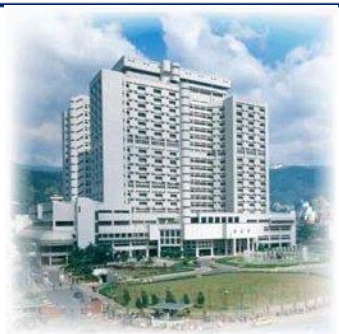

Taipei Veterans General Hospital Practice Guidelines Oncology

Multiple Myeloma

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2022年11月24日

Multidisciplinary Team

- ❑ Hematology-Oncology
- ❑ Radiology
- ❑ Radiation Oncology
- ❑ Pathology
- ❑ Hospice care
- ❑ Radiology
- ❑ Specialized Nursing Care
- ❑ Social Workers
- ❑ Nutritional Support

血液腫瘤多專科團隊

- ❑ 團隊召集人:蕭樑材主任
- ❑ 團隊副召集人: 劉嘉仁醫師

核心成員	非核心成員
血液科 蕭樑材主任、劉嘉仁醫師、劉耀中醫師 王浩元醫師、柯博伸醫師、簡聖軒醫師 林庭安醫師、陳玟均醫師、蔡淳光醫師	**核醫部** 胡蓮欣醫師
	護理部 黃子珍督導
放射線部 吳禕闓醫師	**藥劑部** 林子超藥師
病理部 楊靜芬醫師	**營養部** 血液科負責營養師
腫瘤醫學部放射腫瘤科 楊婉琴醫師/林佑蓉醫師	**社會工作室** 吳宛儀社工師
個管師 吳宜萃護理師、謝艷秋護理師	**安寧照護** 陳計伶安寧共照師

ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken MM, et al. Am J Clin Oncol. 1982 Dec;5(6):649-55.

Grading for Adverse Effect from Chemotherapy: CTCAE v5.0

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

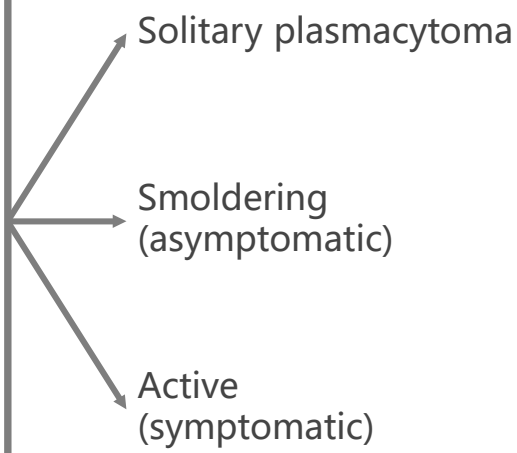
Initial Diagnostic Workup

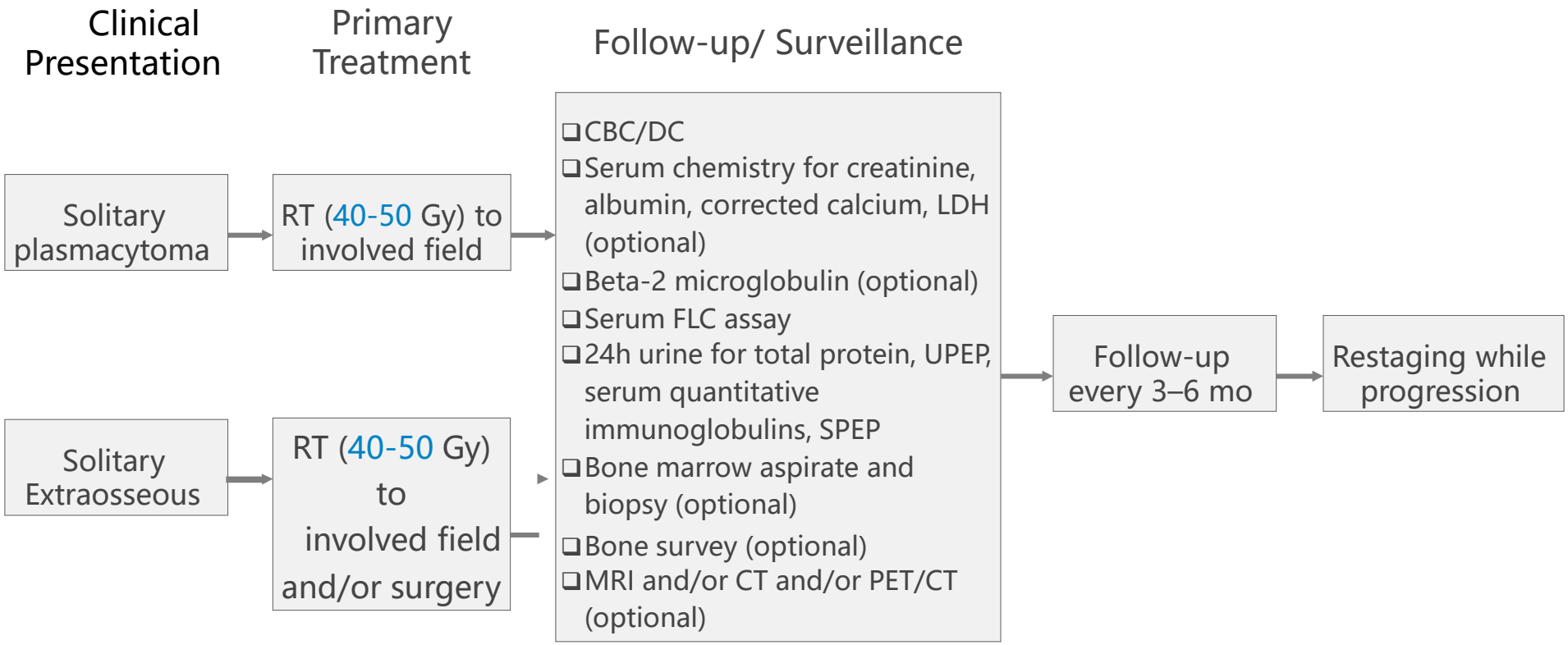
- ❑ History and physical exam
- ❑ CBC/DC, and **peripheral blood smear**
- ❑ Serum BUN/creatinine, electrolytes, liver function tests, UA, LDH, calcium, albumin, and beta-2 microglobulin
- ❑ Creatinine clearance (calculated or measured directly)
- ❑ Serum free light chain (FLC) assay
- ❑ Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP)
- ❑ 24 h urine for total protein, urine protein electrophoresis (UPEP)
- ❑ Unilateral bone marrow aspirate +biopsy, including cytogenetics, bone marrow immunohistochemistry, and bone marrow flow cytometry
- ❑ HBV, HCV, and HIV screening
- ❑ NT-proBNP

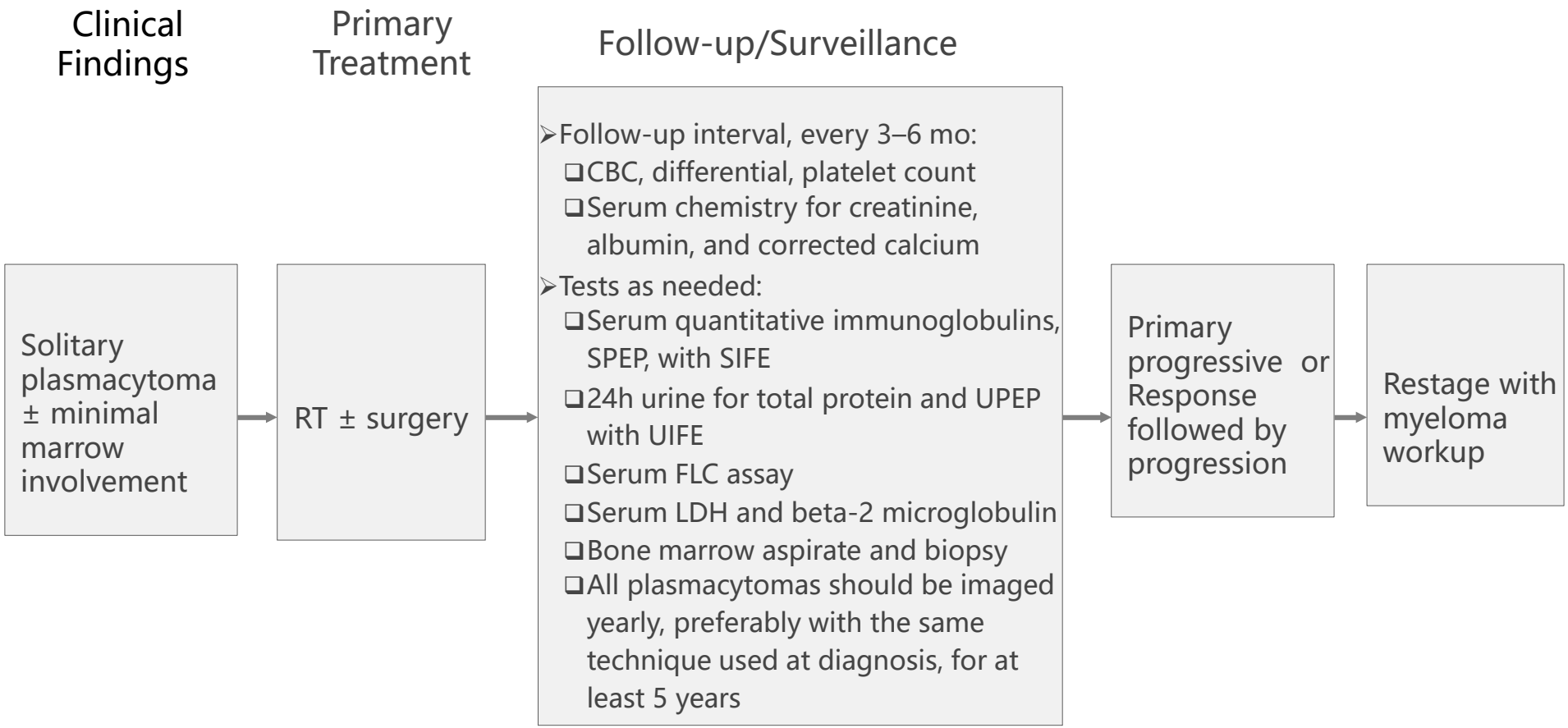
Useful Tests

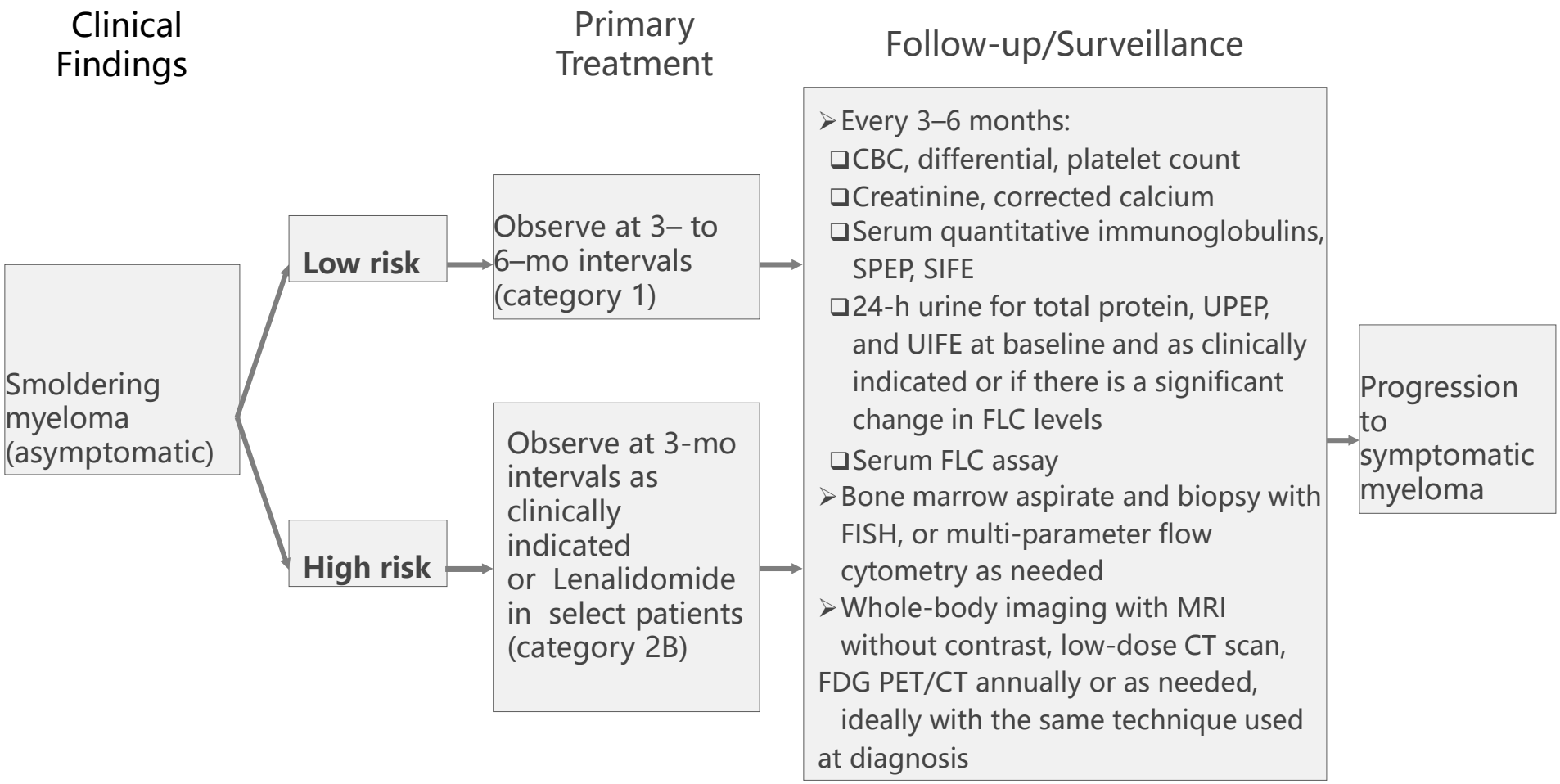
- ❑ Plasma cell FISH: del(13), del(17p13), t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/amplification, 1p deletion
- ❑ Whole-spinal MRI
- ❑ Whole-body low-dose CT scan
- ❑ Whole-body PET/CT
- ❑ Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- ❑ Bone densitometry
- ❑ Evaluation for light chain amyloidosis
- ❑ Serum viscosity
- ❑ HLA typing
- ❑ Echocardiogram
- ❑ Minimal residual disease (MRD) assessment

Clinical Findings




Clinical Presentation
Primary Treatment
Follow-up/ Surveillance
Solitary plasmacytoma
RT (40-50 Gy) to involved field
Solitary Extraosseous
RT (40-50 Gy) to involved field and/or surgery
❑CBC/DC
❑Serum chemistry for creatinine, albumin, corrected calcium, LDH (optional)
❑Beta-2 microglobulin (optional)
❑Serum FLC assay
❑24h urine for total protein, UPEP, serum quantitative immunoglobulins, SPEP
❑Bone marrow aspirate and biopsy (optional)
❑Bone survey (optional)
❑MRI and/or CT and/or PET/CT (optional)
Follow-up every 3–6 mo
Restaging while progression


Clinical Findings
Primary Treatment
Follow-up/Surveillance
Solitary plasmacytoma ± minimal marrow involvement
RT ± surgery
➢Follow-up interval, every 3–6 mo:
❑CBC, differential, platelet count
❑Serum chemistry for creatinine, albumin, and corrected calcium
➢Tests as needed:
❑Serum quantitative immunoglobulins, SPEP, with SIFE
❑24h urine for total protein and UPEP with UIFE
❑Serum FLC assay
❑Serum LDH and beta-2 microglobulin
❑Bone marrow aspirate and biopsy
❑All plasmacytomas should be imaged yearly, preferably with the same technique used at diagnosis, for at least 5 years
Primary progressive or Response followed by progression
Restage with myeloma workup


Clinical Findings
Primary Treatment
Follow-up/Surveillance
Smoldering myeloma (asymptomatic)
Low risk
High risk
Observe at 3– to 6–mo intervals (category 1)
Observe at 3-mo intervals as clinically indicated or Lenalidomide in select patients (category 2B)
➢ Every 3–6 months:
❑ CBC, differential, platelet count
❑ Creatinine, corrected calcium
❑ Serum quantitative immunoglobulins, SPEP, SIFE
❑ 24-h urine for total protein, UPEP, and UIFE at baseline and as clinically indicated or if there is a significant change in FLC levels
❑ Serum FLC assay
➢ Bone marrow aspirate and biopsy with FISH, or multi-parameter flow cytometry as needed
➢ Whole-body imaging with MRI without contrast, low-dose CT scan, FDG PET/CT annually or as needed, ideally with the same technique used at diagnosis
Progression to symptomatic myeloma

Clinical Findings	Primary Treatment	Follow-up/Surveillance
Multiple myeloma (symptomatic)	Myeloma therapy + bisphosphonates, or denosumab + supportive care treatment as indicated	➢ Laboratory assessments appropriate for monitoring treatment toxicities may include: CBC, differential, platelet count, blood glucose and electrolytes, and metabolic panel ➢ Serum quantitative immunoglobulins, SPEP, and SIFE ➢ 24-h urine for total protein, UPEP, and UIFE at baseline and as clinically indicated or if there is a significant change in FLC levels ➢ Serum FLC assay ➢ Whole-body imaging with MRI without contrast, low-dose CT scan, FDG PET/CT annually or as clinically indicated, ideally with the same technique used at diagnosis ➢ Bone marrow aspirate and biopsy at relapse with FISH as clinically indicated ➢ Assess for hematopoietic cell transplant candidacy: ❑ Refer for evaluation at a hematopoietic cell transplant center ❑ Harvest hematopoietic stem cells (consider for 2 transplants if appropriate) ➢ Consider minimal residual disease (MRD) as indicated for prognostication after shared decision with patient

→ **Response**

→ **No response**

Multiple Myeloma (Symptomatic)

Response after primary therapy

→ Autologous hematopoietic cell transplant (category 1)
or
Continuous myeloma therapy or maintenance therapy
or
Tandem autologous or allogeneic hematopoietic cell transplant under certain circumstances

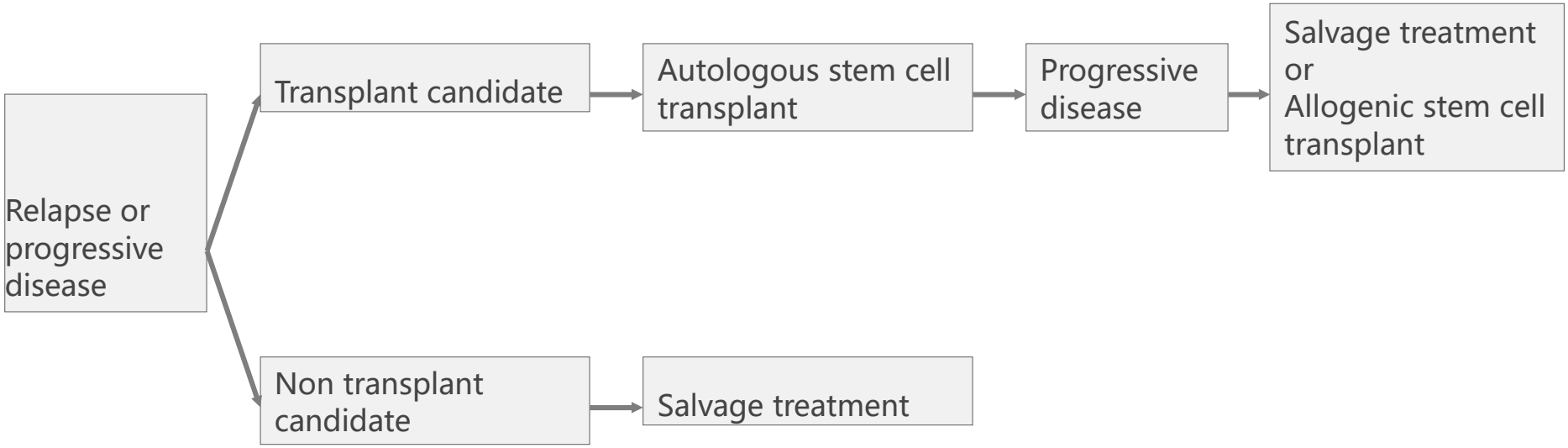
Follow-up/Surveillance

- Laboratory assessments appropriate for monitoring treatment toxicities may include: CBC, differential, platelet count, blood glucose and electrolytes, and metabolic panel
- Serum quantitative immunoglobulins, SPEP, and SIFE
- 24-h urine for total protein, UPEP, and UIFE at baseline and as needed or if there is a significant change in FLC levels
- Serum FLC assay
- Whole-body advanced imaging with FDG PET/CT, low-dose CT scan, MRI without contrast as needed, ideally with the same technique used at diagnosis
- Bone marrow aspirate and biopsy with multiparameter flow cytometry as needed Consider MRD as indicated for prognostication after shared decision with patient

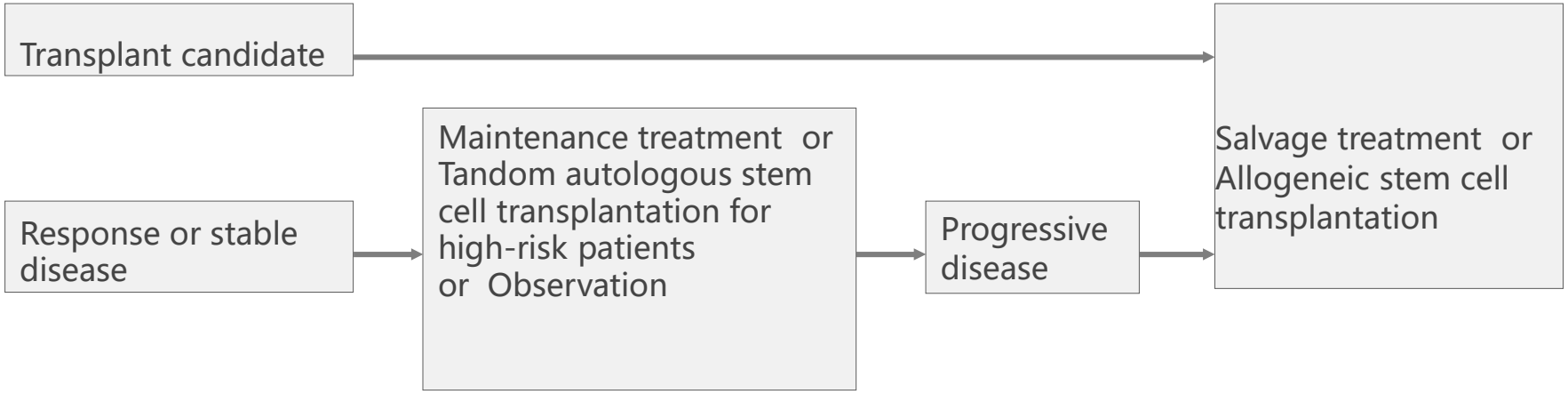
→ For additional treatment post-transplant

→ For additional treatment of relapsed/progressive disease after continuous myeloma therapy or maintenance

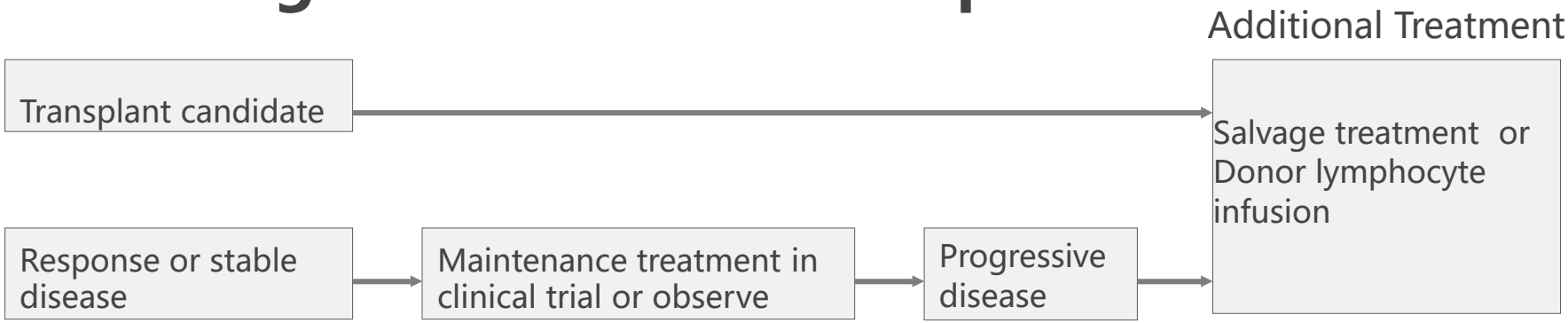
Response After First-Line or Maintenance Treatment



Post-Autologous Stem Cell Transplant



Post-Allogenic Stem Cell Transplant



Myeloma Staging

Stage	ISS	R-ISS
I	β_2M ≤ 3.5 and albumin ≥ 3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by FISH and Serum LDH ≤ the upper limit of normal
II	Neither stage I nor stage III	Neither R-ISS stage I nor stage III
III	β_2M ≥ 5.5	ISS stage III and either high-risk chromosomal abnormalities by FISH or Serum LDH > the upper limit of normal

High-risk: Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16) in FISH.

Factors Considered High Risk for Multiple Myeloma

Factors Considered High Risk for MM		
Cytogenetic	❑ t(4;14) ❑ t(14;16) ❑ Del(17p)/monosomy 17 ❑ 1q21 gain/1q21 amplification	❑ MYC translocation ❑ TP53 mutation [with del(17p)] ❑ Tetrasomies ❑ Complex karyotype (when done) or karyotypic del(13)
Other risk	❑ High-risk gene expression signature ❑ Extramedullary disease ❑ Circulating plasma cells ❑ High plasma cell proliferation ❑ Frailty	❑ Renal failure ❑ Thrombocytopenia ❑ High serum FLC ❑ Lymphopenia ❑ Immunoparesis ❑ Elevated LDH

Definition Of Multiple Myeloma (Smoldering And Active)

Smoldering (Asymptomatic) Myeloma

- ❑ M-protein in serum ≥ 30 g/L

or

- ❑ Bence-Jones protein ≥ 500 mg/24 h

and/or

- ❑ Bone marrow clonal plasma cells 10%–59%
- ❑ Absence of myeloma-defining events or amyloidosis

Active (Symptomatic) Myeloma[1]

- ➢ Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

and

- ➢ Any one or more of the following myeloma-defining events:
  - ❑Calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL)
  - ❑Renal insufficiency (creatinine > 2 mg/dL) [> 177 μmol/L] or creatinine clearance < 40 mL/min
  - ❑Anemia (hemoglobin < 10 g/dL or hemoglobin > 2 g/dL below the lower limit of normal)
  - ❑Clonal bone marrow plasma cells ≥ 60%
  - ❑Abnormal serum FLC ratio ≥ 100 (involved kappa) or ≤ 0.01 (involved lambda)
  - ❑≥ 1 osteolytic bone lesions on skeletal radiography, CT, or FDG PET/CT
  - ❑> 1 focal lesions on MRI studies ≥ 5 mm

[1]Other examples of active disease include: repeated infections, amyloidosis, or hyperviscosity.

Response Criteria For Multiple Myeloma

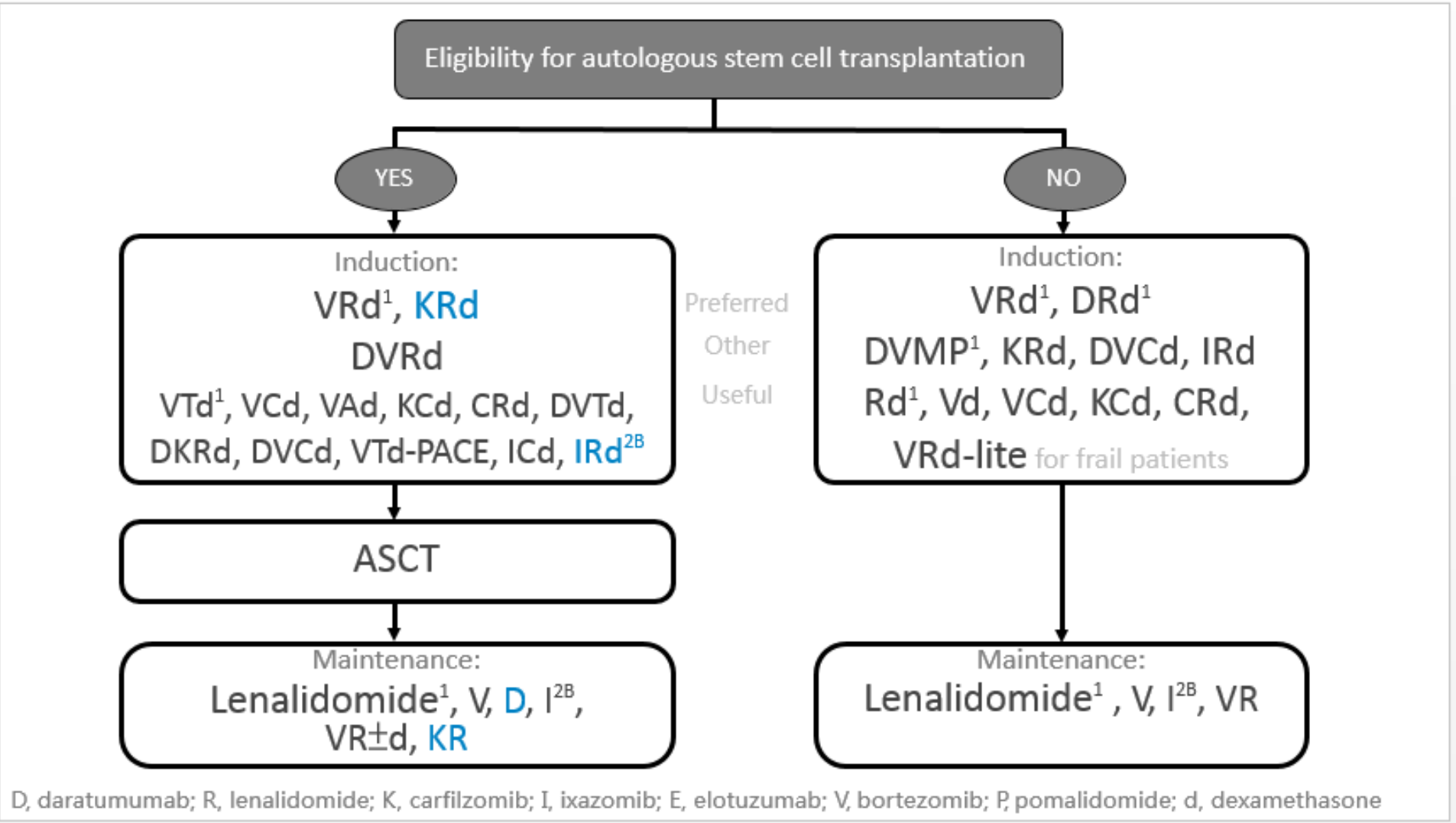
(Revised based on the new criteria by International Myeloma Working Group [IMWG])

IMWG criteria for response assessment including criteria for minimal residual disease (MRD)	
Response Category	Response Criteria
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (next-generation flow [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding FDG PET/CT or decrease to less mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal tissue.
Standard IMWG response criteria	
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells).
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates.
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h.
Partial response	≥ 50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30%. In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions)j of soft tissue plasmacytomas is also required.
Minimal response	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a 25%–49% reduction in SPD of soft tissue plasmacytomas is also required.

Response Criteria For Multiple Myeloma

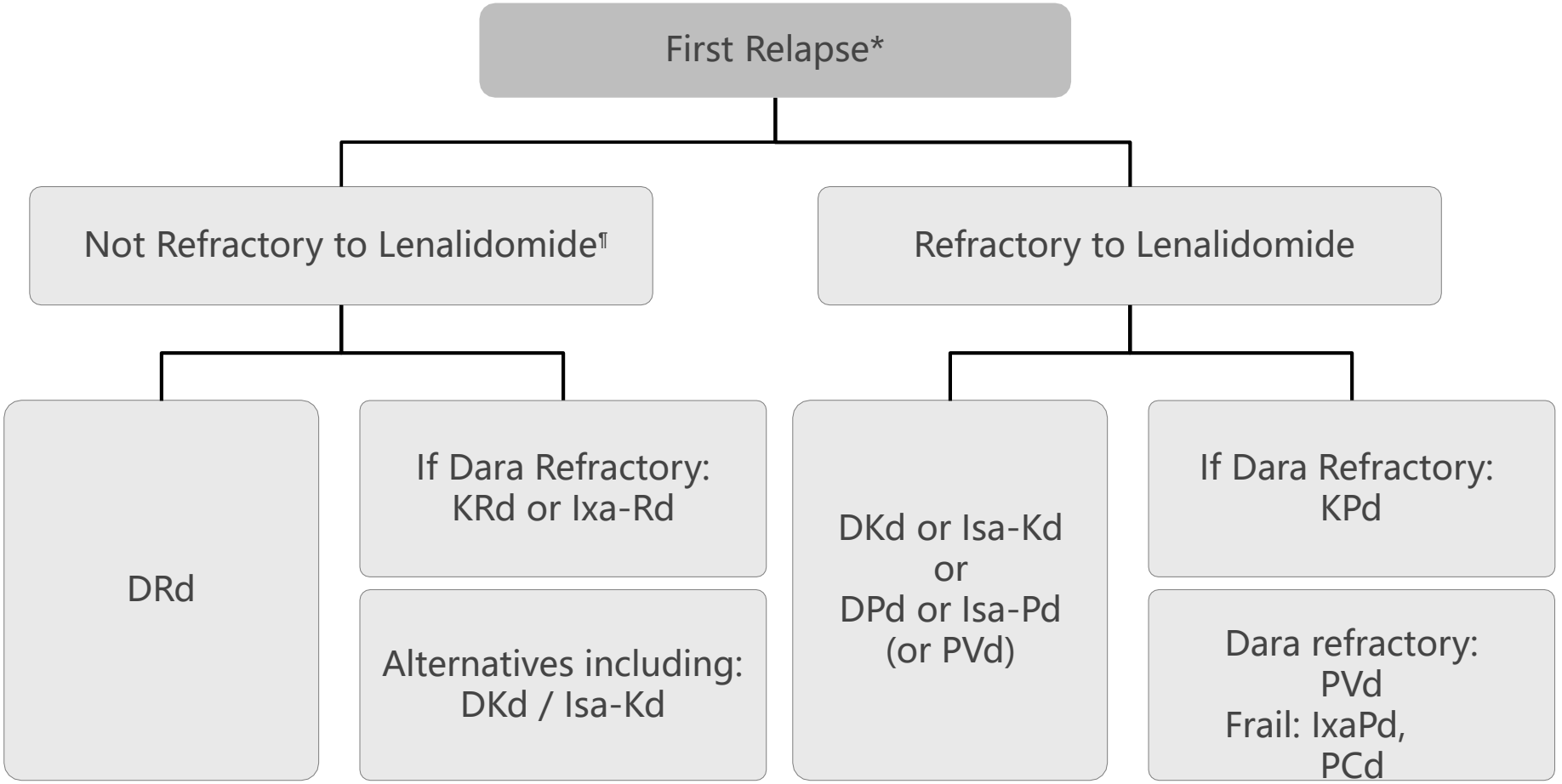
(Revised based on the new criteria by International Myeloma Working Group [IMWG])

Response Category	Response Criteria
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥ 0.5 g/dL); Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL; Urine M-protein (absolute increase must be ≥ 200 mg/24h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%); Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥50 % increase in the longest diameter of a previous lesion > 1 cm in short axis; ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD of the measurable lesion; Hypercalcemia (> 11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non–myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein.
Relapse from complete response (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥ 5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis;



D, daratumumab; R, lenalidomide; K, carfilzomib; I, ixazomib; E, elotuzumab; V, bortezomib; P, pomalidomide; d, dexamethasone

Myeloma: First Relapse



*Consider salvage auto transplant in eligible patients

¶Relapse occurring while off all therapy, or while on small doses of single-agent lenalidomide, or on bortezomib maintenance

Myeloma: Second or Higher Relapse

Previous Relapse Options

- ❑ Any first relapse options that have not been tried

(2 new drugs; triplet preferred)*
DKd, Isa-Kd, DPd, or Isa-Pd

Additional Options

- ❑ KCd, VCd, Ixa-Cd
- ❑ Selinexor-based regimens
- ❑ VDT-PACE like anthracycline containing regimens
- ❑ Venetoclax for t(11;14) or $BCL2^{high}$
- ❑ IV Melphalan
- ❑ Bendamustine-based regimens
- ❑ Quadruplet regimens

*Consider ixazomib instead of carfilzomib or bortezomib if an all-oral regimen is needed

Supportive Care For Multiple Myeloma

Bone Disease

- All patients receiving primary myeloma therapy should be given bisphosphonates (category 1) or denosumab.
  - A baseline dental exam is strongly recommended.
  - Assess Vitamin D status
  - Monitor for renal dysfunction with use of bisphosphonate therapy.
  - Monitor for osteonecrosis of the jaw.
  - Continue bone-targeting treatment (bisphosphonates or denosumab) for up to 2 years. The frequency of dosing (QM vs. Q3M) would depend on the individual patient criteria and response to therapy. Continuing beyond 2 years should be based on clinical judgment.
  - Patients subsequently discontinue denosumab therapy should be given maintenance denosumab Q6M or a single dose of bisphosphonate to mitigate risk of rebound osteoporosis.
- RT
- Orthopedic consultation should be sought for impending or actual long-bone fractures or compression of spinal cord or vertebral column instability.

Hypercalcemia

- Hydration, bisphosphonates (zoledronic acid preferred), denosumab, steroids, and/or calcitonin are recommended.

Hyperviscosity

- Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.

Anemia

- Consider erythropoietin for anemic patients.

Infection

- Intravenous immunoglobulin therapy should be considered in the setting of recurrent serious infection and/or hypogammaglobulinemia (IgG <400 mg/dL).
- The pneumococcal conjugate vaccine should be given followed by the pneumococcal polysaccharide vaccine one year later.
- Influenza vaccination recommended. Consider two doses of the high-dose inactivated quadrivalent influenza vaccine.
- Consider 3 months of levofloxacin 500 mg daily at diagnosis for patients at high risk for infection

Venous Thromboembolism (VTE)

- Prophylaxis, risk stratification, and management of VTE

Management of Venous Thromboembolism (VTE) in Myeloma

IMPEDE Score for Risk Stratification (points assigned)			
Individual Risk Factors	Points	Myeloma Risk Factors Points	Points
Positive Factors			
Central venous catheter/Tunneled central line	+2	Immunomodulatory drug (IMiD)	+4
Pelvic, hip, or femur fracture	+4	Erythropoiesis-stimulating agent	+1
Obesity (Body Mass Index ≥ 25)	+1	Dexamethasone < 160 mg/month	
Previous VTE		Dexamethasone > 160 mg/month	
		Doxorubicin or multiagent chemotherapy	
Negative Factors			
Ethnicity/Race = Asian/Pacific Islander	-3		
Existing thromboprophylaxis: prophylactic LMWH (low-molecular-weight heparin) or aspirin	-3		
Existing thromboprophylaxis: therapeutic LMWH or warfarin	-4		

SAVED Score for Risk Stratification	
Variable	Points
Surgery within 90 days	+2
Asian Race	-3
VTE history	+3
Age ≥ 80 years	+1
Dexamethasone (regimen dose) ・Standard dose (120–160 mg/cycle) ・High dose (> 160 mg/cycle)	 +1 +2

VTE Prophylaxis Recommendations	
≤ 3 Points by IMPEDE Score or < 2 Points by SAVED Score	≥ 4 Points by IMPEDE Score or ≥ 2 SAVED Score
• Aspirin 81–325 mg once daily	• LMWH (equivalent to enoxaparin 40 mg daily) OR • Rivaroxaban 10 mg daily OR • Apixaban 2.5 mg twice daily OR • Fondaparinux 2.5 mg daily OR • Warfarin (target INR 2.0–3.0)

Duration of VTE Prophylaxis

- Indefinite while on myeloma therapy
- 3–6 months followed by aspirin (longer periods of anticoagulation may be considered in the presence of additional patient, treatment-specific, or transient VTE risk factors)

Reference

- NCCN Guidelines Multiple Myeloma Version 1.2023
- Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982
- https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50