LANCASHIRE AND SOUTH CUMBRIA CANCER NETWORK

Guidelines for the diagnosis and management of monoclonal gammopathy of undetermined significance (MGUS), smouldering myeloma, multiple myeloma, plasma cell leukaemia and solitary plasmacytoma (2021 Version)

Contents

1. Definitions and diagnostic criteria (see algorithm also)

1.1 Definitions:

- **Monoclonal gammopathy of undetermined significance (MGUS)**
  - MGUS is a premalignant clonal plasma cell disorder characterised by the presence of a monoclonal (M) protein* quantified at < 30g/L (levels of 30 g/l or more signify myeloma) with < 10% plasma cells in the bone marrow and the absence of features of multiple myeloma (as described below) or other related lymphoplasmacytoid malignancies.
- **Smouldering myeloma**
  - Smouldering myeloma is an asymptomatic malignant clonal plasma cell disorder characterised by the presence of a monoclonal (M) protein (though a minority of cases are non-secretory) with 10% to 59% plasma cells in the bone marrow but the absence of other features of multiple myeloma (as described below)
- **Multiple myeloma****
  - Multiple myeloma is a malignant clonal plasma cell disorder characterised by the presence of a monoclonal (M) protein (though a minority of cases are non-secretory) with >10% plasma cells in the marrow with one or more associated 'CRAB' criteria***: hypercalcaemia, renal failure, anaemia and bone disease, or one or more of the following 3 additional features:
    - Serum free light chain ratio ≥ 100
    - Plasma cells ≥ 60% in the marrow
    - More than one focal lesion, ≥ 5mm in size, on MR, CT or PET-CT
- **Plasma cell leukaemia**
  - Plasma cell leukaemia is a rare highly aggressive malignant clonal plasma cell disorder characterised by the presence of > 2 x 10^9/L peripheral blood plasma cells or >20% plasma cells on the blood film differential white cell count. Primary plasma cell leukaemia (pPCL) does not arise from pre-existing multiple myeloma whereas secondary plasma cell leukaemia (sPCL) does.
- **Solitary plasmacytoma**
  - Solitary plasmacytoma is a malignant plasma cell disorder characterised by the presence of a single bone lesion (solitary plasmacytoma of bone) or, less commonly, a single soft tissue mass (extramedullary soft tissue plasmacytoma). The presence of a monoclonal (M) protein is possible but there must be no features of multiple myeloma (as described above) and the lesion must be solitary. Presence of more than one lesion changes the diagnosis to that of multiple myeloma.

*****An M-protein (also referred to as paraprotein or M-component) is a monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells in an amount that can be visualised by immunofixation of serum and/or urine, or by serum free light chain analysis. They can be intact, consisting of both heavy and light chains, or just immunoglobulin free light chain alone.
******as multiple myeloma requiring therapy can be asymptomatic, the terms 'symptomatic' and 'asymptomatic' myeloma are no longer used to distinguish whether or not therapy is required
*** see Rajkumar et al, Lancet oncology 2014 for IMWG definitions of each of the CRAB criteria
For investigational algorithm references see reference section near end of the guideline.

Investigational algorithm for patients with a monoclonal band on serum electrophoresis

- Level of monoclonal protein (**not** the total Ig class): IgG < 15 g/L or IgA/IgM < 10 g/L (not IgD/E)
- Normal serum free light chain ratio
- No symptoms, signs, or abnormal and **unexplained** blood or previous X-ray results

If **all** the above apply, **diagnosis = low risk MGUS**

Low risk MGUS patients do **not** require bone marrow investigation or further imaging

For MDT registration list only
NOT for full MDT discussion

Discharge and ask GP to check band in 6 months. If level stable then GP should recheck every 2 years

- Level of monoclonal protein (**not** the total Ig class): IgG > 15 g/L or IgA/IgM > 10 g/L or any IgD/E
- Abnormal serum free light chain ratio
- Symptoms/signs of myeloma, lymphoma, AL amyloidosis, POEMS (e.g. sweats, wt loss, neuropathy, purpura, heart failure, macroglossia, adenopathy, proteinuria)

Further investigations and full MDT discussion required:
For IgG > 15 g/L or IgA > 10 g/L or any IgD/E:

- FBC, U&E, calcium, albumin, β2 microglobulin, LDH
- Bone marrow aspirate and trephine biopsy
- Skeletal survey

For IgM > 10 g/L exclude Waldenström macroglobulinaemia (lymphoplasmacytoid lymphoma) with above investigations but request CT thorax abdomen and pelvis instead of skeletal survey and consider biopsy of any enlarged nodes
To exclude AL amyloidosis, POEMS or solitary plasmacytoma see further text in guideline on these below.

- Normal Hb (or clear other reason for low Hb), normal calcium, normal renal indices
- No lytic lesions on skeletal survey
- Marrow plasma cell % **by light microscopy** < 10%
- Level of monoclonal protein < 30 g/L (if ≥ 30g/L the diagnosis is myeloma)

If **all** the above apply, **diagnosis = high risk MGUS** for haematology clinic monitoring 3-4 monthly
If monoclonal protein > 30 g/L **or** bone marrow plasma cell % **by light microscopy** > 10% but < 60% **and** serum free light chain ratio < 100, do imaging to confirm smouldering myeloma

Request **one** of:

- whole body MRI
- MRI spine and pelvis
- low dose whole body CT
- PET-CT (depending on local resources)

If only one or no focal lesions present **diagnosis = smouldering myeloma** for haematology clinic monitoring 2-3 monthly

If **any** of the below are seen this confirms a **diagnosis of multiple myeloma :**

- Anaemia not otherwise explained
- Renal impairment (no other cause)
- Hypercalcaemia
- Serum free light chain ratio >100
- Lytic lesions or compression fractures on skeletal survey, or more than one focal lesion on CT / MRI / PET-CT
- Bone marrow shows > 60% plasma cells **by light microscopy**

Patients must be offered appropriate therapy and entered into a trial if possible. AL amyloidosis, POEMS syndrome and solitary plasmacytoma also require therapy

1.2 Epidemiology

MGUS

Monoclonal gammopathy of undetermined significance (MGUS) is a term originally coined by the Mayo Clinic group (Kyle, R.A. 1978). MGUS is present in 3% of the population ≥ 50 years old. (Kyle, R.A., et al, NEJM, 2018). There is a higher risk and earlier stage of onset in Afro-Caribbean populations. It is now considered a requisite precursor of multiple myeloma and can be detected years before the diagnosis (Landgren et al, 2009).

Smouldering Myeloma

Incidence and prevalence data is given for myeloma as a whole under the heading multiple myeloma below. This includes both cases of multiple myeloma and smouldering myeloma (SMM). SMM is distinguished from MGUS because the risk of progression to multiple myeloma is different in the first 5 years: 10% per year in SMM verses 1% per year in MGUS (Kyle et al, 2007). After 5 years however the rate of progression of SMM cases slows to match that of MGUS cases (see fig 1). Thus around 50% of cases in the SMM group behave like MGUS but, at the time of writing, there is no way to predict this at the time of diagnosis.

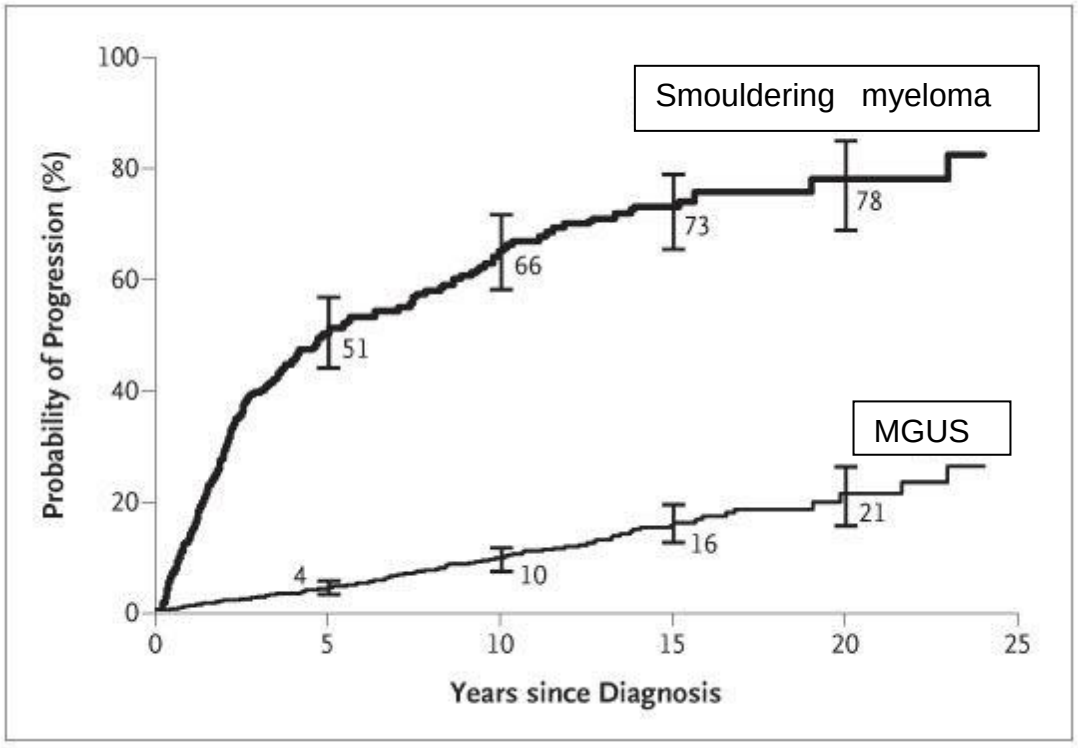


Figure 1

Multiple myeloma

- Cancer research UK data from 2015 showed that 2% of all cancers diagnosed in the UK were myeloma, representing a 32% increase in incidence rate since the early 1990s and making it the 19th most common UK cancer. Interestingly, because of the explosion of new therapies in myeloma, the disease accounted for 20% of the UK Cancer Drugs Fund budget in 2019. Myeloma represents around 10% of all haematological malignancy.
- Incidence in England according to Cancer Research UK 2015 data: 8.5/100,000 population per annum with around 90-100 cases per annum in the Lancashire and South Cumbria Cancer Network area
- 58% of cases were in males and 42% in females
- The median age at presentation is approximately 70 years. Only 15% of patients are aged less than 60 years.
- Prevalence appears to be increasing as evidenced by improving survival rates with a median survival of around 7.7 years in patients aged 65 or younger, and 3.4 years in those aged 66 or older in real world data from the Swedish Myeloma Registry (Blimark et al, 2018)

Plasma cell leukaemia

Plasma cell leukaemia is rare with an incidence of only 1% that of myeloma. In spite of treatment developments overall survival remains dismal at a median of only 11 months.

Solitary plasmacytoma

Less than 5% of patients with plasma cell malignancies present with a single lesion and these are subdivided into those which arise in bone (solitary plasmacytoma of bone) and those that arise in soft tissue (solitary extramedullary plasmacytoma). Solitary plasmacytoma of bone (SBP) is more common, has a male : female ratio of 2:1, a median age of presentation of 55 years and primarily affects the axial skeleton, especially the vertebrae. The majority of patients with SBP progress to multiple myeloma with a median time to progression of 2 – 4 years. Almost 90% of cases of solitary extramedullary plasmacytoma (SEP) arise in the head and neck, especially the upper respiratory tract including the nasal cavity, sinuses, oropharynx, salivary glands and larynx. SEP has a high cure rate with radiotherapy.

Other rare forms of myeloma

The large majority of myeloma cases excrete intact IgG, IgA or light chains only. IgD myeloma may comprise only 1.8% of the total and care must be exercised to avoid a false

diagnosis of non-secretory myeloma. The clinical features are similar to that of other myelomas but Bence-Jones proteinuria, extramedullary involvement, lytic lesions and amyloidosis seem to be more frequent (Jancelewicz *et al,* 1975). Relatively few cases of IgE myeloma have been reported. There may be similarities to IgD myeloma and in both conditions the prognosis appears to be poor. IgM myeloma may comprise up to 0.4% of all myeloma. It is important these cases are distinguished from Waldenström macroglobulinaemia / lymphoma, there is a high incidence of t(11;14) and prognosis appears to be poor. The clinical presentation of non-secretory myeloma is similar to standard myeloma but anaemia and lytic lesions may be seen more frequently while renal failure is uncommon (Morris et al, 2010; BSCH Feb 2014). The SFLC assay is informative in approximately two thirds of patients (Drayson et al*,* 2001).

AL Amyloidosis (AL = Amyloid Light chain)

This rare condition was formerly known as primary amyloidosis to distinguish it from amyloidosis which occurs secondary to inflammatory conditions associated with prolonged high levels of serum protein A such as rheumatoid arthritis (also known as AA amyloidosis). AL amyloidosis occurs when a plasma cell dyscrasia produces 'amyloidogenic' light chains – i.e. light chains that have a propensity to link together into long chains to form amyloid protein, which then becomes deposited in tissues. These patients represent a therapeutic challenge as the deposition of amyloid in organs such as the heart, kidneys, bowel and nerves can lead in turn to cardiac failure, arrhythmias, proteinuria, renal failure, malabsorption, GI bleeding and peripheral and autonomic neuropathy. If amyloidosis is found in MGUS or smouldering myeloma then this requires consideration for therapy and a 'watch and wait' policy is no longer appropriate. AL amyloidosis complicates 10 – 15% of cases of multiple myeloma. Any therapy directed at the plasma cell clone will of course only serve to cut off the supply of new amyloid production and does nothing to treat amyloid already deposited in tissues. This can only be removed very gradually by the body so there is a lag time between the commencement of myeloma-type therapy and any clinical improvement in the patient's condition. The prognosis in patients with AL amyloidosis is poor. Some tissues, e.g. cardiac, are very difficult to clear of amyloid even with the use of myeloma-type therapy and so cardiac involvement conveys an even poorer prognosis. Therapies designed to remove the amyloid protein directly from tissues remain in trials only at the time of writing.

POEMS syndrome

This extremely rare but important to recognise paraneoplastic syndrome takes its name from less than half of the defining features of the disease, that is, **p**olyradiculoneuropathy, **o**rganomegaly, **e**ndocrinopathy, **m**onoclonal plasma cell neoplasm, and **s**kin changes.

In clinical practice the diagnosis of POEMS syndrome can be difficult to make. It is confirmed when both of the two mandatory criteria, 1 of the 3 major criteria, and 1 of the 6 minor criteria are present. Thus, it requires two mandatory criteria:

- polyradiculoneuropathy (typically demyelinating)
- monoclonal plasma cell disorder (almost always with lambda light chain involvement)

both must be present, along with **at least one** major criterion:

- Castleman disease,
- sclerotic bone lesions
- VEGF elevation

and **at least one** minor criterion

- organomegaly [splenomegaly, hepatomegaly, or lymphadenopathy],
- extravascular volume overload [oedema, pleural effusion, or ascites],
- endocrinopathy [adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic],
- skin changes [hyperpigmentation, hypertrichosis, glomeruloid haemangiomata, plethora, acrocyanosis, flushing, white nails],
- papilloedema,
- thrombocytosis/polycythemia.

Other symptoms and signs include clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhoea, low vitamin B_{12} values. (Dispenzieri, A, 2012)

1.3 Clinical Presentation of multiple myeloma:

Presenting clinical features include symptoms of:

- Hypercalcemia
- Renal impairment
- Anaemia
- Bone disease with bone pain and pathological fractures. This can include spinal cord compression when vertebral bodies are involved
- Recurrent or persistent bacterial infection
- Hyperviscosity
- Amyloidosis – periorbital purpura, macroglossia, proteinuria, heart failure, neuropathy
- Patients without the above can also be identified by the finding of a monoclonal band on serum or urine electrophoresis or an abnormal serum free light chain ratio following screening tests showing a raised ESR, raised total protein, hyper or hypo-gammaglobulinaemia.

Spinal cord compression, hypercalcemia, hyperviscosity and acute renal failure require immediate investigations and treatment.

Patients with suspected multiple myeloma without spinal cord compression, hypercalcaemia, hyperviscosity or acute renal failure require fast track haematology out-patient referral.

2. Multiple Myeloma: Diagnosis, prognostic factors and disease monitoring

2.1 Investigation and diagnosis

- FBC, blood film, ESR, coagulation screen, group and save
- U+Es, LFTs, adjusted calcium and albumin, LDH
- β2-microglobulin
- Immunoglobulins with serum electrophoresis and immunofixation of serum and urine with quantification of monoclonal protein plus serum free light chain analysis
- Skeletal survey
- Bone marrow aspirate and trephine with review of all samples by HMDS Leeds
- Virology Hep B , Hepatitis C, HIV 1 and 2

Additional test that may be required are:

- Plasma viscosity (if suspected hyperviscosity)
- 24 hour urine for Bence-Jones protein quantification
- Creatinine clearance
- MRI, CT or PET-CT scan.
- HLA Typing (If potential candidate for Allograft)

2.2 Diagnostic criteria and differential diagnosis

- The diagnosis (and differentiation from MGUS) should be made using the IMWG criteria as outlined in the BCSH guidelines for the Diagnosis and Management of Multiple Myeloma (Feb 2014).
- To exclude AL amyloidosis, POEMS or solitary plasmacytoma see text in guideline above

  Also consider using the **NUTS** criterion to exclude Amyloidosis:
  Neuropathy- Peripheral or Autonomic at the time of diagnosis
  Urine Dipstick for protein to exclude proteinuria
  Troponin T or BNP – If high, proceed with an ECG and an ECHO to look for Amyloid
  Soft tissue involvement- Large tongue, Bruising related to Factor X deficiency
- All diagnoses should be made or reviewed by the Multidisciplinary Team (MDT) (National Institute for Health and Clinical Excellence [NICE], 2003).

2.3 Monitoring and indications for starting therapy:

- Chemotherapy is indicated for the management of multiple myeloma defined by the IMWG 2014 criteria as described above.
- Smouldering myeloma patients should be monitored under the supervision of a Consultant Haematologist. (BCSH Feb 2014)
- Monitoring of patients with smouldering myeloma should include regular (typically 3 - 6 monthly) clinical assessment for the emergence of CRAB features and measurement of serum and urinary M-protein (or SFLC when indicated). (BCSH Feb 2014)
- Repeat BM examination and skeletal imaging should be considered prior to the start of treatment (BCSH Feb 2014)

2.4 Prognostic factors and staging in multiple myeloma

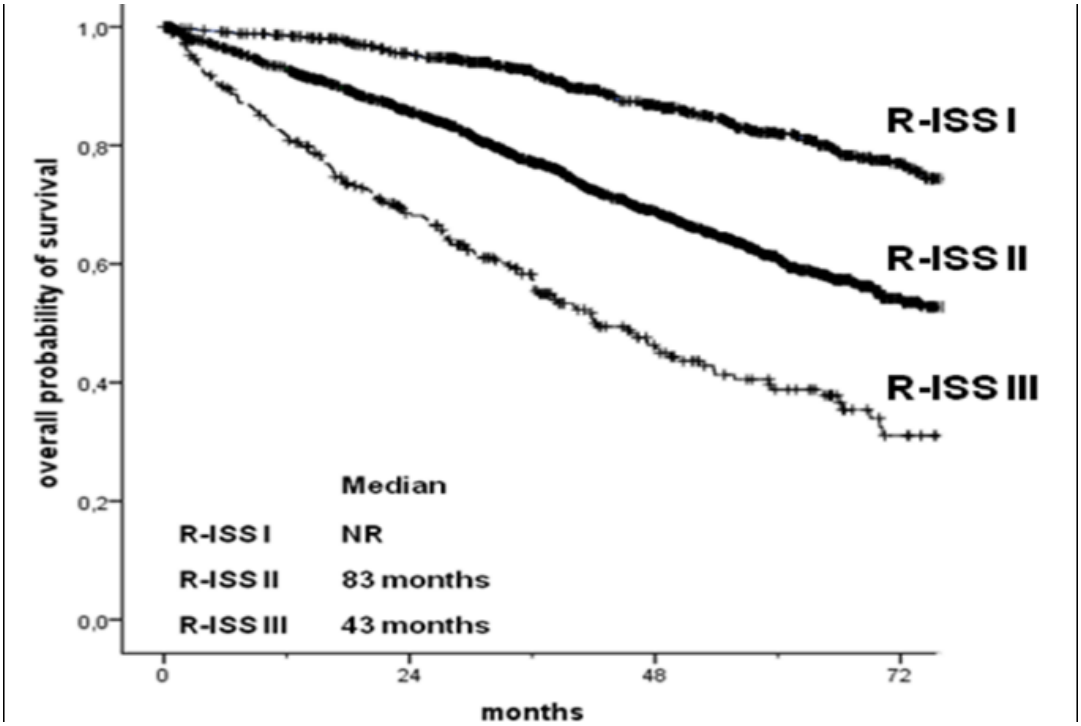
- **The International Staging System (ISS)** is based on serum albumin and 2-microglobulin:

Stage I: Serum β2-microglobulin < 3.5mg/l and serum albumin ≥ 35g/l
Median survival- 62 months
Stage II: Neither I nor III
Median survival- 45 months
Stage III: Serum β2-microglobulin ≥5.5mg/l
Median survival: 29 months

- **The Revised International Staging System (R-ISS) for Multiple Myeloma** was published by the IMWG in the Journal of Clinical Oncology August 2015 and this builds on the foundation of the ISS but with the addition of inclusion of genetic data and LDH level.

R-ISS Stage I = serum β2-microglobulin level < 3.5 mg/L and serum albumin level ≥ 35 g/L, no high-risk cytogenetics [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH level (less than the upper limit of normal range);
R-ISS Stage III = serum β2-microglobulin level > 5.5 mg/L and high-risk cytogenetics or high LDH level
R-ISS II = all the other possible combinations.

At a median follow-up of 46 months, the 5-year OS rate was 82% in the R-ISS I, 62% in the R-ISS II, and 40% in the R-ISS III groups; the 5-year PFS rates were 55%, 36%, and 24%, respectively.



2.5 Measuring Response to Therapy

- Response to therapy should be defined using the IMWG uniform response criteria (Appendix 2)
- The SFLC assay should be used to assess response in all patients with light chain only, non-secretory and oligosecretory disease

3. Use of Imaging

- The skeletal survey remains a valid screening tool at the time of writing but the use of CT, MR and PET-CT is quickly gaining ground as evidence builds for their use (Chantry A et al, 2017, BSH guidelines for the use of imaging in the management of patients with myeloma). The NICE guideline 'Myeloma: diagnosis and management' published in 2016 actually states 'only consider skeletal survey as first-line imaging if whole body MRI and whole-body low-dose CT are unsuitable or the person declines them'. Unfortunately, at the time of writing, whole body MRI and whole body low-dose CT remain unavailable in many hospital radiology departments, and there remains resistance to use of spinal MR and CT TAP on grounds of lack of resource at some centres.
- The skeletal survey should include a postero-anterior (PA) view of the chest, antero-posterior (AP) and lateral views of the cervical spine, thoracic spine, lumbar spine, humeri and femora, AP and lateral view of the skull and AP view of the pelvis; other symptomatic areas should be specifically visualized with appropriate views
- CT or MR should be used to clarify the significance of ambiguous plain radiographic findings, such as equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualize on plain radiographs, such as ribs, sternum and scapulae
- Urgent MR is the diagnostic procedure of choice to assess suspected cord compression in myeloma patients with or without vertebral collapse. Urgent CT scanning is an alternative, when MR is unavailable, intolerable or contraindicated.
- CT or MR is indicated to delineate the nature and extent of soft tissue masses and where appropriate, tissue biopsy may be guided by CT scanning
- The IMWG recommendations for the use of PET-CT (Cavo 2017) specify that a diagnosis of solitary plasmacytoma can only be made if PET-CT is negative outside the index lesion if whole body MRI is unavailable, mandating the use of PET-CT in this rare setting in our

Network. The IMWG also suggest that patients with negative skeletal surveys who otherwise would be considered to be in the smouldering myeloma group should have PET-CT if whole body MR is unavailable. This more common setting may be more challenging in terms of resource.

- Bone scintigraphy has no place in the routine staging of myeloma
- Routine assessment of bone mineral density cannot be recommended, owing to the methodological difficulties of the technique and the universal use of bisphosphonates in all multiple myeloma patients.

4. Management of common medical emergencies in multiple myeloma

4.1 Hyperviscosity

- All patients with high paraprotein levels should undergo fundoscopy, which may demonstrate retinal vein distension, haemorrhages and papilloedema.
- Patients usually have raised plasma viscosity and symptoms commonly appear when it exceeds 4 or 5 mPa. This usually corresponds to a serum IgM level of at least 30 g/l, an IgA level of 40 g/l and an IgG level of 60 g/l (Mehta and Singhal 2003).

Management:

- Symptomatic hyperviscosity should be treated with therapeutic plasma exchange with saline fluid replacement
- If plasmapheresis is not immediately available but hyperviscosity symptoms are present, consider isovolaemic venesection with saline replacement as a holding measure
- Effective treatment of the underlying disease should be started as soon as possible

4.2 Hypercalcaemia

- Up to 30% of myeloma patients present with hypercalcaemia in the context of active disease.
- Exclude other causes such as hyperparathyroidism

Management:

- If corrected Ca^{2+} = 2.6-2.9 – re-hydrate with oral and/or IV fluids
- If corrected Ca^{2+} > 2.9- re-hydrate with IV fluids +/- frusemide and give bisphosphonate - Zoledronate is the bisphosphonate of choice. (Reduced dose Pamidronate [30mg] to be considered in Renal impairment)
- Refractory Hypercalcemia: If persistent beyond 72 hours, consider repeat Bisphosphonate therapy+/- Corticosteroids and Calcitonin.

4.3 Spinal Cord compression

Compression of the spinal cord from extramedullary foci of disease occurs in 5% of patients with myeloma during the course of their disease (Kyle *et al,* 2003).

Symptoms to look for and management should be in accordance with the Metastatic Spinal Cord Compression pathway for the network, with the involvement of the MSCC co-ordinator at Lancashire Teaching Hospitals (see appendices 3, 4 and 5)

- If cord compression is suspected on clinical grounds, start dexamethasone 40 mg daily for 4 days with appropriate PPI cover.
- Urgent MR should be performed and neurosurgical or spinal surgical / clinical oncology consultation obtained
- Local radiotherapy is the treatment of choice for non-bony lesions and should be commenced as soon as is possible, preferably within 24 h of diagnosis. A dose of 30Gy in 10 fractions is recommended.
- Surgery is recommended for emergency decompression in the setting of bony compression and/or to stabilize the spine
- If cord compression is a presenting symptom, it is important to concurrently pursue a rapid diagnosis and to institute systemic therapy as soon as possible

4.4 Early Infection

- It has been reported that up to 10% of patients die of infective causes within 60 days of diagnosis (Augustson *et al,* 2005). Neutropenia is not usually a factor in early infection (Augustson *et al,* 2005)
- 24-h access to specialist advice for the patient and/or primary care team is crucial.
- Any febrile myeloma patient should be treated promptly with broad-spectrum antibiotics. Intravenous antibiotics are required for severe systemic infection or neutropenic sepsis as per the Neutropenic sepsis policy. Aminoglycosides should be avoided, if possible.
- The TEAMM trial (Drayson et al 2017) showed that prophylactic use of 500mg daily levofloxacin for the first 12 weeks in patients undergoing treatment for active myeloma

significantly reduced febrile episodes and deaths without increasing healthcare associated infections or carriage of key nosocomial pathogens.

5. Myeloma bone disease

5.1 Clinical features of bone disease

- Bone disease occurs in 80-90% of myeloma patients.
- This can present as bone pain, pathological fractures/spinal cord compression and hypercalcaemia (Coleman 1997; Croucher and Apperley 1998; Terpos and Dimopoulos 2005).
- Skeletal events compromise mobility and day-to-day independence, decrease quality of life (Cocks *et al,* 2007; Terpos and Rahemtulla 2004; Vogel *et al,* 2004) and increase overall treatment costs.

5.2 Bone fractures

Appropriate specialist input should to be sought

- Local radiotherapy is helpful for pain control
- Long bone fractures require stabilization and subsequent radiotherapy
- Large lytic lesions may cause skeletal instability. An orthopaedic opinion should be sought and pre-emptive surgery considered in selected patients.
- Vertebral fractures may require specialized clinical interventions including vertebroplasty and kyphoplasty. Myeloma UK facilitated a Spinal Myeloma working group Pathway is attached below in appendices 5 and 6.

5.3 Bisphosphonates and Denosumab

- Bisphosphonate therapy is recommended for all patients with symptomatic multiple myeloma, whether or not bone lesions are evident (BCSH Feb 2014)
- Zoledronic acid should be the bisphosphonate of choice and there was even some evidence of a survival benefit in the Myeloma IX trial. (Morgan et al. 2010)
- Sodium clodronate is less effective than zoledronic acid but has a significantly lower incidence of BONJ (Myeloma IX trial- Morgan et al, 2010)

- A duration of treatment of 2 years was suggested in 2018 by the American Society of Clinical Oncology (Anderson K, et al). The practice guideline update also suggests that in patients who do not have active myeloma and are on maintenance therapy, a 3 month interval of bisphosphonate administration is reasonable. In those patients whom bisphosphonates were withdrawn after 2 years, the drug should be resumed on relapse.
- Renal impairment: Dose modifications as listed in Appendix 1
- Dental evaluation should be carried out before starting IV bisphosphonate therapy
- Denosumab is a humanised monoclonal antibody that targets RANKL which plays a key role in the pathophysiology of bone disease in multiple myeloma by activating osteoclasts. Denosumab is not cleared by the kidney and so may be a safer alternative than zoledronic acid particularly in patients with renal impairment, with data from an ongoing trial showing a 10% rate of renal adverse events compared to 17.1% for zoledronic acid, p<0.001 (Raje et al, 2017). Denosumab has a licence for use in multiple myeloma but is not yet NICE approved.

6. Renal Impairment

6.1 Incidence and pathophysiology

- Incidence is about 20-25% (Knudsen *et al,* 1994) at the time of presentation and about 50% at some time during their disease (Eleutherakis-Papaiakovou et al*,* 2007; Kyle 1975).
- It is possible to reverse renal insufficiency in approximately half of patients but the remainder will have some degree of persistent renal impairment and of these, 2-12 % will require renal replacement therapy (Clark et al*,* 1999).
- Patients presenting with renal failure have a high early death rate; of 367 newly diagnosed myeloma patients with serum creatinine >199 mmol/l, 29.4% died within 60 days of diagnosis (Augustson et al*,* 2005).
- It is therefore critically important to prevent renal failure, or if established, to reverse it as this will significantly improve survival (Knudsen et al*,* 2000).

6.2 Prevention of Renal Failure

- Early diagnosis of both new and relapsed myeloma enables early intervention and thus prevention of renal damage (Augustson et al*,* 2005; Drayson et al*,* 2006).
- Investigations for Amyloidosis need to be considered pro-actively – NUTS Criterion

- Renal function is optimized by maintenance of a high fluid intake, at least 3 litres/day (MRC Working Party on Leukaemia in Adults, 1984) and all patients should be instructed as to the importance of this throughout the course of the disease.

6.3 Early Management of Renal Failure

- Vigorously rehydrate with at least 3 litres of normal saline daily
- Treat precipitating events, e.g. hypercalcaemia, sepsis and hyperuricaemia and discontinue nephrotoxic drugs, particularly NSAIDs
- Administer high dose dexamethasone unless otherwise contraindicated pending initiation of definitive treatment which should be started without delay
- Monitor SFLC levels
- Identify and treat infection vigorously
- Renal dose modification of drugs and particularly the bisphosphonates is critical

7. Multiple Myeloma Therapy – 7.1 algorithm summary table for NHS practice

Therapy Algorithm	Transplant eligible	Transplant ineligible
Induction	VTD (use VCD if thalidomide contraindicated – e.g. significant thrombosis, bradycardia) + Melphalan autograft NICE TA311 April 2014 Lenalidomide maintenance[1] NICE approved Jan 2021 (Dara-VTD approved by SMC in Scotland only Jan 2021[2] and Myeloma XV RADAR trial imminent – not yet at BVH)	Myeloma XIV (FiTNEss) trial[3] = IRD induction Lenalidomide[4] + dex in patients who can't have thalidomide (NICE TA 587 June 2019) & CTDa / MPT / VMP / VCD all acceptable outside of trial (NICE TA 228 July 2011) VMP / VCD maybe better for high risk esp t(4;14), AKI &/or AL amyloidosis
2nd line	Myeloma XII (ACCoRD) trial if PFS longer than 1 yr post first melphalan autograft (the trial uses Ixazomib, Thal, Dex re-induction prior to a second melphalan autograft with an ixazomib maintenance randomisation).	DVd or Carfilzomib / dex (see box below) can be used and as daratumumab is now delivered s/c this is simpler for older patients, though carfilzomib remains an IV only preparation. Carfilzomib, Lenalidomide & dex coming very soon,
	DVd[5](Daratumumab, Velcade, dex) NICE TA 573 April 2019. Carfilzomib[6] + dex NICE TA 457 Oct 2020 update but beware cardiac toxicity especially in older patients. [7]Lenalidomide + dex (induction with bortezomib required – NICE TA 587 June 2019)	
3rd line	Ixazomib[8] / len / dex (IRD) NICE TA 505 Feb 2018 Panobinstat[9]/ velcade / dex (FVD) NICE TA 380 Jan 2016	
4th line	Isatuximab / pomalidomide / dex[10] NICE TA 658 Nov 2020 Daratumumab[11] monotherapy NICE TA 510 March 2018	
5th line	Consider FVD if not yet used, low dose melphalan if naïve, CTD (Benda/thal/dex not NICE approved & removed from CDF 2020)	

[1]Maintenance lenalidomide, dosed as per Myeloma XI trial, (Jackson et al, 2016b) NICE approved Jan 2021 on CDF only after 'recent' autograft. Continue until disease progression.

[2]Dara-VTD approval in Scotland was based on the CASSIOPEIA trial (Moreau et al 2019)

[3]The trial involves a randomisation between standard dose ixa / len / dex (IRD) induction (where doses are only adjusted if side effects occur) or dose-adjusted IRD depending on frailty scoring at outset. All patients get maintenance therapy but there is a second randomisation between single agent lenalidomide maintenance or lenalidomide and ixazomib used together.

[4] NICE now allows the use of lenalidomide with dexamethasone as induction therapy in patients who are not eligible for a melphalan autograft, but only if thalidomide is contraindicated or the patient is intolerant (see main text of the guideline p23 and 24 for discussion regarding potential contraindications to thalidomide which only apply to a very small proportion of patients). During the covid pandemic, len / dex has been allowed as induction for transplant eligible patients also as it is an oral regime thus preventing day unit visits required for VTD but this is likely to be temporary. Cyclophosphamide can be added to len/ dex at the discretion of consultant.

[5] NICE allows re-use of velcade as part of DVd in patients who had a velcade induction regime as long as they weren't refractory to velcade.

[6] NICE allows use of Carfilzomib with dexamethasone at second line only and the October 2020 update of the 2017 NICE TA 457 allows its use if the patient has received velcade at induction, as long as there has been at least a 6 month proteasome inhibitor treatment-free interval (the original 2017 TA 457 required patients to be velcade naïve).

[7] NICE now allows the use of lenalidomide with dexamethasone second line for both transplant eligible and ineligible patients but only in those who had a bortezomib containing regimen at induction. NICE allows re-use of lenalidomide in IRD third line (see below) in patients who have had lenalidomide + dexamethasone first of second line as long as they were not refractory to lenalidomide. During the covid pandemic the use of IRD has been allowed second line also but this is likely to be temporary.

[8] NICE allows use of IRD at 3rd or 4th line, but only in patients who were not refractory to lenalidomide if used first or second line. (Moreau et al, 2016a Tourmaline trial).

[9] NICE allows use of FVD at any time after 2 previous lines of therapy that must have included a PI and an IMiD so can use FVD 3rd line and beyond

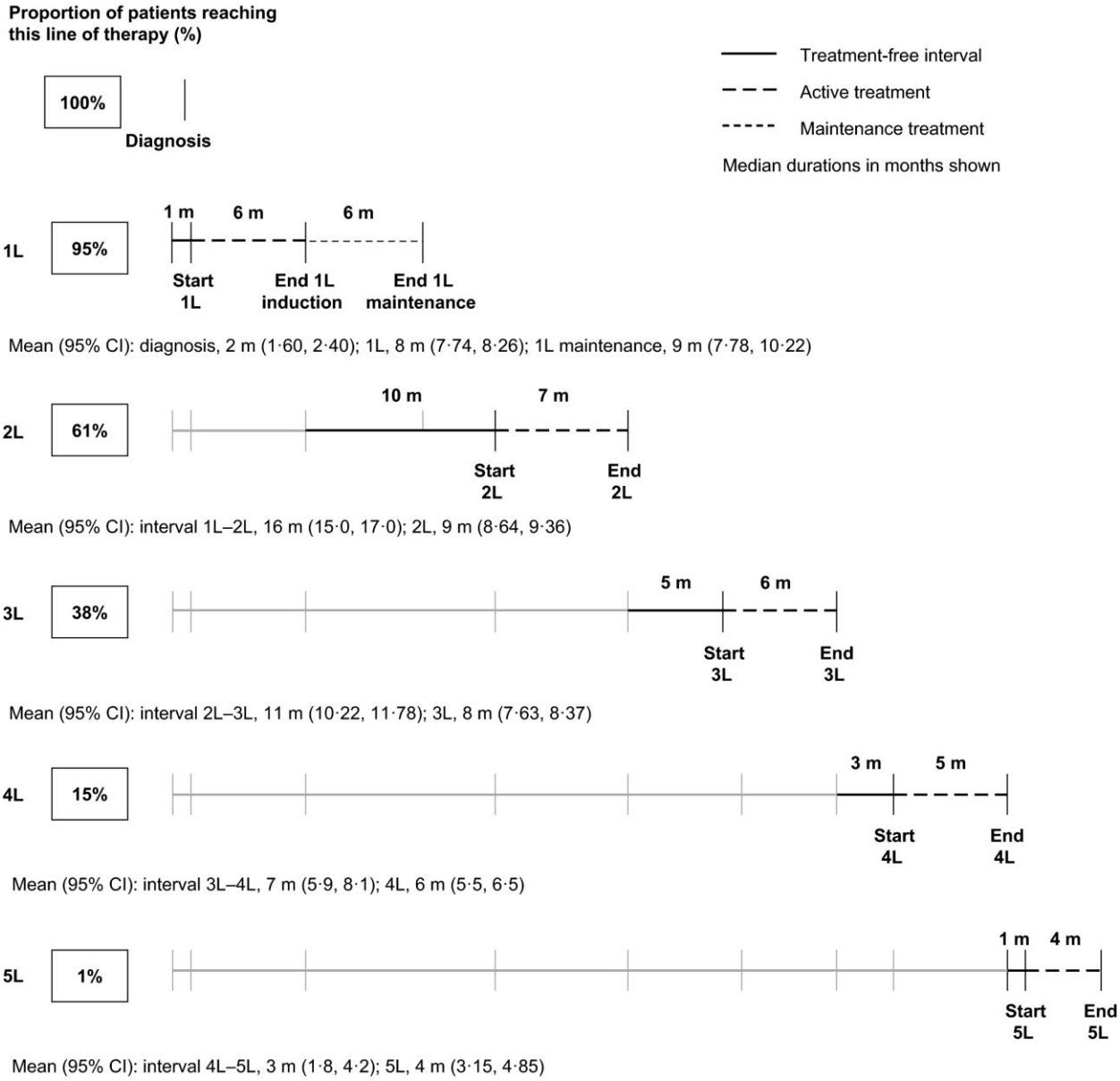
[10]Nov 2020 NICE allows use of the isatuximab, pomalidomide & dexamethasone 4th line, but patients must not have progressed within 60 days of the last dose of previous daratumumab

[11] NICE allows use of daratumuab monotherapy at 4th line only but only if daratumumab naïve which will become unusual in 2021/22

11

7.2 Real world data (Kwee Yong et al, 2016) shows only 61% of patients able to commence second line therapy and this drops quickly to 38% for third line and only 15% for fourth line. This supports the argument to get best therapy in quickly up front. For each line PFS is shorter than the previous line.

Proportion of patients reaching further lines of therapy after induction (taken from Kwee Yong et al, 2016)



7.3 Induction therapy for Myeloma patients suitable for High Dose Melphalan

NICE technology appraisal guidance [TA311] published on 23rd April 2014 stated:

Bortezomib is recommended as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

- Since this technology appraisal guidance VTD (Velcade® [bortezomib] + Thalidomide + Dexamethasone) became a standard option for patients who are transplant eligible in the UK as it allowed the combination of a proteasome inhibitor (PI) in the form of Velcade® (bortezomib) and an immunomodulatory agent (IMiD) in the form of thalidomide for the first time in the UK as induction therapy.
- VTD has shown superior response rates to VCD (Velcade® [bortezomib] + Cyclophosphamide + Dexamethasone) with less haematological toxicity, though there is more neurotoxicity. (Moreau et al, 2016b, Leiba et al, 2014).
- The increased neurotoxicity of VTD is related to the use of both Velcade® and thalidomide together as they are both potentially neurotoxic drugs. In patients suffering significant neurotoxicity consideration should be given to limiting the thalidomide dose to 100 mg nocte (rather than the maximum dose of 200mg) and switching Velcade to weekly dosing (rather than twice weekly for 2 weeks followed by a 1- 2 week break per cycle). In patients who still suffer toxicity then changing to VCD (i.e. using cyclophosphamide instead of thalidomide) can be considered.
- The aim of induction therapy prior to autografting should be to achieve VGPR or better. It was confirmed in the Myeloma XI trial (Jackson et al, 2016a) that patients who only achieved MR or PR after 4 cycles of CTD induction benefitted from a switch to VCD with 118/289 (41%) of evaluable patients moving to VGPR/CR pre-transplant. This led to improved response rates post-transplant (65% VGPR or better v 38%) and improved PFS with a median PFS with no therapy switch of 31 months vs 55 months in those who switched, p=0.0003.
- The number of cycles of VTD required prior to autografting has not been studied in randomised trials. A minimum of 4 cycles of VTD has become accepted and there is some evidence that there is no benefit to giving more than 4 cycles of induction therapy with a single centre study of 596 patients showing a median PFS of 28 months in patients who received 4 cycles or less of induction therapy compared to 26 months for those who

received more than 4 cycles (Chakraborty et al, 2018). Achievement of VGPR or better with less than 4 cycles would therefore be acceptable induction prior to autograft.

- VTE risk stratification should be used to select antithrombotic prophylaxis required for thalidomide e.g. Aspirin 75mg or prophylactic doses of LMWH.
- Assess response after each cycle and after maximal response mobilise peripheral blood stem cells with 1.5 - 3 g/m^2 Cyclophosphamide and/or G-CSF (doses as per local protocols). Mobilisation with GCSF alone has gained more widespread use during the covid pandemic as a non-chemo option and is effective, although the addition of plerixafor (Mozobil®) is more commonly required to ensure adequate stem cell collection. Plerixafor, a selective inhibitor of the CXCR4 chemokine receptor, helps to release stem cells from the marrow microenvironment. It can be added to GCSF as a 'rescue' therapy for day 2 after a day 1 poor harvest, or can be added as part of a separate second attempt following a previous failed mobilisation with GCSF alone. Plerixafor is also given s/c but has to be administered at 10pm on the night before a harvest, which can cause logistical problems for patient living a distance away. The standard dose is 0.24 mg/Kg but if the patient's weight is ≤ 83Kg a 20mg dose is used (a single vial has 24mg). Plerixafor requires cancer drugs fund approval with only 3 doses allowed for each patient.
- A total of 2 x 10^6/Kg stem cells (as measured using CD34 counting) are required to safely rescue a patient after high dose melphalan. A target of 4.5 x 10^6 is thus the aim to allow a second melphalan autograft to occur in future without the need for further harvesting.
- After successful harvest proceed to high dose melphalan 200 mg/m^2 with stem cell rescue (renal dose modification: if eGFR 30-50 ml/min use a 50% dose of melphalan but if the eGFR is less than 30 ml/min then high dose melphalan is contraindicated)
- Dara-VTD approval in Scotland in January 2021 was based on the CASSIOPEIA trial (Moreau et al 2019) but approval in England is awaited at the time of writing.

7.4 Induction therapy for Primary Plasma cell leukaemia

- There are no effective options available for this disease. (The Myeloma UK 9 trial is closed) Standard myeloma therapies can be used but survival is usually measured in months as mentioned above.
- Although induction with bortezomib +lenalidomide + dexamethasone is suggested by the wording of the NICE Guideline NG35 2016, which states in section 1.5.9 'Consider bortezomib-based **and**/or lenalidomide-based combination induction chemotherapy for people with primary plasma cell leukaemia,' this is not actually formally funded.

7.5 Induction for Patients not suitable for High Dose Melphalan (HDM)

The Myeloma XIV (FiTNEss) trial opened in Blackpool in November 2020 and should be extended across the network as an option to offer all patients who are not suitable for HDM, apart from end-of-life patients. As mentioned in the summary page above all patients receive Ixazomib / Lenalidomide / dexamethasone (IRD) induction.

NICE technology appraisal guidance [TA 228] published in July 2011 stated:

1.1 Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.

1.2 Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:

- high-dose chemotherapy with stem cell transplantation is considered inappropriate **and**
- the person is unable to tolerate or has contraindications to thalidomide.

- CTDa chemotherapy (Cyclophosphamide + Thalidomide + Dexamethasone with dose attenuation), if tolerated, remains a reasonable option at the time of writing. Maximum of 9 courses.
- MPT (Melphalan + Prednisolone + Thalidomide) may be preferred if the patient is intolerant of high dose steroids or requires a simpler scheduled regimen.
- For both CTDa and MPT, VTE risk assessment followed by Aspirin 75mg or prophylactic doses of LMWH should be used as thromboprophylaxis.
- Velcade® [Bortezomib] based regimes Vel/Dex, VCDa, VMP (Velcade®, Melphalan and Prednisolone) should be used in patients either unable to tolerate or who have contra-indications to thalidomide. Also, patients with t(4:14), AKI or amyloidosis may benefit.
- All patients receiving Bortezomib should be monitored closely for peripheral neuropathy. See LSCCN Myeloma Chemotherapy Regimens for details.
- Once weekly Bortezomib can be used with equal efficacy and less toxicity as evidenced in several clinical trials. This should be used as an alternative schedule, particularly in older patients.

NICE TA 587 June 2019 stated:

1.1 Lenalidomide plus dexamethasone is recommended as an option for previously untreated multiple myeloma in adults who are not eligible for a stem cell transplant, but only if:

- thalidomide is contraindicated (including for pre-existing conditions that may aggravate) or
- the person cannot tolerate thalidomide, and
- the company provides lenalidomide according to the commercial arrangement

Potential contraindications to thalidomide put forward by NICE include patients who:

- couldn't tolerate a 3-drug regimen
- have pre-existing neuropathy
- need to use opiates because of bone involvement by myeloma (both opiates and thalidomide can cause drowsiness)
- have somnolence

8. Intensification for non-responders (primary refractory disease)

- Primary refractory disease is seen in about 5% of patients. They are defined as those with <25% reduction in paraprotein after 2 cycles of induction therapy (i.e. equivalent to no change by IMWG criteria) or < 50% reduction after 4 cycles (i.e. equivalent to minimal response by IMWG criteria)
- For transplant eligible patients refractory to VTD, a lenalidomide-based regime should be considered.

9. Allogeneic stem cell transplantation and CAR-T cell therapies

- Consider opinion from an allogeneic transplant centre for patients who are <40 years old with17p deletion and/or primary plasma cell Leukaemia. Also consider for selected patients with early relapse post autograft or who are refractory to multiple lines of therapy, with good performance status. CAR-T cell therapy shows some promise and it is hoped that trials will be available in Manchester in 2021.

10. Maintenance therapy

- Lenalidomide maintenance therapy was finally approved by NICE January 2021 for patients after 'recent' autograft using a dose of 10mg for 21 days out of a 28-day cycle until progression. A number of trials, the UK Myeloma XI trial (Jackson et al, 2016B) being the largest, have shown the benefit of lenalidomide maintenance therapy. In Myeloma XI there was a doubling of progression free survival after autografting (median PFS 60 vs 28 months, p<0.0001) and this was also seen in non-transplant eligible patients (median PFS 26 vs 12 months, p<0.0001).No benefit has been demonstrated for maintenance with melphalan or interferon however (Belch et al, 1988; Drayson et al, 1998).

11. Second line

NICE Technology appraisal guidance [TA573] published on 10th April 2019 stated:

Daratumumab plus bortezomib plus dexamethasone (DVd) is recommended as an option for treating relapsed myeloma in people who have had 1 previous treatment.

This therefore applies to both transplant eligible and ineligible patients. In the CASTOR trial DVd gave an overall response of 82.9% (versus 63.2% with vel / dex) with a VGPR rate or better of 59.2% (versus 32.9% with vel / dex) in relapsed myeloma patients (Palumbo et al, 2016 for the CASTOR trail investigators). Daratumumab is also highly active in combination with lenalidomide and dex (Dimopoulos M et al, 2016 for the POLLUX Investigators) but at the time of writing this is not NICE approved.

- Daratumumab is a monoclonal antibody that binds to CD38 which is expressed on plasma cells. CD38 is also expressed to a lesser degree on red cells so the use of daratumumab may result in a positive DAT and interfere with grouping and cross-matching in this group of relapsed myeloma patients who may be transfusion dependent.(The same applies to isatuximab which is also an anti-CD38 monoclonal antibody – see fourth line options below)
- When daratumumab is prescribed (and before administration) the following transfusion testing is required:
    - Two group and save samples (to ensure the patient has a confirmed blood group and antibody screen)
    - DAT

- Extended phenotype or genotype by NHSBT.

- Daratumumab may continue to interfere with serological testing and the provision of blood up to 6 months after the last dose.

The October 2020 update of the NICE Technology appraisal guidance [TA457] published on 19th July 2017 stated:

Carfilzomib in combination with dexamethasone is recommended as an option for treating multiple myeloma in adults, only if:

- they have had only 1 previous therapy,
- if induction included velcade, then there has to be at least a 6-month proteasome inhibitor treatment-free interval prior to commencing carfilzomib (the original 2017 TA 457 required patients to be velcade naïve).
- the company provides carfilzomib with the discount agreed in the patient access scheme.

- Carfilzomib can have cardiac toxicity in a small percentage of patients so this needs to be borne in mind for older patients with a history of cardiac problems. It can also only be given intravenously which may present logistical problems in older patients and is a commitment for patients who need to attend day units regularly. Cycles should be repeated every 28 days until disease progression or unacceptable toxicity.

NICE TA171 published June 2019 stated:

Lenalidomide plus dexamethasone is recommended as an option for treating relapsed multiple myeloma in adults only if:

- They have had only 1 previous therapy, which included bortezomib, and
- The company provides it according to the commercial arrangement

As stated above, NICE now allows clinicians to re-use lenalidomide after first or second-line lenalidomide + dexamethasone so that this no longer precludes the use of the highly active triplet regimen ixazomib + lenalidomide + dexamethasone (see third line options below) which is normally only available third line but has been made available for second line use during the covid epidemic reducing day unit attendance.

11.1 Second line in transplant eligible patients

All transplant-eligible patients relapsing more than 1 year after their first melphalan autograft should be considered for entry into the Myeloma XII (ACCoRD trial) open at Blackpool. This involves re-induction with ITD (Ixazomib + Thalidomide + Dexamethasone) followed by a randomisation to a second melphalan autograft which is either standard or 'augmented' (a standard autograft involves 200 mg/m^2 melphalan given 24 prior to infusion of peripheral blood stem cells whereas an 'augmented' autograft involves ixazomib 4 mg oral day -4, melphalan 100mg/m^2 day -3, melphalan 100mg/m^2 day -2 and ixazomib 4 mg oral day -1 followed by infusion of stem cells 24 hours later). 3 months post second autograft there is then a second randomisation to a further 2 cycles of ITD 'consolidation' followed by ixazomib maintenance verses no further therapy. This trial builds on results from the preceeding Myeloma X trial (Cook G et al 2014) which showed improved efficacy of high-dose melphalan plus salvage ASCT when compared with cyclophosphamide in patients with relapsed multiple myeloma following previous autograft eligible for further intensive therapy.

- For transplant eligible patients excluded from or not consenting for the Myeloma XII trial and who relapsed within 6 months of velcade-based induction making them ineligible for re-induced with carfilzomib + dexamethasone, it would seem reasonable to use DVd if they were not velcade-refractory at induction. IRD (see third line options below) is also an attractive option second line whilst its use is allowed during covid epidemic as mentioned above.

11.2 Second line in non-transplant eligible patients

- For patients who are transplant ineligible, either since diagnosis or who are not candidates for second autograft having been autografted in the past, carfilzomib + dexamethasone can be considered as above.
- In patients with cardiac problems a bortezomib-based regime may be preferred in patients who did not receive this at induction and has the advantage of subcutaneous administration (carfilzomib has to be administered intravenously), though bortezomib can rarely be associated with heart failure so it is not without potential cardiac complications.
- If bortezomib was given as first line treatment then a thalidomide or lenalidomide containing regimen may be offered as a second line option and IRD (see third line options below) is again attractive whilst allowed during covid epidemic.

11.3 Third line

At this point therapeutic options for both transplant eligible and non-transplant eligible patients are the same

NICE technology appraisal guidance [TA505] published 7th February 2018 stated:

Ixazomib, with lenalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating multiple myeloma in adults only if:

- they have already had 2 or 3 lines of therapy and
- the conditions in the managed access agreement for ixazomib are followed

As mentioned above second line use is allowed during covid epidemic.

NICE technology appraisal guidance [TA380] published on 27th January 2016 stated:

Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation, as an option for treating multiple myeloma, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent' when the company provides panobinostat with the discount agreed in the patient access scheme.

- It is thus possible to use bortezomib + panobinostat + dexamethasone as third line therapy but because the guidance allows the use of this combination at any time after 2 prior lines of therapy (which included bortezomib and an IMiD) many haematologists opt to use this as a later option as the guidance for other drugs competing for use at these stages of a patient's journey are more prescriptive

11.4 Fourth line

NICE technology appraisal guidance [TA658] published on 18th Nov 2020 stated:

Isatuximab, plus pomalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment, only if:

- they have had 3 previous lines of treatment

- the conditions in the managed access agreement for isatuximab plus pomalidomide and dexamethasone are followed.

- The use of isatuximab is only permitted in patients who did not progress within 60 days of the final dose of previous daratumumab therapy

  The Icaria Study (Attal et al, 2019) showed that the addition of isatuximab to pomalidomide-dexamethasone significantly improved progression-free survival in patients with relapsed and refractory multiple myeloma. At a median follow-up of 11·6 months, median progression-free survival was 11·5 months (95% CI 8·9-13·9) in the isatuximab-pomalidomide-dexamethasone group versus 6·5 months (4·5-8·3) in the pomalidomide-dexamethasone group (hazard ratio 0·596, 95% CI 0·44-0·81; p=0·001)

NICE technology appraisal guidance [TA510] published on 14th March 2018 stated:

Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if:

- they have daratumumab after 3 previous therapies and
- the conditions in the managed access agreement are followed.

- Prior to TA573 published in April 2019, which allowed the use of DVd second line, daratumumab, could only be used as a monotherapy in the UK and only at fourth line (i.e. after 3 previous therapies). Response rates with monotherapy at this late stage are only around 30% however, though 10% of patients can achieve VGPR or better. The use of daratumumab monotherapy is not permitted after previous therapy with DVd and would very likely be ineffective as the DVd protocol has a daratumumab maintenance element which patients would have to had to relapse through in order to have moved on to a requirement for further therapy. For patients who are daratumumab naïve at fourth line the triplet of isatuximab with pomalidomide and dexamethasone may be a more attractive option than daratumumab alone.

NICE technology appraisal guidance [TA427] published on 11th January 2017 stated:

Pomalidomide, in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib, only when the company provides pomalidomide with the discount agreed in the patient access scheme.

- There is more wiggle room here as pomalidomide can be used at third or subsequent relapse (i.e. fourth line or beyond)

Although venetoclax showed high efficacy in combination with velcade and dex in patients with t(11:14) in the Bellini trial (Kumar et al, October 2020), there is no licence at time of writing.

11.5 Local radiotherapy

Some patients may relapse with local disease, e.g. spinal plasmacytoma, with little evidence of active disease elsewhere. Such patients, especially if they are beyond first relapse, may be treated with local radiotherapy, avoiding the additional toxicity of systemic therapy, which would be an option for subsequent disease re-activation.(BCSH Feb 2014)

12. Management of solitary plasmacytoma

Solitary plasmacytoma should now only be diagnosed if a PET-CT is negative outside of the index lesion (Cavo M et al, 2017 for the IMWG).

12.1 Solitary bony plasmacytoma (SBP)

- Most cases arise in the axial skeleton, especially the vertebrae. Whilst a proportion of cases of SBP can be cured with involved field radiotherapy (IFRT), it is clear that the majority will progress to multiple myeloma.

- All patients with SBP should be referred for entry into the IDRIS trial. This trial is designed to look at the role of lenalidomide and dexamethasone following radiotherapy in high risk SBP. High risk is defined by the presence of clonal plasma cells by flow cytometry in the bone marrow aspirate by HMDS Leeds. Those patients lacking marrow clonal plasma cells are designated as good risk and followed up without any further therapy in the trial following IFRT. Those with poor risk disease defined as presence of clonal plasma cells in the marrow however, are randomised between watch & wait and additional therapy with lenalidomide and dexamethasone following IFRT. The trial has

not been recruiting well but it is designed to answer an important question so we should support it in our network.

12.2 Solitary Extramedullary Plasmacytoma (SEP)

- Most cases arise in the head and neck.
- SEP has a high cure rate with IFRT.

13 POEMS Syndrome

13.1 Diagnosis

This is dealt with on page 6.

13.2 Therapy

The best choice of therapy has not been derived through clinical trials, but rather through case series, and ASCT has become a favoured therapy. Other therapies that are effective in myeloma also appear to be effective in patients with POEMS syndrome as well. Both therapies directed at other features of the disease as well as emotional support should be a major part of the care plan. Follow-up and measurement of response are difficult at best because no one measurement is reliable enough to direct therapy. VEGF response appears to correlate with disease activity better than serum M-spike or PET scan. (Disperienzi A, 2012)

14.1 References used for investigational algorithm

UK Myeloma Forum and Nordic Myeloma Study Group guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS) BJHaem 2009, **147**, 22-42.

Monoclonal Gammopathy of Undetermined Significance (MGUS) & Smoldering Myeloma: IMWG consensus perspectives risk factors for progression & guidelines for monitoring & management. Leukemia 2010, **24,** 1121–1127.

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncology 2014, **15** (12), 1279-1406.

BCSH Guidelines on the diagnosis and investigation of AL amyloidosis. BJHaem 2015, **168**, 207–218.

How I treat POEMS syndrome. Blood 2012, **119** (24), 5650-5658.

Guidelines on the diagnosis and management of solitary plasmacytoma. BJHaem 2004, **124**, 717-726.

14.2 References used for remainder of guideline

Anderson K, et al (2018) Role of bone-modifying agents in multiple myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update Summary. Journal of Oncology Practice 14 (4) 266.

Michel Attal, Paul G Richardson, S Vincent Rajkumar, Jesus San-Miguel, Meral Beksac, Ivan Spicka, Xavier Leleu, Fredrik Schjesvold, Philippe Moreau, Meletios A Dimopoulos, Jeffrey Shang-Yi Huang, Jiri Minarik, Michele Cavo, H Miles Prince, Sandrine Macé, Kathryn P Corzo, Frank Campana, Solenn Le-Guennec, Franck Dubin, Kenneth C Anderson. ICARIA-MM study group. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019 Dec 7;394(10214):2096-2107. doi: 10.1016/S0140-6736(19)32556-5.

Augustson, B.M., Begum, G., Dunn, J.A., Barth, N.J., Davies, F., Morgan, G., Behrens, J., Smith, A., Child, J.A. & Drayson, M.T. (2005) Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. Journal of Clinical Oncology, 23, 9219-9226.

Belch, A., Shelley, W., Bergsagel, D., Wilson, K., Klimo, P., White, D. & Willan, A. (1988) A randomized trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients. British Journal of Cancer, 57, 94-99.

Blimark et al (2018) Outcome And Survival Of Myeloma Patients Diagnosed 2008–2015. Real-World Data On 4904 Patients From The Swedish Myeloma Registry. Haematologica March 2018 103: 506-513

Brenner, H., Gondos, A., & Pulte, D. (2009). Expected long-term survival of patients diagnosed with multiple myeloma in 2006–2010. *haematologica*, *94*(2), 270-275.

Cavo, M et al. (2017) Role of 18F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the international myeloma working group. Lancet Oncology, 18, 4, 206-217.

Chakraborty, R et al, (2018) Impact of duration of induction therapy on survival in newly diagnosed multiple myeloma patients undergoing upfront autologous stem cell transplantation. British Journal of Haematology, 182, 71-77.

Chantry A, Kazmi M, Barrington S, Goh V, Mullholland N, Streetly M, Lai M, Pratt G on behalf of the British Society for Haematology Guidelines. (2017) Guidelines for the use of imaging in the management of patients with myeloma. BJHaem, 178, 380-393.

Cocks, K., Cohen, D., Wisloff, F., Sezer, O., Lee, S., Hippe, E., Gimsing, P., Turesson, I., Hajek, R., Smith, A., Graham, L., Phillips, A., Stead, M., Velikova, G. & Brown, J. (2007) An

international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. European Journal of Cancer, 43, 1670-1678.

Cook G et al (2014) High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. Lancet Oncology 2014 Jul;15(8):874-85. doi: 10.1016/S1470-2045(14)70245-1.

Clark, A.D., Shetty, A. & Soutar, R. (1999) Renal failure and multiple myeloma: pathogenesis and treatment of renal failure and management of underlying myeloma. Blood Reviews, 13, 79-90.

Coleman, R.E. (1997) Skeletal complications of malignancy. Cancer, 80, 1588-1594.

Croucher, P.I. & Apperley, J.F. (1998) Bone disease in multiple myeloma. British Journal of Haematology, 103, 902-910

Dimopoulos M et al (2016) for the POLLUX Investigators. Daratumumab, lenalidomide and Dexamethasone for Multiple Myeloma. N Engl J Med 375:1319 – 1331.

Dispenzieri, A (2012) How I treat POEMS Syndrome. Blood, Jun 14; 119(24): 5650–5658.

Drayson, M.T., Chapman, C.E., Dunn, J.A., Olujohungbe, A.B. & Maclennan, I.C. (1998) MRC trial of alpha2b-interferon maintenance therapy in first plateau phase of multiple myeloma. MRC Working Party on Leukaemia in Adults. British Journal of Haematology, 101, 195-202.

Drayson, M., Tang, L.X., Drew, R., Mead, G.P., Carr-Smith, H. & Bradwell, A.R. (2001) Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. Blood, 97, 2900-2902.

Drayson, M., Begum, G., Basu, S., Makkuni, S., Dunn, J., Barth, N. & Child, J.A. (2006) Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials. Blood, 108, 2013-2019.

Drayson, M, Stella Bowcock, Tim Planche, Gulnaz Iqbal, Jill Wood, Kerry Raynes, Guy Pratt, KweeYong, Peter Hawkey, Helen Higgins and Janet Dunn. (2017) Tackling Early Morbidity and Mortality in Myeloma (TEAMM): Assessing the Benefit of Antibiotic Prophylaxis and Its Effect on Healthcare Associated Infections in 977 Patients Blood 130: 903

Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., 55 Kyle, R.,

Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G. & Rajkumar, S.V. (2006) International uniform response criteria for multiple myeloma. Leukemia, 20, 1467-1473.

Eleutherakis-Papaiakovou, V., Bamias, A., Gika, D., Simeonidis, A., Pouli, A., Anagnostopoulos, A., Michali, E., Economopoulos, T., Zervas, K. & Dimopoulos, M.A. (2007) Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. Leukemia and Lymphoma, 48, 337-341.

Jackson G et al (2016a) Response Adapted Induction Treatment Improves Outcomes for Myeloma Patients; Results of the Phase III Myeloma XI Study. Blood 128: 244

Jackson G et al (2016b) Lenalidomide Is a Highly Effective Maintenance Therapy in Myeloma Patients of All Ages; Results of the Phase III Myeloma XI Study. Blood 128:1143

Jancelewicz, Z., Takatsuki, K., Sugai, S. & Pruzanski, W. (1975) IgD multiple myeloma. Review of 133 cases. Archives of Internal Medicine, 135, 87-93

Knudsen, L.M., Hippe, E., Hjorth, M., Holmberg, E. & Westin, J. (1994) Renal function in newly diagnosed multiple myeloma--a demographic study of 1353 patients. The Nordic Myeloma Study Group. European Journal of Haematology, 53, 207-212.

Knudsen, L.M., Hjorth, M. & Hippe, E. (2000) Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. European Journal of Haematology, 65, 175-181.

Kumar, S., Hayman, S., Buadi, F., Lacy, M., Stewart, K., Allred, J., ... & Dispenzieri, A. (2008, December). Phase II trial of lenalidomide (RevlimidTM) with cyclophosphamide and dexamethasone (RCd) for newly diagnosed myeloma. In *Blood (ASH Annual Meeting Abstracts)* (Vol. 112).

Kumar, S., Flinn, I.W., Parameswaran, Hari, N., Callander, N., Noga, S.J., Stewart, A.K., Glass, J., Raje, N., Rifkin, R.M., Shi, H., Webb, I.J., Richardson, P.G. & Rajkumar, S.V. (2009) Novel three- and four-drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for newly diagnosed multiple myeloma: encouraging results from the multi-center, randomized, phase 2 EVOLUTION Study. Blood (ASH Annual Meeting Abstracts), 114, Abstract 127.

Kumar Shaji K, Simon J Harrison, Michele Cavo, Javier de la Rubia, Rakesh Popat, Cristina Gasparetto, Vania Hungria, Hans Salwender, Kenshi Suzuki, Inho Kim, Elizabeth A Punnoose, Wan-Jen Hong, Kevin J Freise, Xiaoqing Yang, Anjla Sood, Muhammad Jalaluddin, Jeremy A Ross, James E Ward, Paulo C Maciag, Philip Moreau.
Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncology, October 29, 2020, published on-line. https://doi.org/10.1016/S1470-2045(20)30525-8

Kwee Yong et al (2016) Multiple myeloma: patient outcomes in real-world practice. British Journal of Haematology, 175 (2), p252 – 264.

Kyle, R.A. (1975) Multiple myeloma: review of 869 cases. Mayo Clinic Proceedings, 50, 29-40

Kyle, R.A., Maldonado, J.E. & Bayrd, E.D. (1974) Plasma cell leukemia. Report on 17 cases. Archives of Internal Medicine, 133, 813-818.

Kyle, R. A. (1978) Monoclonal gammopathy of undetermined significance. Natural history in 241 cases. Am J Med 64(5):814-826

Kyle, R.A., Gertz, M.A., Witzig, T.E., Lust, J.A., Lacy, M.Q., Dispenzieri, A., Fonseca, R., Rajkumar, S.V., Offord, J.R., Larson, D.R., Plevak, M.E., Therneau, T.M. & Greipp, P.R. (2003) Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clinic Proceedings, 78, 21-33.

Kyle, R.A., Larson D.R., Therneau T. M., Dispenzieri A., et al. Long term follow up of monoclonal gammopathy of undetermined significance (2018) N Engl J Medicine, 378: 241-249.

Kyle, R.A., Remstein, E.D., Therneau T.M., et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. (2007) N Engl J Med 356 (25): 2582-2590.

Landgren, O., Kyle, R. A., Pfeiffer, R. M., Katzmann, J. A., Caporaso, N. E., Hayes, R. B., ... & Rajkumar, S. V. (2009). Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood*, *113*(22), 5412-5417.

Leiba M et al (2014). Bortezomib-cyclophosphamide-dexamethasone (VCD) verses bortezomib-thalidomide-dexamethasone (VTD)-based regimens as induction therapies in newly diagnosed transplant eligible patients with multiple myeloma: a meta-analysis. British Journal of Haematology, 166, 702-710.

Mehta, J. & Singhal, S. (2003) Hyperviscosity syndrome in plasma cell dyscrasias. Seminars in Thrombosis and Hemostasis, 29, 467-471.

Moreau, P et al (2016a) Oral Ixazomib, lenalidomide and dexamethasone of multiple myeloma. Tourmaline-MM1 Study Group. NEJM; 374: 1621-1634

Moreau, P et al (2016b) VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood, 127, 2569 – 2574.

Moreau, P et al (2019) Bortezomib, thalidomide and dexamethasone before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA) a randomised, open label, phase 3 study. The Lancet, 394, 10192, 29-38.

Morgan G., DaviesF., GregoryW., Bell S.E., SzubertA., Navarro CoyN., DraysonM., Owen R.G., Jackson G.H., Child J.A.(2010) Evaluating the effects of zoledronic acid (ZOL) on overall

survival (OS) in patients (Pts) with multiple myeloma (MM): Results of the Medical Research Council (MRC) Myeloma IX study J Clin Oncol 28:7s, (suppl; abstr 8021)

Morris, C., Drake, M., Apperley, J., Iacobelli, S.,van Biezen, S.,Bjorkstrand, B.,Goldschmidt,H., Jouet, J.P., Harousseau, J-L, Morgan, G., de Witte, T., Niederwieser, D., Gahrton, G. for the myeloma subcommittee of the chronic leukaemia working party of the EBMT (2010) Efficacy and outcome of autologous transplantation in rare myelomas. Haematologica, in press

MRC working party on leukaemia in adults (1984) Analysis and management of renal failure in fourth MRC myelomatosis trial. British Medical Journal, 288, 1411-1416.
National Institute for Health and Clinical Excellence. (2003) Improving outcomes in haematological cancers-The Manual.
Available at: http://www.nice.org.uk/docref.asp?d=90429

Palumbo A et al for the CASTOR trial investigators (2016) Daratumumab, Bortezomib and Dexamethasone for Multiple Myeloma. NEJM; 375:754 – 766.

Raje et al (2017) Impact of denosumab (DMB) compared with zoledronic acid (ZA) on renal function in the treatment of myeloma bone disease. Journal of clinical oncology, 35, (15) 8005.

Rajkumar et al (2014) International Myeloma Working Group (IMWG) updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014 Nov;15(12): 538-48.

Terpos, E. & Dimopoulos, M.A. (2005) Myeloma bone disease: pathophysiology and management. Annals of Oncology, 16, 1223-1231.
Terpos, E. & Rahemtulla, A. (2004) Bisphosphonate treatment for multiple myeloma. Drugs Today (Barc), 40, 29-40.

Vogel, C.L., Yanagihara, R.H., Wood, A.J., Schnell, F.M., Henderson, C., Kaplan, B.H., Purdy, M.H., Orlowski, R., Decker, J.L., Lacerna, L. & Hohneker, J.A. (2004) Safety and pain palliation of zoledronic acid in patients with breast cancer, prostate cancer, or multiple myeloma who previously received bisphosphonate therapy. Oncologist, 9, 687-695.

15 APPENDICES

Appendix 1 – Dose modifications of Bisphosphonates

Bisphophonates

Recommended dose reductions of bisphosphonates in renal impairment

Creatinine Clearance	Sodium clodronate	Pamidronate	Zoledronate
>30mls /min	No dose modification	If Cr Cl: 30-60mls/min: The infusion rate should not exceed 90mg over 4 hours >60mls/min: 90mg over 2 hrs	If Cr Cl: 30-39mls/min: 3mg 40-49mls/min: 3.3mg 50-59mls/min: 3.5mg ≥ 60mls/min: 4mg
10 -30 ml/min	Half dose	30 mg to be given over 2-4 hours	Not recommended
< 10 ml/min	Contra indicated	30 mg to be given over 2-4 hours	Not recommended

Appendix 2: Modified International Myeloma Working Group Uniform Criteria of Response and Progression* [46]

Paraprotein responses should only be calculated using sequential paraprotein measurements made in the same laboratory using the same method.

All response categories require 2 consecutive assessments made at any time before the initiation of any new therapy. All categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

Stringent Complete Response (sCR)**

1. Complete response as below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

Complete Response (CR) requires all the following

1. Absence of the original monoclonal paraprotein in serum / urine by immunofixation. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.

2. <5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed.

3. No increase in size or number of lytic bone lesions. Development of a compression fracture does not exclude response.

4. Disappearance of soft tissue plasmacytomas.

5. For patients with light chain myeloma (the serum and urine M-protein are unmeasurable), a normal FLC ratio of 0.26 to 1.65 (or laboratory-specific normal FLC ratio reference rand) in addition to the CR criteria above

Very Good Partial Response (VGPR)

1. Serum and urine M-protein detectable by immunofixation but not on electrophoresis

or

2. ≥90% reduction in serum M protein plus urinary light chain excretion <100mg per 24h.
3. No increase in size or number of lytic bone lesions on radiological investigations, if performed
4. For patients with light chain myeloma (the serum and urine M-protein are unmeasurable), >90% decrease in the difference between involved and uninvolved FLC levels

Partial Response (PR)

1. ≥50% reduction in the level of the serum monoclonal paraprotein
   and
2. Reduction in 24 hour urinary light chain excretion either by a ≥90% or to <200 mg per 24h if measured

3. For patients with light chain myeloma (serum and urine M protein unmeasurable), ≥50% reduction in the difference between involved and uninvolved serum FLC levels

4. For patients with non-secretory myeloma only, ≥50% reduction in plasma cells, in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, provided baseline bone marrow plasma cell percentage was ≥30%

5. ≥50% reduction in the size of soft tissue plasmacytomas by radiological or physical examination

6. No increase in size or number of lytic bone lesions. Development of a compression fracture does not exclude response.

7. Patients in whom some but not all of the criteria for PR are fulfilled are classed as MR

Minimal Response (MR)

1. 25-49% reduction in the level of the serum monoclonal paraprotein

2. 50-89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24h

3. For patients with non-secretory myeloma only, 25-49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed

4. 25-49% reduction in the size of soft tissue plasmacytomas by radiological or physical examination

5. No increase in size number of lytic bone lesions. Development of a compression fracture does not exclude response.

MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements of MR.

Stable Disease (SD) or No Change (NC)

Not meeting the criteria of either minimal response or progressive disease.

Progressive Disease (PD) requires one or more of the following

1. Increase of ≥25% from lowest response in serum M protein (absolute increase must be ≥5g/L) and confirmed by at least one repeated investigation

2. Increase of ≥25% from lowest response in urinary light chain excretion (absolute increase must be ≥200mg/24h and confirmed by at least one repeated investigation)

3. For patients with light chain myeloma (the serum and urine M-protein are unmeasurable) ≥25% increase from lowest response level in the difference between involved and uninvolved FLC levels (the absolute increase must be >100mg/L).

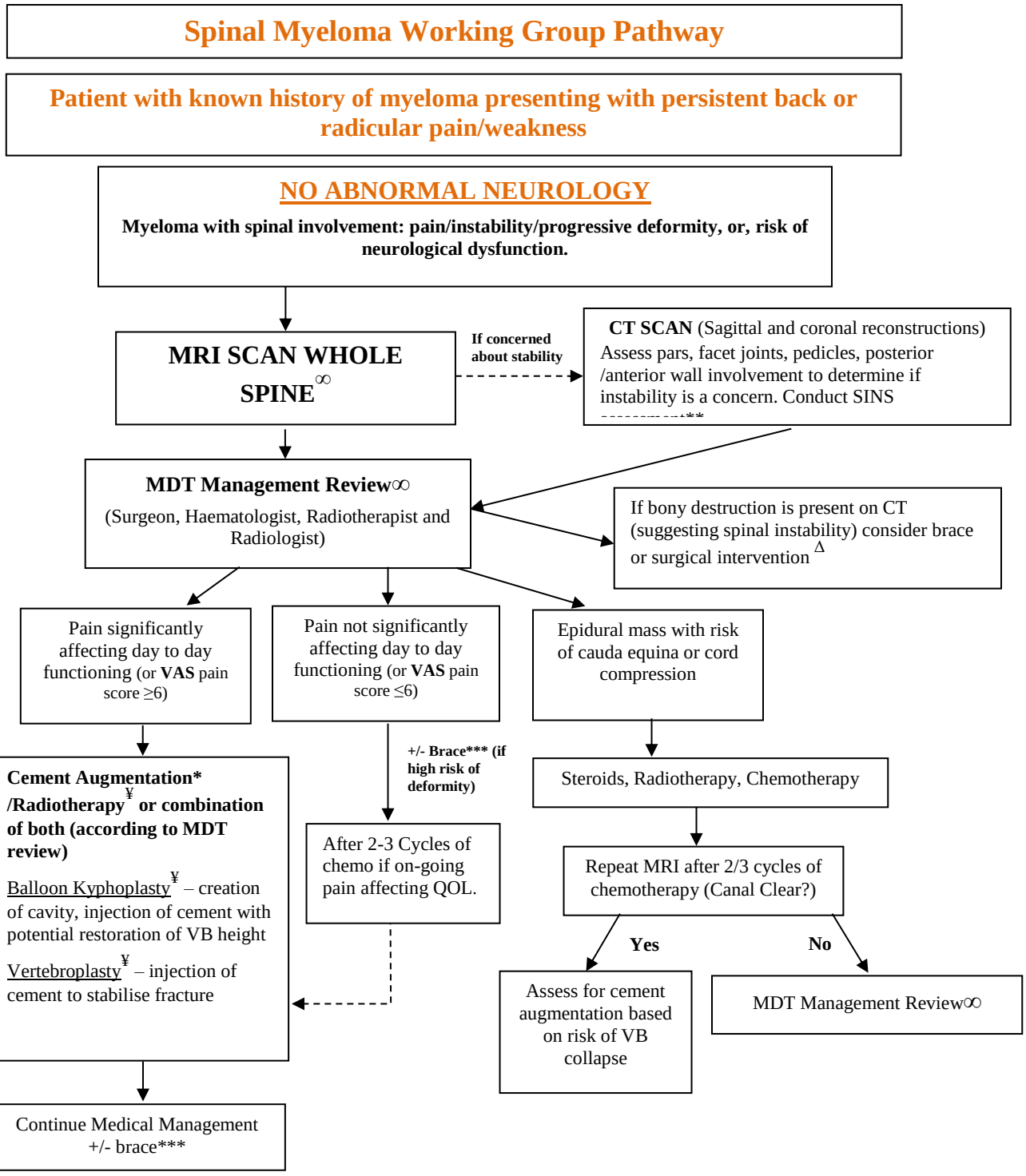
4. ≥25% plasma cells in bone marrow, which must also be an absolute increase of at least 10%)

5. Development of new lytic bone lesions or soft tissue plasmacytomas. Development of a compression fracture does not exclude response.

6. Definite increase in the size of residual bone lesions or soft tissue plasmacytomas.

7. Development of hypercalcaemia, corrected serum calcium >11.5mg/dL or 2.8 mmol/L, attributable solely to the myeloma

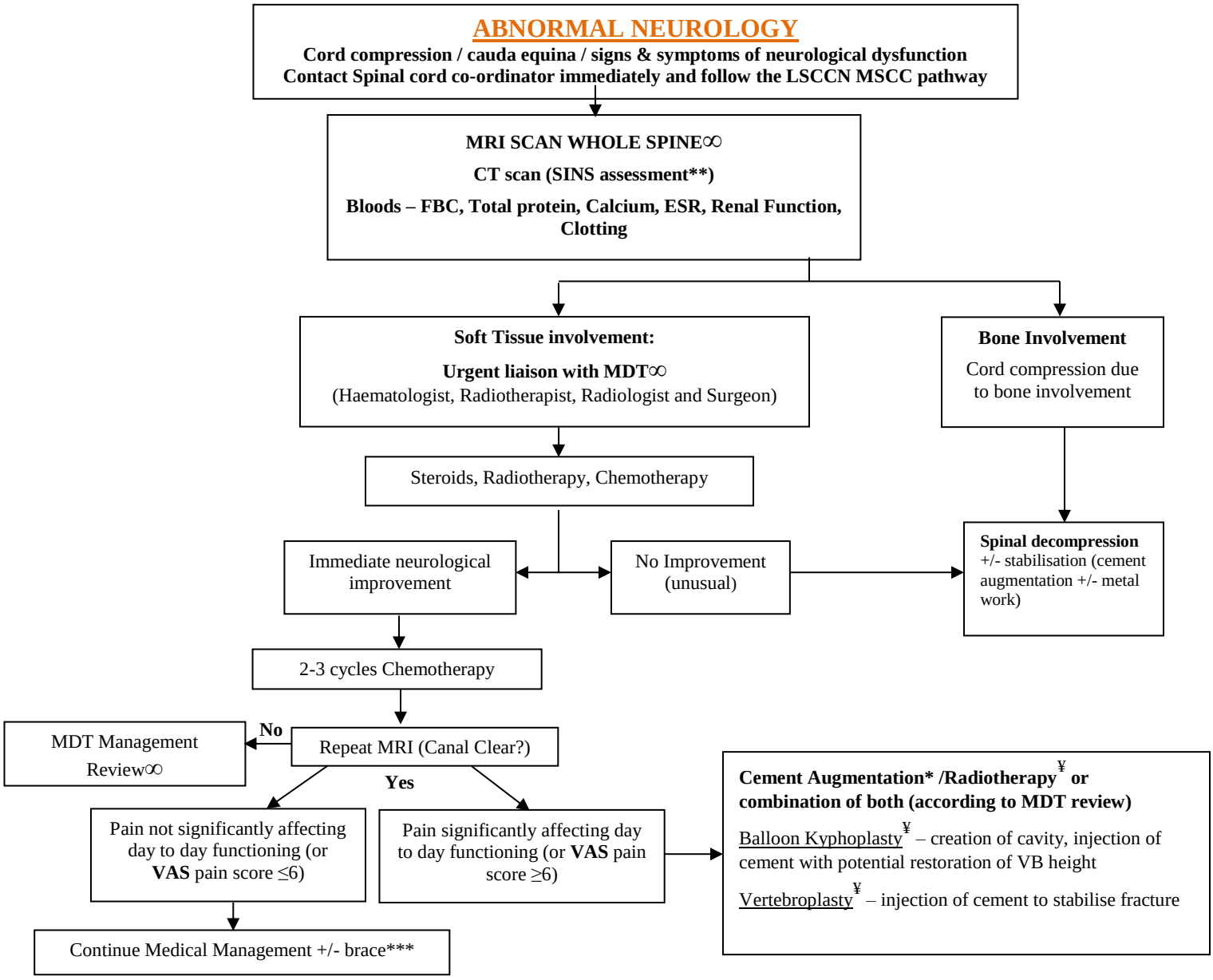
Appendix 3 - Spinal Pathway



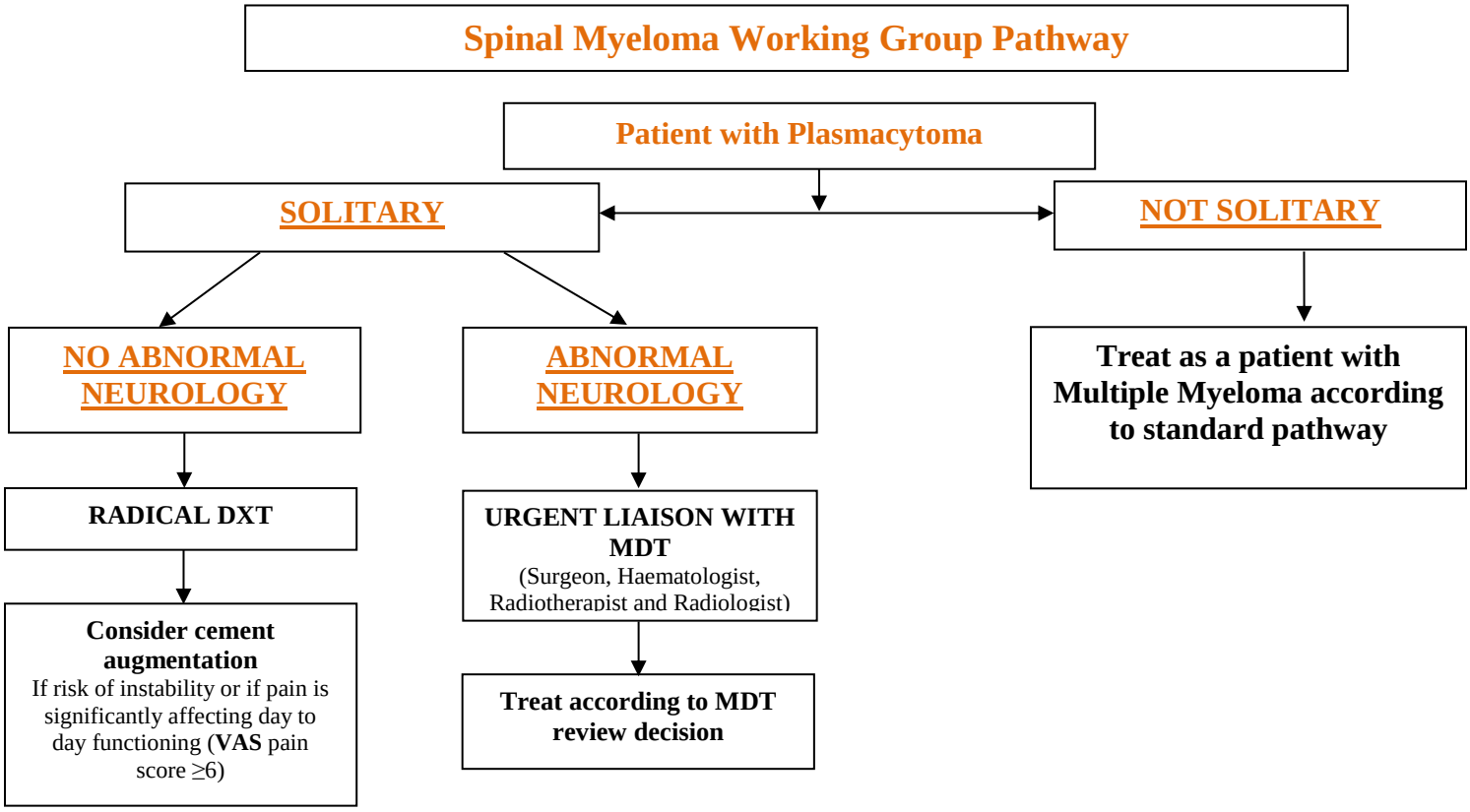
* Antibiotic prophylaxis recommended for all patients undergoing cement augmentation (to avoid potential risk of severely debilitating discitis)
** Spinal Instability Neoplastic Score
*** Thermoplastic/TLSO brace if available to prevent progressive deformity +/- further vertebral body collapse
Δ High risk patient – e.g., patient with bilateral facet joint destruction, therefore posing risk of spondylolisthesis
¥ See appendix for clinical data pertaining to Balloon Kyphoplasty, Vertebroplasty and Radiotherapy
∞ **As per National Cancer Guidelines**
NOTE: Start Bisphosphonate treatment as soon as possible. Avoid metalwork where possible to reduce risk of infection and potential screw pull-out in weakened bone

Spinal Myeloma Working Group Pathway

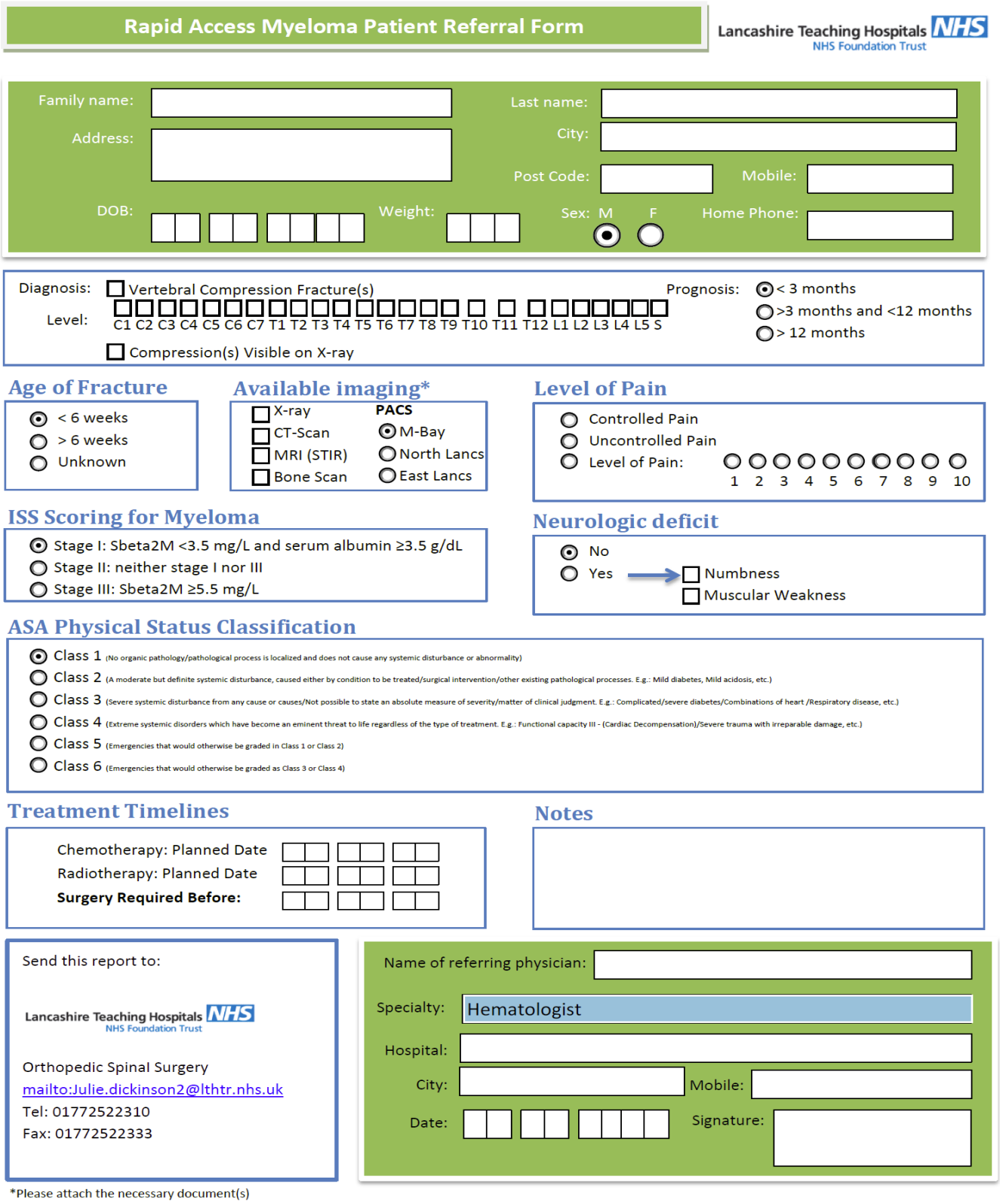
Patient with known history of myeloma presenting with persistent back or radicular pain/weakness



* Antibiotic prophylaxis recommended for all patients undergoing cement augmentation (to avoid potential risk of severely debilitating discitis)
** Spinal Instability Neoplastic Score
*** Thermoplastic/TLSO brace if available to prevent progressive deformity +/- further vertebral body collapse
Δ High risk patient – e.g., patient with bilateral facet joint destruction, therefore posing risk of spondylolisthesis
¥ See appendix for clinical data pertaining to Balloon Kyphoplasty, Vertebroplasty and Radiotherapy
∞ **As per National Cancer Guidelines**
NOTE: Start Bisphosphonate treatment as soon as possible. Avoid metalwork where possible to reduce risk of infection and potential screw pull-out in weakened bone


Spinal Myeloma Working Group Pathway
Patient with Plasmacytoma
SOLITARY
NOT SOLITARY
NO ABNORMAL NEUROLOGY
ABNORMAL NEUROLOGY
Treat as a patient with Multiple Myeloma according to standard pathway
RADICAL DXT
URGENT LIAISON WITH MDT
(Surgeon, Haematologist, Radiotherapist and Radiologist)
Consider cement augmentation
If risk of instability or if pain is significantly affecting day to day functioning (VAS pain score ≥6)
Treat according to MDT review decision

Appendix 4 - Spinal Team Referral form



Rapid Access Myeloma Patient Referral Form

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Family name: | Last name:
Address: | City:
Post Code: | Mobile:
DOB: | Weight: | Sex: M F | Home Phone:

Diagnosis: ☐ Vertebral Compression Fracture(s)
Level: C1 C2 C3 C4 C5 C6 C7 T1 T2 T3 T4 T5 T6 T7 T8 T9 T10 T11 T12 L1 L2 L3 L4 L5 S
☐ Compression(s) Visible on X-ray

Prognosis:
◉ < 3 months
○ >3 months and <12 months
○ > 12 months

Age of Fracture
◉ < 6 weeks
○ > 6 weeks
○ Unknown

Available imaging*
☐ X-ray
☐ CT-Scan
☐ MRI (STIR)
☐ Bone Scan

PACS
◉ M-Bay
○ North Lancs
○ East Lancs

Level of Pain
○ Controlled Pain
○ Uncontrolled Pain
○ Level of Pain: ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

ISS Scoring for Myeloma
◉ Stage I: Sbeta2M <3.5 mg/L and serum albumin ≥3.5 g/dL
○ Stage II: neither stage I nor III
○ Stage III: Sbeta2M ≥5.5 mg/L

Neurologic deficit
◉ No
○ Yes → ☐ Numbness
☐ Muscular Weakness

ASA Physical Status Classification
◉ Class 1 (No organic pathology/pathological process is localized and does not cause any systemic disturbance or abnormality)
○ Class 2 (A moderate but definite systemic disturbance, caused either by condition to be treated/surgical intervention/other existing pathological processes. E.g.: Mild diabetes, Mild acidosis, etc.)
○ Class 3 (Severe systemic disturbance from any cause or causes/Not possible to state an absolute measure of severity/matter of clinical judgment. E.g.: Complicated/severe diabetes/Combinations of heart /Respiratory disease, etc.)
○ Class 4 (Extreme systemic disorders which have become an eminent threat to life regardless of the type of treatment. E.g.: Functional capacity III - (Cardiac Decompensation)/Severe trauma with irreparable damage, etc.)
○ Class 5 (Emergencies that would otherwise be graded in Class 1 or Class 2)
○ Class 6 (Emergencies that would otherwise be graded as Class 3 or Class 4)

Treatment Timelines
Chemotherapy: Planned Date
Radiotherapy: Planned Date
Surgery Required Before:

Notes

Send this report to:

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Orthopedic Spinal Surgery
mailto:Julie.dickinson2@lthtr.nhs.uk
Tel: 01772522310
Fax: 01772522333

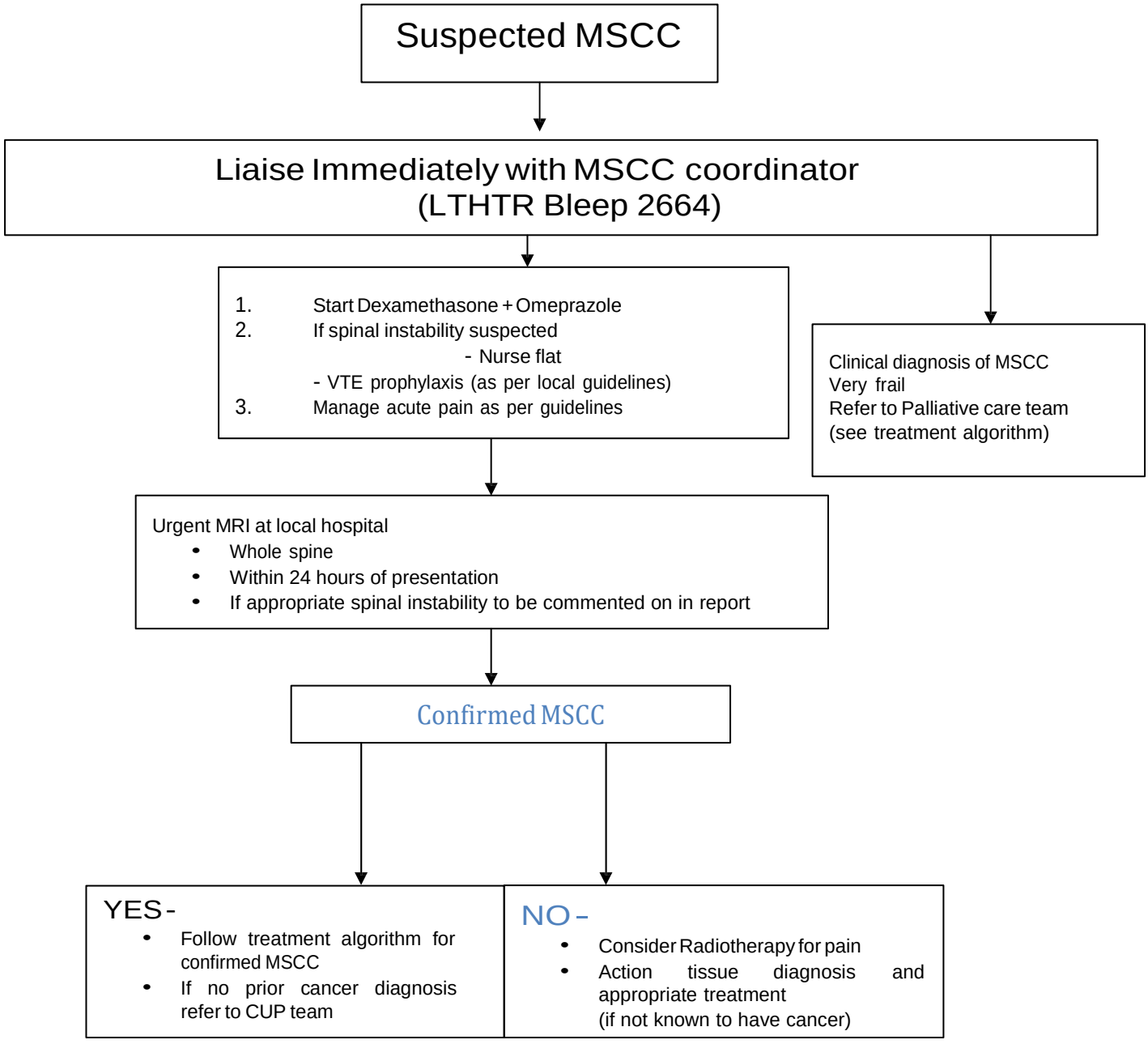
Name of referring physician:
Specialty: Hematologist
Hospital:
City: | Mobile:
Date: | Signature:

*Please attach the necessary document(s)

Lancashire and South Cumbria Cancer Network

Appendix 5- MSCC pathway
http://online.lthtr.nhs.uk/start.asp

Diagnostic Algorithm for Suspected Metastatic Spinal Cord Compression (MSCC)



Connecting Communicating Improving

Lancashire Teaching Hospitals main switchboard:01772 716565

Lancashire and South Cumbria Cancer Network

Treatment Algorithm for Metastatic Spinal Cord Compression (MSCC)