.3	1.8
	Dyspnoea	10.3	0.6

Specific drug related side effects:**Cytokine Release Syndrome**

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, may occur in patients receiving Teclistamab. The median time to onset is 2 days (range 1-6 days) and the median time to resolution is 2 days (range 1-9 days). Clinical signs and symptoms may include fever, hypoxia, chills, hypotension, tachycardia, headache and elevated liver enzymes. If CRS is suspected treatment should be withheld and the following investigations should be performed:

- FBC, U&Es, LFTs, bone profile, CRP, ferritin and coagulation screen, CXR and ECG

Management of CRS should be as the table below:

Grade	Symptoms	Management
1	Temp >38 °C AND no hypoxia or hypotension	<ul style="list-style-type: none"> • Monitor vital signs every 4 hours • Treat as per neutropenic sepsis guidelines • Consider early tocilizumab use • If persistent fevers (>24-48 hrs), consider IV tocilizumab 8mg/kg (max 800mg) over 1 hr*
2	Temp >38 °C WITH hypotension responsive to fluids OR hypoxia requiring <6L/min O2	<ul style="list-style-type: none"> • Monitor vital signs every 4 hours • Treat as per neutropenic sepsis guidelines • Administer IV tocilizumab 8mg/kg (max 800mg) over 1 hr, repeat every 8 hours as needed* • Consider IV methylprednisolone 1mg/kg bd • Inform ICU/consider transfer • Administer O2 and fluids
3	Temp >38 °C WITH hypotension requiring vasopressors OR hypoxia requiring >6L/O2	<p>TRANSFER TO ITU</p> <ul style="list-style-type: none"> • Treat as per neutropenic sepsis guidelines • Perform continuous cardiac monitoring and echo • Administer vasopressors as required • Administer O2 as required • Administer IV tocilizumab 8mg/kg (max 800mg) over 1 hr, repeat every 8 hours as needed* • Administer IV methylprednisolone 1mg/kg bd • If refractory, consider IV methylprednisolone 1g and/or alternative immunosuppressive agents (e.g. anakinra) • For recurrent grade 3 CRS, permanently discontinue teclistamab.
4	Temp >38 WITH hypotension requiring multiple vasopressors OR hypoxia requiring CPAP/BiPAP/ventilation	<p>TRANSFER TO ITU</p> <ul style="list-style-type: none"> • Treat as per neutropenic sepsis guidelines • Perform continuous cardiac monitoring and echo • Administer vasopressors • Administer O2 • Administer IV tocilizumab 8mg/kg (max 800mg) over 1 hr, repeat every 8 hours as needed* • Administer IV methylprednisolone 1g OD and/or alternative immunosuppressive agents (e.g. anakinra) • Permanently discontinue teclistamab.

* Max 3 doses in a 24 hours period, maximum total of 4 doses.

Immune Effector Cell Neurotoxicity Syndrome (ICANS)

Immune effector cell neurotoxicity syndrome (ICANS) is a potential neurological complication seen in patients receiving teclistamab. The incidence of ICANS with teclistamab is reported to be 14.5%, with all events being grade 1 or 2, aside from 1 patient who experienced a seizure during an episode of bacterial meningitis. Clinical signs of ICANS can include a change in cognitive state, fall in GCS and seizures.

ICANS monitoring

- Check Immune effector Cell Encephalopathy (ICE) score using ICE assessment tool, prior to receiving teclistamab
- Check ICE score twice a day whilst an inpatient and twice a day for 48 hours as an outpatient during step up dosing
- If grade 2 or higher ICANS experienced, patients should be monitored as an inpatient for 48 hours following the next dose.
- If ICANS is suspected a neurological examination should be performed, in addition to the following investigations:
 - ECG
 - Three times a day ICE assessment
 - MRI brain/CT brain
 - Consider diagnostic lumbar puncture

ICE assessment tool

	Question	Points
1	Which year is it?	1
2	Which month is it?	1
3	Which city/town are we in?	1
4	Which hospital are we in?	1
5	Follow an instruction e.g. touch your nose, lift your right arm, shrug your shoulders	1
6	Name 3 objects Point to three different objects	3
7	Write a sentence	1
8	Count backwards from 100 in 10's	1

Management of ICANS should be as the table below, with grading based on score from the ICE assessment:

ICE score and symptoms	Management	
	Monitoring/Investigations	Treatment
Score 10	No ICANS present	
Grade 1 - Score 7-9 Awakes spontaneously	Score 3-9 <ul style="list-style-type: none"> • Three times a day ICE score • Regular neurological observations • Consider tocilizumab if concurrent CRS 	Score 7-9 <ul style="list-style-type: none"> • If persistent symptoms (>48 hrs), consider IV dexamethasone (10mg qds) until resolution, then taper • Consider seizure prophylaxis*
Grade 2 - Score 3-6 Awakes to voice		Score 3-6 <ul style="list-style-type: none"> • Administer IV dexamethasone (10mg qds) until resolution to grade 1 or less, then taper • Administer antiepileptics • Consider EEG and imaging

ICE score and symptoms	Management	
	Monitoring/Investigations	Treatment
Grade 3 - Score 0-2 AND Awakes to tactile stimuli Seizures resolve rapidly Focal cerebral oedema on imaging	Score 0-2 TRANSFER TO ICU <ul style="list-style-type: none"> Regular neurological observations Three times a day ICE score Perform neuroimaging and EEG 	Score 0-2 and rousable <ul style="list-style-type: none"> Administer IV dexamethasone (10mg qds) until resolution to grade 1 or less, then taper If refractory consider IV methylprednisolone 1g daily for 3 days. Taper when symptoms improve
Grade 4 - Score 0 AND Unroutable, prolonged (>5 min) or frequent seizures, motor weakness, diffuse cerebral oedema on imaging	<ul style="list-style-type: none"> Administer antiepileptics Consider CSF evaluation for other causes/pressure measurement Consider tocilizumab if concurrent CRS 	Score 0 and unroutable <ul style="list-style-type: none"> Administer IV methylprednisolone 1g daily for 3 days. Taper when symptoms improve For refractory patients consider alternative therapies (e.g. anakinra)

*Seizure prophylaxis includes levetiracetam 500mg po/IV bd, up to 2000mg bd

Infections

Infections occurred in approximately 76.4% of trial patients with 44.8% being grade 3 and above. 39.4% of patients received immunoglobulin replacement whilst on trial.

Additional information

Nil

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

No formal drug interactions have been identified. Based on in vitro and clinical data, there is a low risk of pharmacokinetic or pharmacodynamic drug interactions.

CYP450 substrates with narrow therapeutic index: transient elevation of proinflammatory cytokines when starting treatment with teclistamab may suppress CYP450 activities, consider therapeutic monitoring of substrate if narrow therapeutic index.

References

- Moreau, P et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med 2022; 387(6): 495-505
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Version	Issue date	Review date	Revision	Written/Checked/Authorised
1	Oct 2024	Oct 2027	New protocol	Written: Dr S Moore (Consultant Haematologist, UHBW NHS Trust) Checked: Kate Gregory (Lead Pharmacist for SACT Protocols, SWAG Cancer Alliance) Authorised: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

Schedule of investigations and treatment plan

Activity	Pre-tx	Cycle 1	Cycle 1 D3	Cycle 1 D5	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed consent	x							
Clinical assessment	x	x			x	x	x	Every cycle
FBC	x	x			x	x	x	Every cycle
U&E, LFTs & bone profile	x	x			x	x	x	Every cycle
CrCl	x	x			x	x	x	Every cycle
Imaging as per guidance	x							Repeat if clinically indicated
Serum Igs, electrophoresis, SFLC (if indicated)	x				x	x	x	Every cycle
ECG/ECHO (if indicated)	x							If clinically indicated
Blood pressure	x	x	x	x	x	x	x	Repeat if clinically indicated
Temperature, RR, pulse	x	x	x	x	x	x	x	If clinically indicated
Weight recorded	x							Repeat if necessary
Height recorded	x							Repeat if necessary
CRS assessment		x	x	x	x			Once daily during step up dosing. Repeat if needed
ICE assessment		x	x	x	x			Once daily during step up dosing. Repeat if needed
Hep B core Ab and surface Ag, Hep C & HIV	x							If clinically indicated
Serum pregnancy test (where appropriate)	x							Where appropriate