PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

TECLISTAMAB (JNJ-64007957)
Relapsed & Refractory Multiple Myeloma
Via Managed Access Program

PROTOCOL REF: MPHATECLIS
(Version No. 2.0)

Approved for use in:

- Patients with relapsed and refractory multiple myeloma who have exhausted all available standard of care therapies and who are not eligible for an ongoing clinical trial or Named Patient Program/Early Access Program in the period prior to marketing authorization of teclistamab.

Requires approval and ordering of stock via Janssen Managed Access Scheme

Note: Unlicensed medicinal product

Dosage:

Cycle ONE (28 day cycle)

Drug	Dose	Route	Frequency	Dose escalation
Teclistamab	0.06 mg/kg	Subcutaneous Injection	Day 1 only	First step-up dose
Teclistamab	0.3 mg/kg	Subcutaneous Injection	Day 4	*Second step-up dose
Teclistamab	1.5 mg/kg	Subcutaneous Injection	Day 8, 15 and 22	**First Treatment Dose

*The second step-up dose must be separated by 2-4 days from the first step-up dose

**The first treatment dose must be separated by 2-4 days from the second step-up dose

Cycle Two (28-day cycles)

Drug	Dose	Route	Frequency
Teclistamab	1.5 mg/kg	Subcutaneous Injection	Day 1, 8, 15 and 22 of a 28 day cycle

To be continued until disease progression, unacceptable toxicity or withdrawal of consent

Administration:

Teclistamab: Subcutaneous Injection

The preferred location for subcutaneous injection is the abdomen. An alternative injection site location such as the thigh or arm may be utilized if there are scars, tattoos, skin imperfections or if all locations of the abdomen were used for other subcutaneous injections. If a drug other than teclistamab is administered subcutaneously within 24 hours of teclistamab, then the injections should be administered in different anatomical locations (at least 10 cm apart). Do NOT press or rub the site of injection.

Due to risk of Cytokine Release Syndrome (CRS) and Immune-effector Cell Neurotoxicity Syndrome (ICANS) patients must be admitted and inpatients for the dose-escalation period and until at least 48 hours after administration of the first treatment dose.

Due to dosing schedule, risk of toxicity, the product expiry and the need for aseptic manipulation of the product, it is recommended that treatment start (Cycle 1, Day 1) on a Monday where possible.

Doses of >2mL will be split into 2 separate syringes for administration.

See Appendix 1 for Guidelines for the management of CRS and ICANS in patients treated with teclistamab.

Monitoring

Observations: four-hourly temperature, pulse, blood pressure, oxygen saturations and respiratory rates during teclistamab treatment days as an inpatient. This can be once prior and once once following administration on treatment days.

Patient should undertake a twice daily ICE assessment throughout cycle 1 then once weekly as an outpatient.

(See appendix 4 for ICE assessment details).

Supportive treatments:

Teclistamab pre-infusion medications:

- Dexamethasone PO 16mg STAT
- Chlorphenamine 10mg IV STAT
- Paracetamol PO 1g STAT

Required before the first treatment dose and with each step-up dose, thereafter as clinically indicated. (Due to risk of CRS post dose delay, pre-infusion medication is recommended upon re-initiation of teclistamab).

Supportive Medications:

- Aciclovir PO 400mg BD
- Fluconazole PO 50mg OD
- Co-trimoxazole PO 480mg OD
- Allopurinol PO 100mg or 300mg OD (depending on renal function) for first cycle only

Consider Rasburicase 3mg IV OD for up to 3 days and IV hydration as alternative to allopurinol in patients with high risk of TLS (i.e. ≥80% plasma cell infiltrate on either bone marrow biopsy/aspirate).

Interactions:

No formal non-clinical pharmacokinetic drug interaction studies have been conducted. Please ensure any suspected drug interactions are reported.

CYP substrates such as warfarin and ciclosporin with a narrow therapeutic index should be used with caution or avoided in patients receiving teclistamab.

Janssen disallow the following as part of the Managed Access Scheme:

- Any other chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy
- Medications used for other indications that have anti-myeloma properties such as Interferon (IFN) and clarithromycin (with exception for treatment of infection for ≤14days)
- Systemic corticosteroids and other immunosuppressant agents should be avoided other than those used for management of AEs and pretreatment medication
- IV contrast Infusions
- Vaccination with live, attenuated vaccines is prohibited during treatment and for 30 days after the last dose of teclistamab. (Annual inactivated influenza or SARS CoV-2 vaccines are allowed). However, antibody responses to vaccines may be suboptimal treatment with teclistamab
- Use of transdermal patches at the injection site
- Routine blood transfusions given on **dosing days** of teclistamab administration

Treatment schedule:

Cycle ONE (28-day cycle)

Day	Drug	Dose	Route	Additional infomation
1	**Chlorphenamine**	10mg	IV	60 mins before teclistamab
	Dexamethasone	16mg	PO	60 mins before teclistamab
	Paracetamol	1g	PO	60 mins before teclistamab
	Teclistamab	0.06 mg/kg	S/C	Over 3-5 minutes
4	**Chlorphenamine**	10mg	IV	60 mins before teclistamab
	Dexamethasone	16mg	PO	60 mins before teclistamab
	Paracetamol	1g	PO	60 mins before teclistamab
	Teclistamab	0.3 mg/kg	S/C	Over 3-5 minutes
8	**Chlorphenamine**	10mg	IV	60 mins before teclistamab
	Dexamethasone	16mg	PO	60 mins before teclistamab
	Paracetamol	1g	PO	60 mins before teclistamab
	Teclistamab	1.5 mg/kg	S/C	Over 3-5 minutes
15	**Teclistamab**	1.5 mg/kg	S/C	Over 3-5 minutes
22	**Teclistamab**	1.5 mg/kg	S/C	Over 3-5 minutes

Cycle Two onwards (28-day cycles)

Day	Drug	Dose	Route	Additional infomation
1	**Teclistamab**	1.5 mg/kg	S/C	Over 3-5 minutes
8	**Teclistamab**	1.5 mg/kg	S/C	Over 3-5 minutes
15	**Teclistamab**	1.5 mg/kg	S/C	Over 3-5 minutes
22	**Teclistamab**	1.5 mg/kg	S/C	Over 3-5 minutes

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, lymphopenia, systemic administration-related reactions (sARRs), raised intracranial pressure, cerebral oedema, ICANS, injection site reactions, tumour lysis syndrome (TLS), immune-related adverse events (irAEs), nausea, fatigue and HBV Reactivation.

CRS

Clinical symptoms indicative of CRS may include, but are not limited to fever (with or without rigors), arthralgia, nausea, vomiting, tachypnoea, hypoxia, tachycardia, hypotension, headache, confusion, tremor, delirium, dyspnoea, pulmonary oedema and capillary leak.

Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.

In the MajesTEC-1 trial 72.1% of patients experienced a grade of CRS.

For CRS management see appendix 1 and 3

For ICANS management see appendix 2 and 4

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D4	Cycle 1 D8	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	X							
Clinical Assessment	X	X	X	X	X	X	X	Every cycle
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFTs & Calcium profile	X	X	X	X	X	X	X	Every Cycle
CrCl (Wright formula)	X	X	X	X	X	X	X	Every cycle
CT scan/bone marrow biopsy /MRI brain	X							At the end of treatment and if clinically indicated
ECG/ECHO	X							If clinically indicated
Blood pressure measurement	X	X	X	X				Repeat if clinically indicated
Temperature, respiratory rate, pulse	X	X	X	X				If clinically indicated
Weight recorded	X	X			X	X	X	Every cycle
Height Recorded	X	X				X		Every 3rd cycle
ICE Assessment	X	X	X	X	X	X	X	Continuously throughout treatment (see monitoring section above)
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X							If clinically indicated
Viral swabs (including COVID-19)	X							If clinically indicated

Serum Pregnancy test	X							Where appropriate

Haematological toxicity:

Proceed on each treatment day if:	
ANC	>1.0 × 10^9/L
Haemoglobin	>80 g/L
Platelet count	>75 x 10^9/L

Note: routine blood transfusions are permitted except on teclistamab dosing days.

Note that if cytopenia's are thought to be due to disease, treatment may go ahead at clinician discretion.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Renal Impairment	
CrCl (Wright Formula) <40 mL/min	Not recommended
Hepatic Impairment	
Total bilirubin level >2 × ULN (except for Gilbert Syndrome: direct bilirubin >1.5 × ULN)	Not recommended
ALT ≥2.5 times the ULN	Not recommended
Corrected serum calcium	
>3.5 mmol/L	Not recommended

Note: due to limited experience treating patients with abnormal liver and renal function, treatment should be approached with caution.

Toxicity Management:

The criteria outlined by Janssen for a dose delay are:

- Grade 4 haematological toxicity except lymphopenia
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia
- Grade 3 neutropenia with infection
- Grade 3 or higher non-hematologic toxicities that are clinically significant except of disease-related pain
- First sign of CRS
- First sign of ICANS

Following a dose delay, any non-hematologic toxicity other than CRS or ICANS must resolve to Grade ≤1 or to baseline and there must be no evidence of a serious bacterial, viral, or fungal infection before proceeding to the next dose. CRS and ICANS must fully resolve before preceding to the next dose.

(Severity of grade according to NCI-CTCAE, except ICANS and CRS see appendices 1-2)

Restarting Teclistamab after dose delay

If a dose is delayed, please follow recommendation in the table below:

Delayed dose	Duration from the last dose	Action
*Second step-up dose	≤7 days	Restart teclistamab at 0.3 mg/kg
	>7 days	Restart teclistamab at 0.06 mg/kg
*First treatment dose	≤7 days	Restart teclistamab at 1.5 mg/kg
	8-28 days	Restart teclistamab at 0.3 mg/kg
	>28 days	Restart teclistamab at 0.06 mg/kg
Subsequent treatment doses	≤28 days	Restart teclistamab at 1.5 mg/kg
	>28 days	Restart teclistamab at 0.06 mg/kg

*If the step-up dose schedule is interrupted due to toxicity and later reinitiated, the dose and schedule must be discussed with Janssen before resuming treatment.

After the dose escalation period, if a dose has been missed, do NOT make up the dose but resume administration at the next planned dosing date.

References:

1. Janssen Managed Access Scheme: https://www.janssenmanagedaccess.com
2. Specialist Pharmacy Service: https://www.sps.nhs.uk/articles/diagnosis-and-medical-management-of-acute-car-t-cell-toxicities-in-adults/

Appendices

Appendix 1 - CRS

Most common symptoms of CRS:

- Fever
- Hypotension
- Hypoxia

Other symptoms:

- Constitutional (Fever, Rigors, Maslaise, Fatigue)
- Cardiovascular (Tachycardia, Hypotension, Arrythmias, Decreased LVEF, QT prolongation, Troponinemia)
- Pulmonary (Hypoxia, Tachypnoea)
- Hepatic (Tranaminitis, Hyperbilirubinaemia)
- Gastrointestinal (Nausea, Emesis, Diarrhoea)
- Muscoskeletal (Weakness, Myalgias, Elevated CK)
- Renal (AKI, Hyponatraemia, Hypokalaemia, Hypophosphataaemia, TLS)
- Haematological (Thrombocytopenia, Neutropenia, Anaemia, B cell aplasia, Hypofibrinogenemia, Disseminated intravascular coagulation, Haemophagocytic lymphohistiocytosis)

If CRS is suspected the following investigations should be performed:

- Ferritin
- Coagulation
- FBC
- Daily ECG
- U&Es
- Appropriate imaging (e.g. chest X-ray)
- LFTs
- Blood and urine cultures
- CRP
- Bone profile (if TLS in differential)
- Cytokine profile (if available)

For CRS grade 3 or 4 monitor with continuous cardiac telemetry and pulse oximetry

Consider performing an echocardiogram to assess cardiac function

Symptoms	Management
Grade 1 CRS	
Temp ≥38°C No hypotension No hypoxia	• Monitor vital signs every 4 hours • Treat as per neutropenic sepsis guidelines: • If persistent fevers, consider IV tocilizumab [8mg/kg (max 800mg), every 8 hours, max 4 doses]
Grade 2 CRS	
Temp 38°C **AND** Hypotension responsive to fluids **AND/OR** Hypoxia requiring <6L/min oxygen	• Monitor vital signs hourly • Treat as per neutropenic sepsis guidelines • Administer IV tocilizumab [8mg/kg (max 800mg), every 8 hours, max 4 doses] • Consider IV methylprednisolone 1mg/Kg BD • Inform ICU team/consider transfer • Administer oxygen and fluids as required
Grade 3 CRS	
Temp ≥38°C **AND** Hypotension requiring vasopressors **AND/OR** Hypoxia requiring >6L/min oxygen	**Transfer to ICU** • Treat as per neutropenic sepsis guidelines • Continuous cardiac monitoring, consider ECHO • Administer vasopressors as required • Administer oxygen as required • Administer IV tocilizumab [8mg/kg (max 800mg), every 8 hours, max 4 doses] • Administer IV methylprednisolone 1mg/Kg BD • If refractory, consider IV methylprednisolone 1g and/or alternative immunosuppressive agents.
Grade 4 CRS	
Temp ≥38°C **AND** Hypotension requiring multiple vasopressors **AND/OR** Hypoxia requiring CPAP/BiPAP/Ventilation	**Transfer to ICU** • Treat as per neutropenic sepsis guidelines • Continuous cardiac monitoring, ECHO • Administer vasopressors • Administer oxygen • Administer tocilizumab [8mg/kg (max 800mg), every 8 hours, max 4 doses] • Administer IV methylprednisolone 1g and/or alternative immunosuppressive agents

Appendix 2 – ICANS

If ICANS is suspected a thorough neurological examination should be performed.

Investigations should include:

- EEG
- Three times daily ICE assessment
- MRI / CT Brain
- Consider diagnostic lumbar puncture
- Frequent monitoring for cognitive function e.g. handwriting tests

Alternative causes of neurological dysfunction such as infection, opioid toxicity, haemorrhage, drugs, electrolyte imbalance or metabolic acidosis should be considered and treated.

The following supportive management should be considered:

- Avoid medications that suppress consciousness
- Assess papilloedema
- Assess swallow (aspiration precautions)
- IV hydration
- Manage agitation

Symptoms	Management
Grade 1 ICANS	
ICE score 7-9 Awakes spontaneously	• Close monitoring • Neurological examination • Three times daily ICE score • Consider seizure prophylaxis (e.g levetiracetam) • If persistent symptoms >48hrs discuss treatment options with Myeloma team and consider steroids • Consider tocilizumab if concurrent CRS
Grade 2 ICANS	
ICE score 3-6 Awakes to voice	• Regular neurological observations • Three times daily ICE score • Consider seizure prophylaxis (e.g levetiracetam) • Administer IV dexamethasone [10mg – 20mg BD – QDS] • Inform ICU team • Consider tocilizumab if concurrent CRS
Grade 3 ICANS	
ICE score 0-2 Awakes only to tactile stimuli Seizures that resolve rapidly Focal cerebral oedema on imaging	**Transfer to ICU/Neuro ICU** • Regular neurological observations • Three times daily ICE score • Repeat neuroimaging and EEG • Administer antiepileptics for seizures • Administer IV dexamethasone [10mg – 20mg QDS] • If refractory, consider IV methylprednisolone 1g daily or alternative agents • Administer tocilizumab if concurrent CRS
Grade 4 ICANS	
ICE score 0 Unrousable Prolonged (>5min) or frequent seizures Motor weakness Diffuse cerebral oedema on imaging	**Transfer to ICU/Neuro ICU** • Regular neurological observations • Three times daily ICE score • Repeat neuroimaging and EEG • Administer antiepileptic's for seizures • Administer IV methylprednisolone 1g daily and/or alternative agents • Administer tocilizumab if concurrent CRS

Appendix 3 – Tocilizumab

<table>
<tr><th colspan="2">Tocilizumab</th></tr>
<tr><td>Dose</td><td>
<table>
<tr><th>Weight*</th><th>Dose</th></tr>
<tr><td>>40 and ≤65 kg</td><td>400 mg</td></tr>
<tr><td>>65 and ≤90 kg</td><td>600 mg</td></tr>
<tr><td>>90 kg</td><td>800 mg</td></tr>
</table>
*for lower weights, dosing should be 8mg/kg
(Max dose of 800mg)
</td></tr>
<tr><td>Indication</td><td>CRS</td></tr>
<tr><td>Frequency</td><td>Dose can be repeated every 8 hours
Maximum of 4 doses in total</td></tr>
<tr><td>Dilution</td><td>Dilute required dose to a final volume of 100mL with sodium chloride 0.9%
To mix, gently invert the infusion bag to avoid foaming</td></tr>
<tr><td>Administration</td><td>Intravenous infusion over 1 hour via central or peripheral line</td></tr>
<tr><td>Additional information</td><td>

Does not need to be adjusted for renal or hepatic impairment, but use with caution if deranged LFTs
Tocilizumab can be administered by any member of qualified nursing staff who has been assessed competent in administration of IV drugs,does NOT need to be a SACT trained nurse
Prior to Tocilizumab administration 4 doses of tocilizumab will be supplied on an individual patient basis and stored in the ward fridge

</td></tr>
</table>

Tocilizumab is only licensed to treat CRS, not ICANS. Corticosteroids (IV dexamethasone and methylprednisolone) are recommended to treat both CRS and ICANS.

If required tocilizumab should be prescribed in Meditech.

Appendix 4 - ICE assessment tool

Assign one point for each task performed correctly

(Score of 10 = Normal)

Question	ICE
1	**What year is it?**
2	**What month is it?**
3	**What city/town are we in?**
4	**What hospital are we in?**
5	**Follow instruction** E.g. “touch your nose”, “Lift your left/right arm”, “Lift your left/right arm”,”Shrug your shoulders”. Do NOT demonstrate to the patient
6	**Name 3 objects** (one point for each) Point to an object, patient should name the object without assistance from anyone
7	**Write a standard sentence** (patient can choose but use the same one each time) If a change in handwriting is seen, escalate to Myeloma team. Refer for neurology review
8	**Count backwards from 100 in 10’s**

Grading

Grade	Score (points)
0	10
1	7-9
2	3-6
3	0-2
4	Patient critical/obtunded

Circulation/Dissemination

Date added into Q-Pulse	23rd June 2023
Date document posted on the Intranet	23rd June 2023

Version History

		Author name and designation	Summary of main changes
			To be completed by author
	1.0	**Thomas Sanders (Advanced Pharmacist)**	**New Protocol**
	1.1	**Thomas Sanders (Advanced Pharmacist)**	**Tocilizumab dose banding added**
	2.0	**Thomas Sanders (Advanced Pharmacist)**	**Platelet cut off changed to 75. Comment to allow transfusion xxxxxxx**