

Recent Advances in the Treatment of Newly Diagnosed Multiple Myeloma

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Financial Disclosures

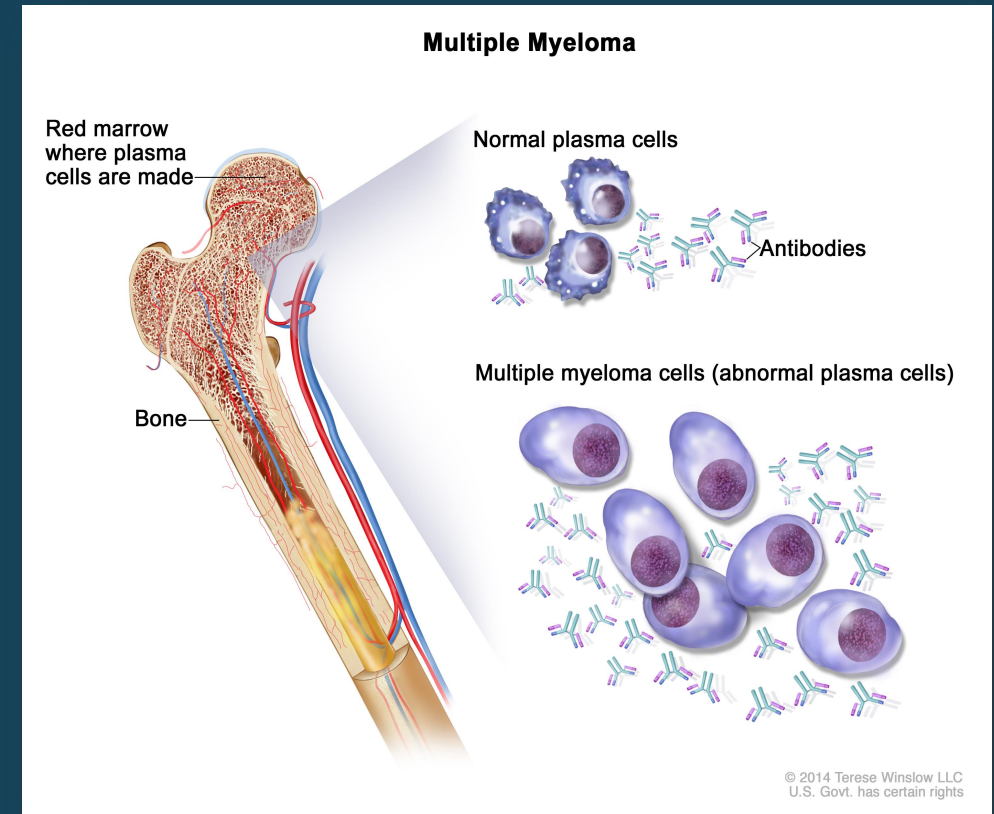
- Dr. Libby has no significant financial disclosures.
- Mr. Epworth has no significant financial disclosures.

Learning Objectives

1. Interpret data on current and novel treatments for multiple myeloma (MM)
2. Select initial therapy for MM based on patient risk and alignment with guidelines and best practices
3. Employ best strategies for management of adverse events associated with MM therapies
4. Evaluate recent advances related to use of minimal residual disease testing in patients with MM

What Is Multiple Myeloma?

A malignancy characterized by clonal proliferation of terminally differentiated plasma cells within the bone marrow



Multiple Myeloma Statistics

- Estimated new cases in 2019: 32,110 (1.8%)
- Estimated deaths in 2019: 12,960 (2.1%)
- Prevalence in 2016: 131,392 in US (18% of all hematologic malignancies)
- Percentage of patients surviving 5 years (2009-15): 52.2%

Signs and Symptoms at Presentation

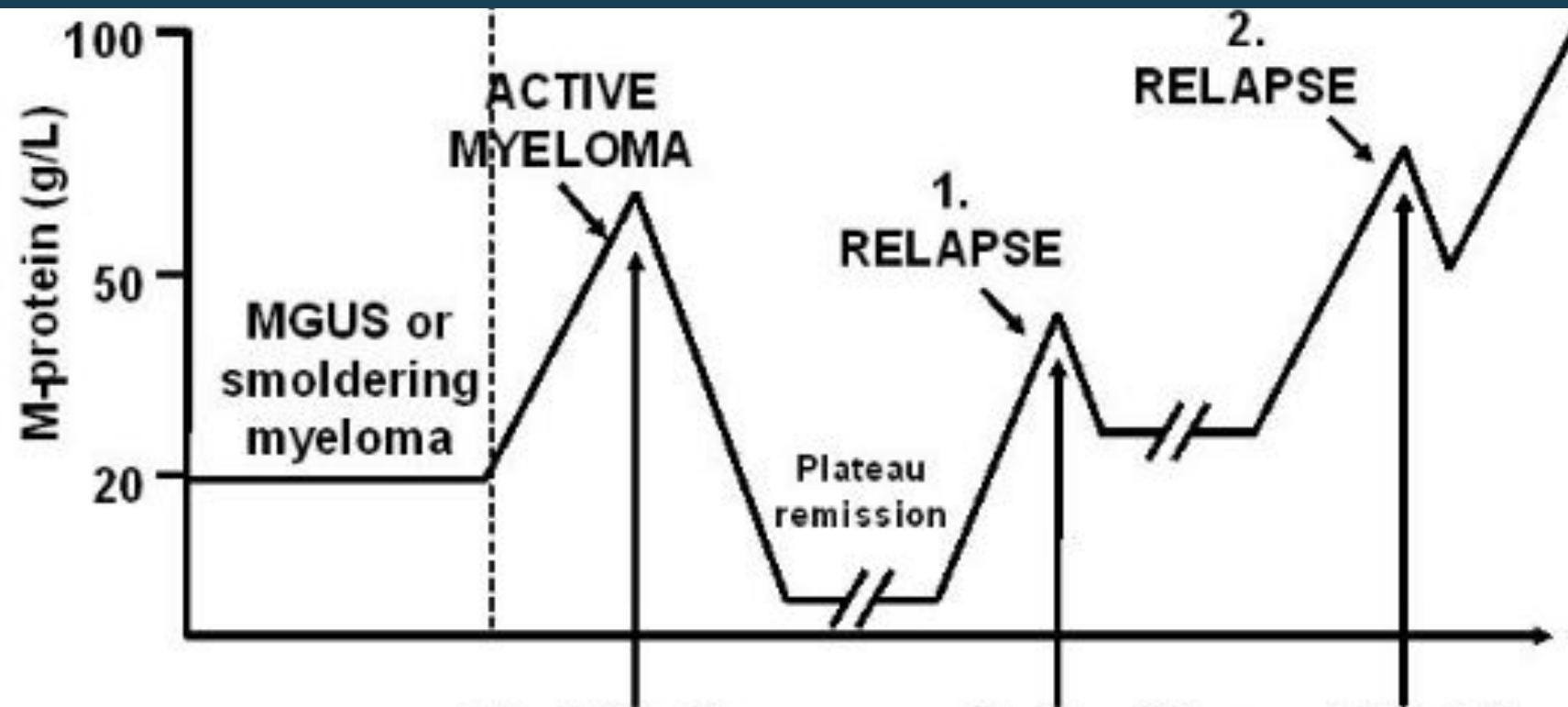
Subjective

- Bone pain
- Frequent infections
- Fatigue
- Unintentional weight loss
- Foaming urine
- Easy bruising and bleeding

Objective

- Hypercalcemia
- Elevated creatinine
- Anemia
- **Bone fractures, lesions, soft tissue masses**
- Pancytopenia
- Elevated serum protein levels

How to Diagnose MM



Case Study 1

- TM is a 60-year-old highly active male who presented to OSH ED with dyspnea following minimal exertion, normally very active
- In ED exhibited the following:
 - Tachycardia and AFib
 - Volume overload
 - Elevated D dimer

Case Study 1

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- In ED exhibited the following:
 - Tachycardia and AFib
 - Volume overload
 - Elevated D dimer
 - CT angiogram of chest exhibited incidental finding of lytic lesions in T and L spine as well as ribs

Labs, Imaging, and Biopsy for NDMM Workup

Labs

Serum protein electrophoresis
Urine protein electrophoresis
Serum immunofixation
Serum free light chains
Complete blood count
Comprehensive metabolic panel
Lactate dehydrogenase
Beta 2 microglobulin

Imaging

Whole body low-dose CT
or
FDG PET/CT
or
Bone marrow MRI*

Bone Marrow Biopsy

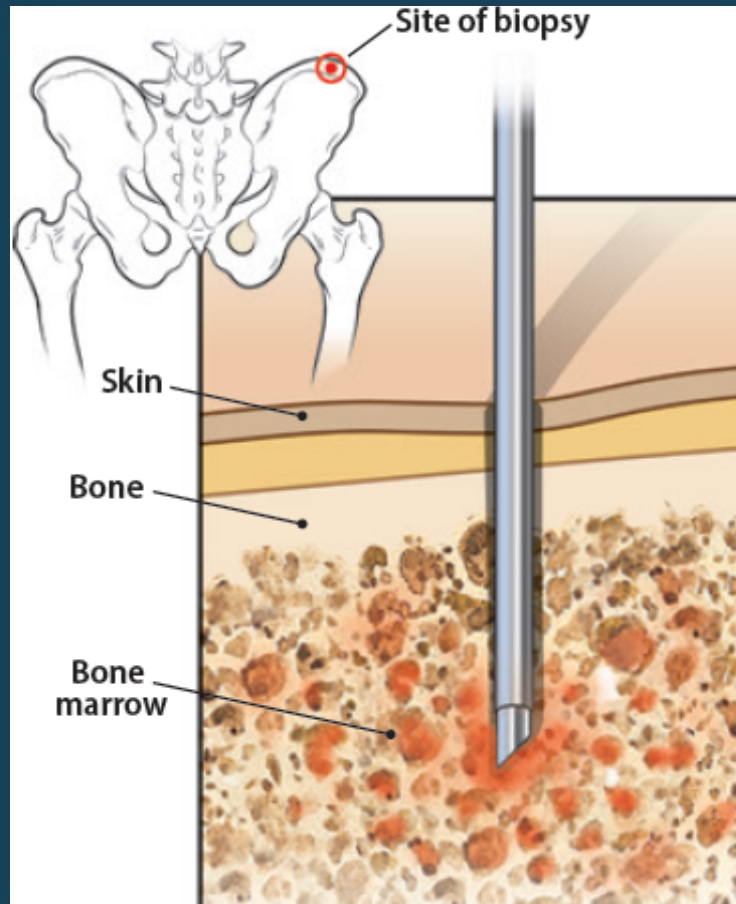
Morphology
Flow cytometry
Cytogenetics
FISH array
Molecular testing

Monoclonal Protein/M-Spike

- Present in approximately 85% of patients
- Made by abnormal plasma cells and detected in serum and/or 24-hour urine. Also referred to as a paraprotein.
- Testing: SPEP or UPEP
- No detectable M-spike 15% (non-secretory)
- Can detect by serum free light chains in these cases

SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

Bone Marrow Biopsy



Whole Body Low-Dose CT

A patient-friendly, fast, low radiation scan without IV contrast that depicts bone damage. Excellent for radiation therapy planning and **evaluation of the stability of bony structures and fractures.**

PET/CT Whole Body

A critical tool for **assessing for the presence of extramedullary disease.** Detects active bone lesions and measures level of disease metabolic activity.

MRI Bone Marrow

Not very patient friendly; long time on scanner required, **highly sensitive for early bone damage** without radiation. Detects pathological fractures and cord compression. Per NCCN guidelines if the whole body low-dose CT or PET/CT is negative, consider this modality to discern smoldering multiple myeloma from multiple myeloma.

Osseous (Skeletal) Survey

A head-to-toe group of x-rays. Inexpensive and widely available. Has a 30% failure rate of detecting lesions that can be found on bone marrow MRI.

Precursors to Symptomatic Multiple Myeloma

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Serum M protein < 3 g/dL **and** clonal bone marrow plasma cells < 10% **and** no myeloma defining events or amyloidosis

Progression rate to MM in 5 years: 1% per year

Smoldering Multiple Myeloma

- Serum protein ≥ 3 g/dL or urinary protein ≥ 500 mg/24 hours **and/or** clonal bone marrow plasma cells 10%-59% **and** no myeloma defining events

Progression rate to MM in 5 years: 10% per year

CRAB Criteria

**$\geq 10\%$ clonal cells in bone marrow or biopsy proven plasmacytoma
PLUS one or more of the following
creates a diagnosis of multiple myeloma**

Ca: 1 mg/dL over ULN or > 11 mg/dL

Cr: > 2 mg/dL or CrCl < 40 mL/min

**Hgb: > 2 g/dL below LLN or
 < 10 g/dL**

Bone lesions (Y/N)

OR

Myeloma Defining Events

Any one of the following creates a diagnosis of multiple myeloma

- BM biopsy $> 60\%$ (Y/N)
- Involved vs. uninvolved free light chain ratio $\geq 100:1$ (Y/N)
- > 1 focal lesion by MRI ≥ 5 mm (Y/N)

Bone Marrow Biopsy: Diagnosis

Hematopathology

Detects the level of plasma cell neoplasm in bone marrow. Presents the percentage of marrow cellularity occupied by disease.
Percentage of plasma cells: Normal range is 1%-2%.

A Positive Diagnosis of Multiple Myeloma, by Either CRAB Criteria or a Myeloma Defining Event, Is the Trigger to Start Treatment

Newly Diagnosed Multiple Myeloma: Case Study

- TM is a 60-year-old highly active male who presented to OSH ED with dyspnea following minimal exertion, normally very active.
- In ED exhibited the following:
 - Tachycardia and AFib
 - Volume overload
 - Elevated D dimer
 - CT scan exhibits lytic lesions

Newly Diagnosed Multiple Myeloma: Case Study

MDE

BM: 30%
FLCR: 67.66
Lesions: No

CRAB

Ca: 9.5 (C: 8.86)
Cr: 1.25
Hb: 14.7
Lesions: Yes

Immunology

M-spike: 1.6 g/dL
KFLC: 39.24 mg/dL
Immunofixation: IgG
Ratio: 67.7

Bone Marrow

30% abnormal plasma
Normal cytogenetics

Imaging

Osseous Survey: Multiple lytic lesions in thoracic and cervical spine. Lytic lesions throughout bilateral femur including a 2.3 x 7.5 cm lytic lesion in right proximal diaphysis with greater than 50% thinning of medial femoral cortex.

Staging and Prognosis in Multiple Myeloma

**Beta 2
Microglobulin**

Albumin

LDH

Genetics

Staging and Prognosis in Multiple Myeloma

Revised International Staging System (R-ISS)

Similar to ISS but incorporates factors including serum LDH and the high-risk chromosomal abnormalities del(17p), t(4;14) and/or t(14;16) by FISH

International Staging System (ISS)

Utilizes data from the serum beta-2 microglobulin and serum albumin to determine three stages with prognostic significance

Durie-Salmon

Staging determined by measurements of tumor cell density in bone marrow combined with assessments of renal function, serum calcium levels, anemia, and presence of bony lesions. Questionable as a method of predicting prognosis.

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International
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(R-ISS)**

Similar to ISS but incorporates factors including serum LDH and the high-risk chromosomal abnormalities del(17p), t(4;14) or t(14;16) by FISH

R-ISS I: B2M < 3.5 mg/L and serum albumin $\geq$ 3.5 g/dL, normal LDH and the absence of del(17p), t(4;14) or t(14;16) by FISH on BM. Estimated PFS at 5 years 55% and OS at 5 years 82%

R-ISS II: Neither stage I or III. Estimated PFS 42 months, estimated OS 83 months.

R-ISS III: B2M $\geq$ 5.5 mg/L and LDH is greater than normal limits and or the detection of del(17p), t(4;14) or t(14;16) by FISH on BM. Estimated PFS 29 months, estimated OS 43 months.

MSSMART (Mayo Clinic) Guidelines

MAYO CLINIC

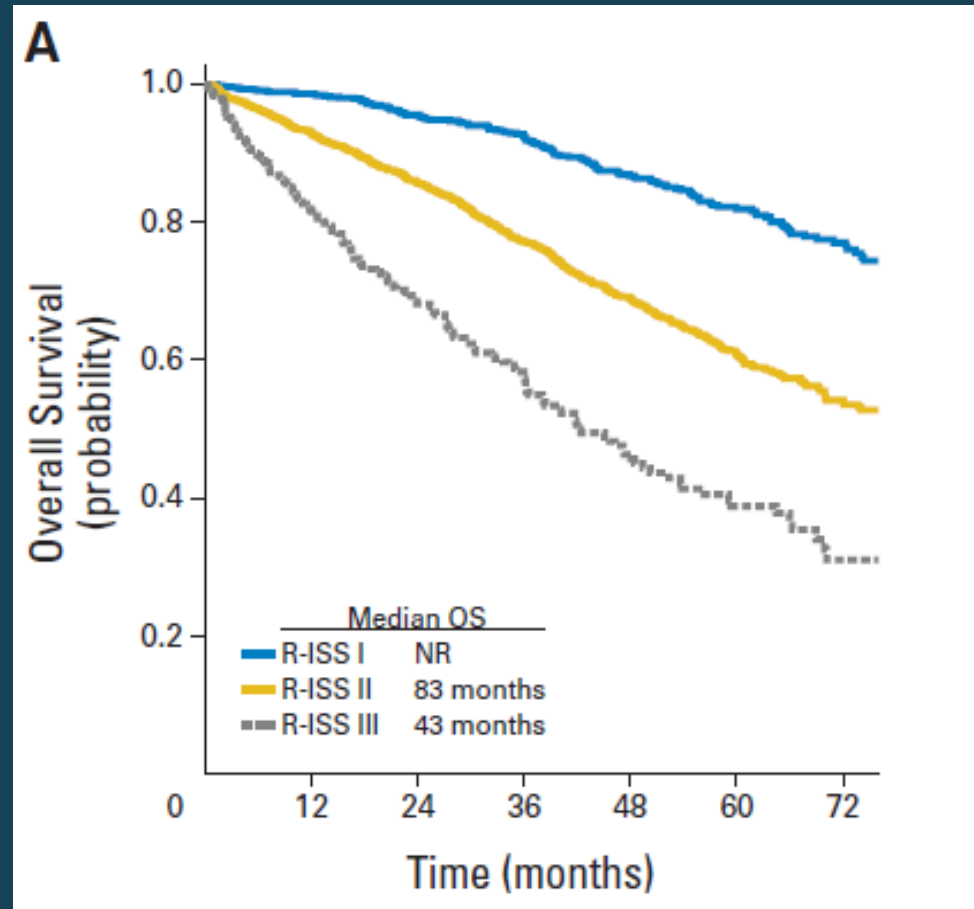
mSMART 3.0: Classification of Active MM

High-Risk	Standard-Risk ^a
▪ High Risk genetic Abnormalities ^{a,b} ▪ t(4;14) ▪ t(14;16) ▪ t(14;20) ▪ Del 17p ▪ p53 mutation ▪ Gain 1q ▪ RISS Stage 3 ▪ High Plasma Cell S-phase^c ▪ GEP: High risk signature	▪ All others including: ▪ Trisomies ▪ t(11;14)^d ▪ t(6;14)

*Trisomies may ameliorate
*By FISH or equivalent method
*Cut-offs vary
*t(11;14) may be associated with plasma cell leukemia

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed August 2018

Survival by R-ISS of NDMM Patients



Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-9.

Treating Newly Diagnosed Multiple Myeloma

Treating Multiple Myeloma

“The significant challenge of current myeloma management is matching the progress made in improved survival through disease control while optimizing quality of life with effective supportive care from initial diagnosis to end-of-life care.”

Front-Line Treatment

RVd

DRd

KRd

DVMP

RVd Lite

Studies

Transplant

Radiation

Lenalidomide, Bortezomib, Dexamethasone (RVd) 21-Day Cycle (Transplant Eligible)

R

Lenalidomide: 25 mg PO on days 1-14

V

Bortezomib: 1.3 mg/m² SC
on days 1, 4, 8, 11

D

Dexamethasone: 20 mg PO on days 1, 2, 4, 5, 8, 9, 11, 12
OR 40 mg PO on days 1, 8, 15

Maintenance: Bortezomib 1.3 mg/m² SC every other week **OR**
Lenalidomide 10 to 15 mg days 1-21 of 28 days

Carfilzomib, Lenalidomide, and Dexamethasone (KRd) for High-Risk NDMM 28-Day Cycle (Transplant Eligible)

K

Carfilzomib: Once or twice weekly dosing starting on C1 days 1&2, 20 mg/m², then increasing up to 27 mg/m² or 70 mg/m² respectively.

R

Lenalidomide: 25 mg PO on days 1-21

D

Dexamethasone: 40 mg PO on days 1, 8, 15, 22

Maintenance: Carfilzomib once or twice weekly every other week or consider KRd maintenance

Lenalidomide, Bortezomib, Dexamethasone (RVd - Lite) 35-Day Cycle (Transplant Ineligible)

R

Lenalidomide: 15 mg PO on days 1-21

V

Bortezomib: 1.3 mg/m² SC on days 1, 8, 15, 22

D

Dexamethasone: 20 mg PO on days 1, 8, 15, 22

Maintenance: Bortezomib 1.3 mg/m² SC every other week OR Lenalidomide 1-21 of 28 days

Daratumumab, Lenalidomide, Dexamethasone (DRd) 28-Day Cycle (Transplant Ineligible)

D

Daratumumab: 16 mg/kg (Cycles 1-2) weekly, (C 3-6) EOW, (C7+) monthly

R

Lenalidomide: 25 mg PO on days 1-21

D

Dexamethasone: 40 mg PO on days 1, 8, 15, 22

Continue treatment until toxicity or progression of disease

Daratumumab, Bortezomib, Melphalan, Prednisone (DVMP) 42-Day Cycle (Transplant Ineligible)

D

Daratumumab: 16 mg/kg (Cycle 1-6) weekly, (C 2-9) EOW, (C10+) monthly

V

Bortezomib: 1.3 mg/m² SC: (C1) twice weekly weeks 1, 2, 4, 5, (C2-9) once weekly 1, 2, 4, 5

M

Melphalan: 9 mg/m² PO days 1-4 of each cycle

P

Prednisone: 60 mg/m² PO days 1-4 of each cycle

VMP stops after Cycle 9, daratumumab continues treatment until toxicity or progression of disease

Transplant: Autologous

- Factors for eligibility: age, performance status, comorbidities
- Transplant pathway
 - 4-6 cycles of induction therapy
 - High-dose melphalan conditioning
 - Transplant
 - Maintenance
- Patients who had upfront ASCT had a greater PFS and response rate compared with those who deferred transplant—no change in OS

Palumbo A, et al. *N Engl J Med*. 2014;371:895-905.

Managing Side Effects

Managing Side Effects

Bone disease

Hypercalcemia

Pain

Anemia

Coagulation/Thrombosis

Infection

Bone Disease

Strengthening

- Zoledronic acid
- Pamidronate
- Denosumab

Assessments

Dental exam (monitor for ONJ)

Orthopedic consult

- Impending or actual bone fractures
- Spinal cord compression
- Vertebral column instability

Hypercalcemia

- Hydration
- Bisphosphonates

Pain

- Short/long-acting opioids
- Radiation

Anemia

- Transfusions
- Erythropoietin

Coagulation/Thrombosis

- ASA (81-325 mg)
- DOAC

Peripheral Neuropathy

Monitor, dose change

Infection

- Monitoring of CBC with neutrophils
- Review infection risk reduction
- Test for hepatitis B prior to start of daratumumab
- Herpes zoster prophylaxis with use of proteasome inhibitor or daratumumab/elotuzumab
- Re-vaccinate ASCT 6-12 months post-transplant

Case Study: X-Ray of Right Femur



Diagnosis

Diagnosis

IgG Kappa multiple myeloma with lytic lesions

Prognosis

Prognosis

- R-ISS Stage I
- B2M: 1.8
Albumin: 4.8
LDH: 242
- No high-risk genetics
- Median OS 62 months

Treatment

Treatment

- RVd 6 cycles to VGPR
- VRD-PACE
(melphalan)
ASCT
- Lenalidomide maintenance

SE Management

SE Management

- Zoledronic acid
2 years
- Ortho consult
with rod
stabilization
- Radiation
- Opioid pain
meds
- ASA 81 mg
- Acyclovir with PI
- Mild paresthesia
tips of toes

Case Study (cont.)

- Patient is currently 2 years status post ASCT, receiving lenalidomide 15 mg days 1-21/28. Mild fatigue, no other significant maintenance related side effects. Will continue maintenance until progression of disease or toxicity.
- Continues in his VGPR, he is assessed with monthly labs and clinical assessment and continues to exhibit disease stability with no indications of progression of disease by labs, ROS, or physical exam.
- Has returned to his active lifestyle with modifications in weight training.

Suggested Reading

- Induction Therapy for Newly Diagnosed Multiple Myeloma, DOI: 10.1200/EDBK_238527 *American Society of Clinical Oncology Education Book*.
- Rajkumar SV. Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management. *Am J Hematology*. 2018; 93: 1091-1110.

Response in Myeloma: Current Definitions and Future Trends

- Partial response (PR)
 - $\geq 50\%$ reduction of serum M-protein plus reduction in 24 h urinary M-protein by $\geq 90\%$ or to < 200 mg per 24 h
 - If the serum and urine M-protein are unmeasurable, a $\geq 50\%$ 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, $\geq 50\%$ reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geq 30\%$.
 - In addition to these criteria, if present at baseline, a $\geq 50\%$ reduction in the size (SPD) of soft tissue plasmacytomas is also required

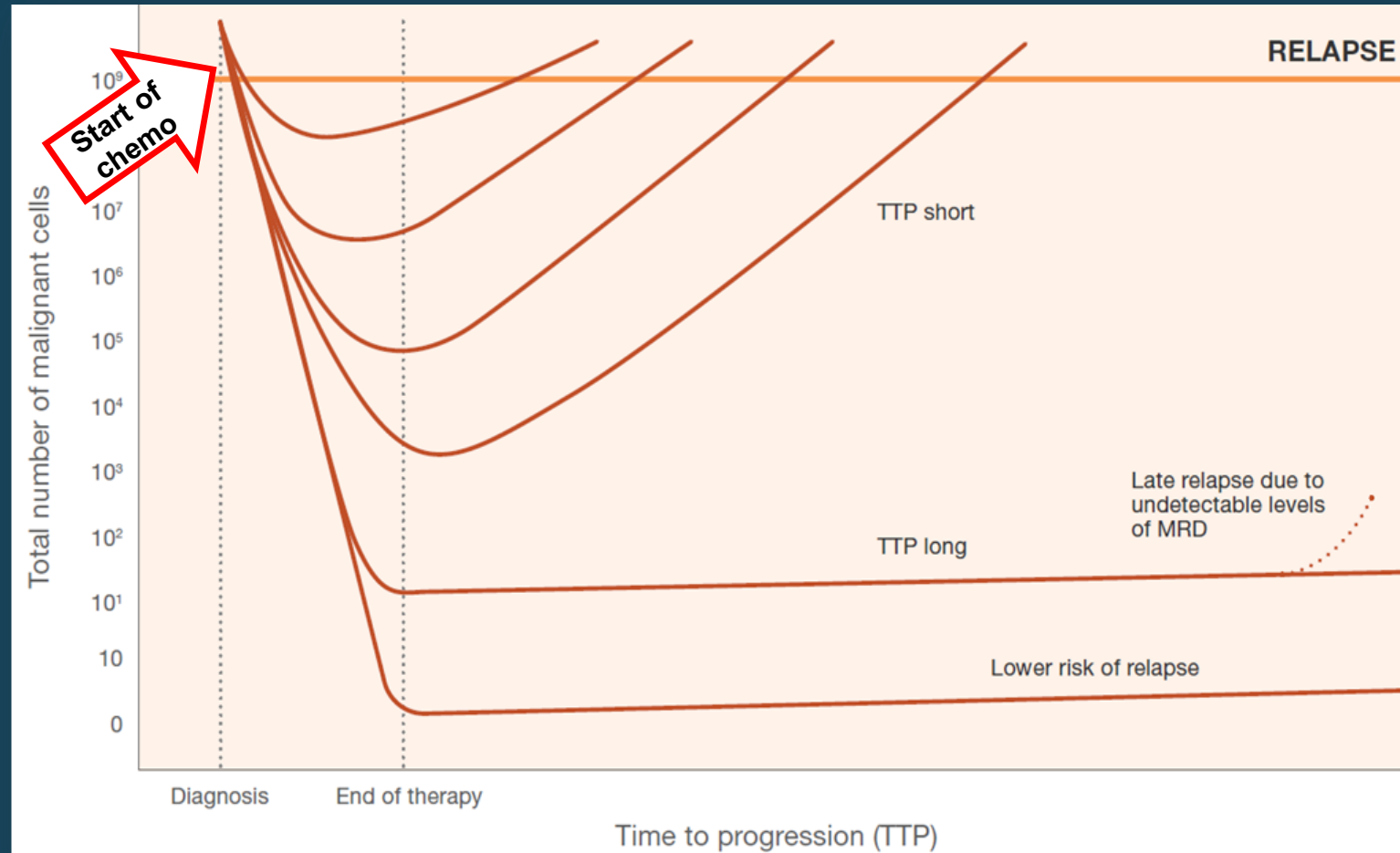
Response in Myeloma: Current Definitions and Future Trends (cont.)

- Very good partial response (VGPR): $\geq 90\%$ reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h.
- Complete response (CR): Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and $< 5\%$ plasma cells in bone marrow aspirates
- Stringent complete response (sCR): Complete response plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio $\leq 4:1$ or $\geq 1:2$ for κ and λ patients, respectively, after counting ≥ 100 plasma cells)

Minimal Residual Disease (MRD) Testing

- New concept in myeloma
- Measurement of residual myeloma cells in marrow after chemotherapy and/or transplant
- Can be done by flow cytometry or using next-generation sequencing (genetic testing)
- Sensitivity between 10^{-5} and 10^{-6}
- Most sensitive technology (NGS) can detect one cancer cell out of 1,000,000 normal cells
- Goal is for patient to be **MRD negative or no residual disease**

Depth of Response Matters

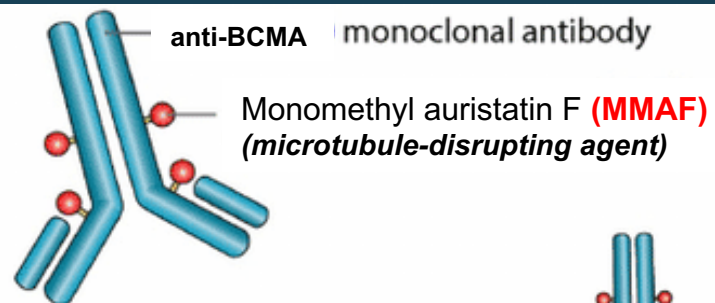


Multiple Myeloma Treatment: The Foreseeable Future

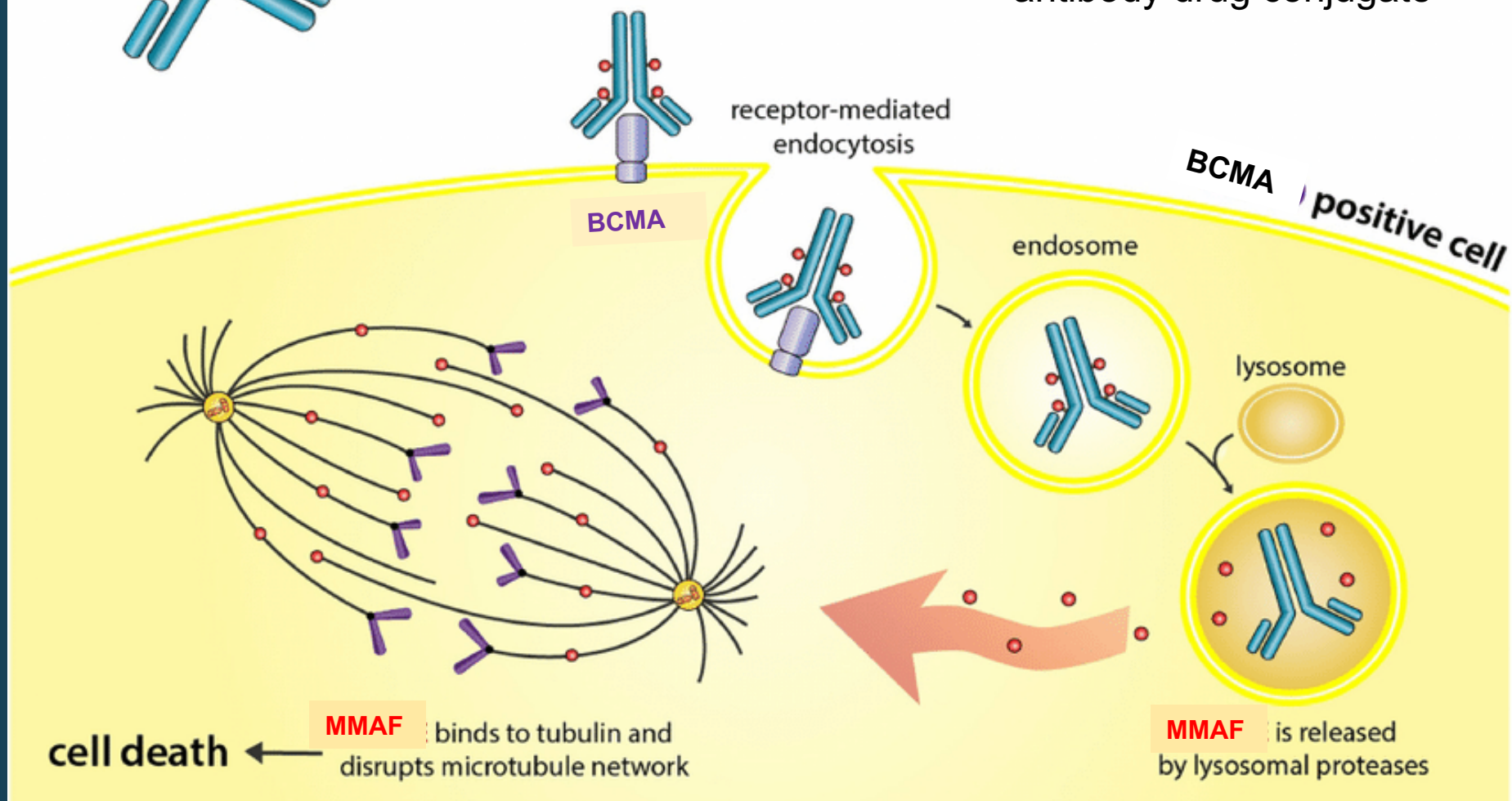


Belantamab Mafodotin (GSK 2857916)

- Antibody drug conjugate
- Many similarities to brentuximab vedotin for Hodgkin disease
- 60% response rate in heavily pretreated patients with RRMM
- 30% response rate in penta-refractory patients (daratumumab refractory)
- IV every 3 weeks
- Thrombocytopenia and keratitis

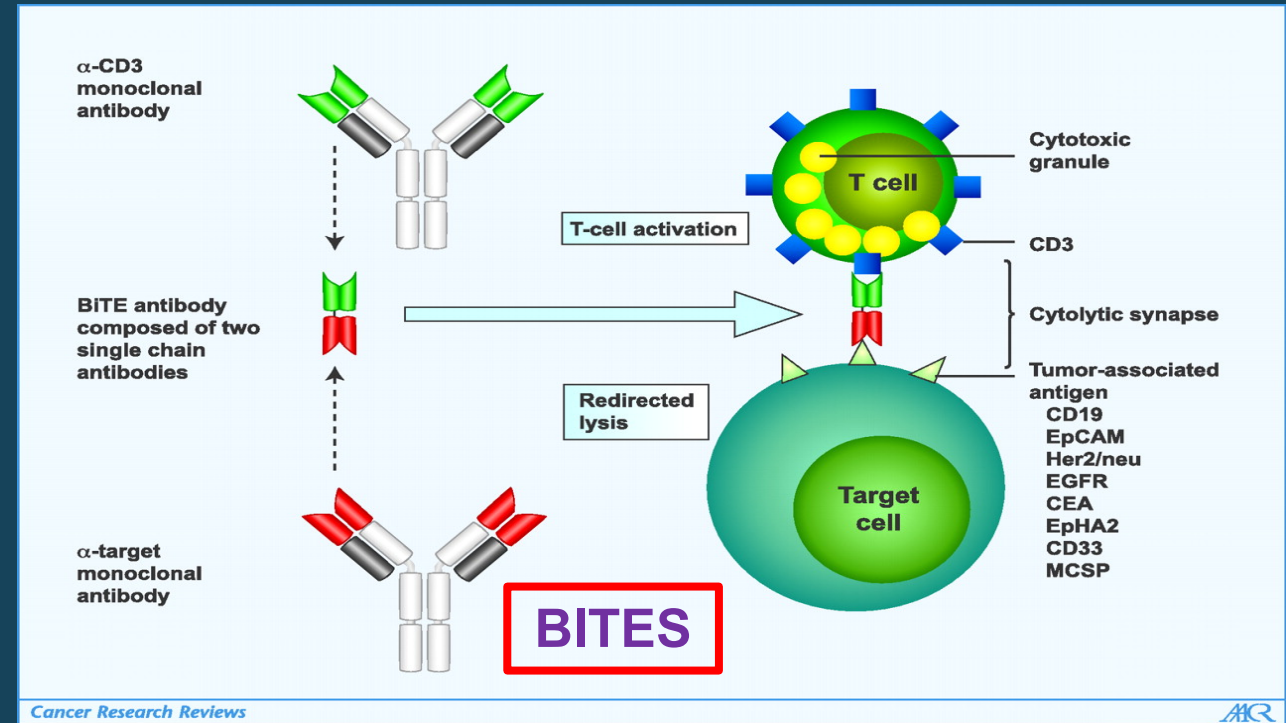


GSK 2857916
Belantamab mafodotin
antibody drug conjugate



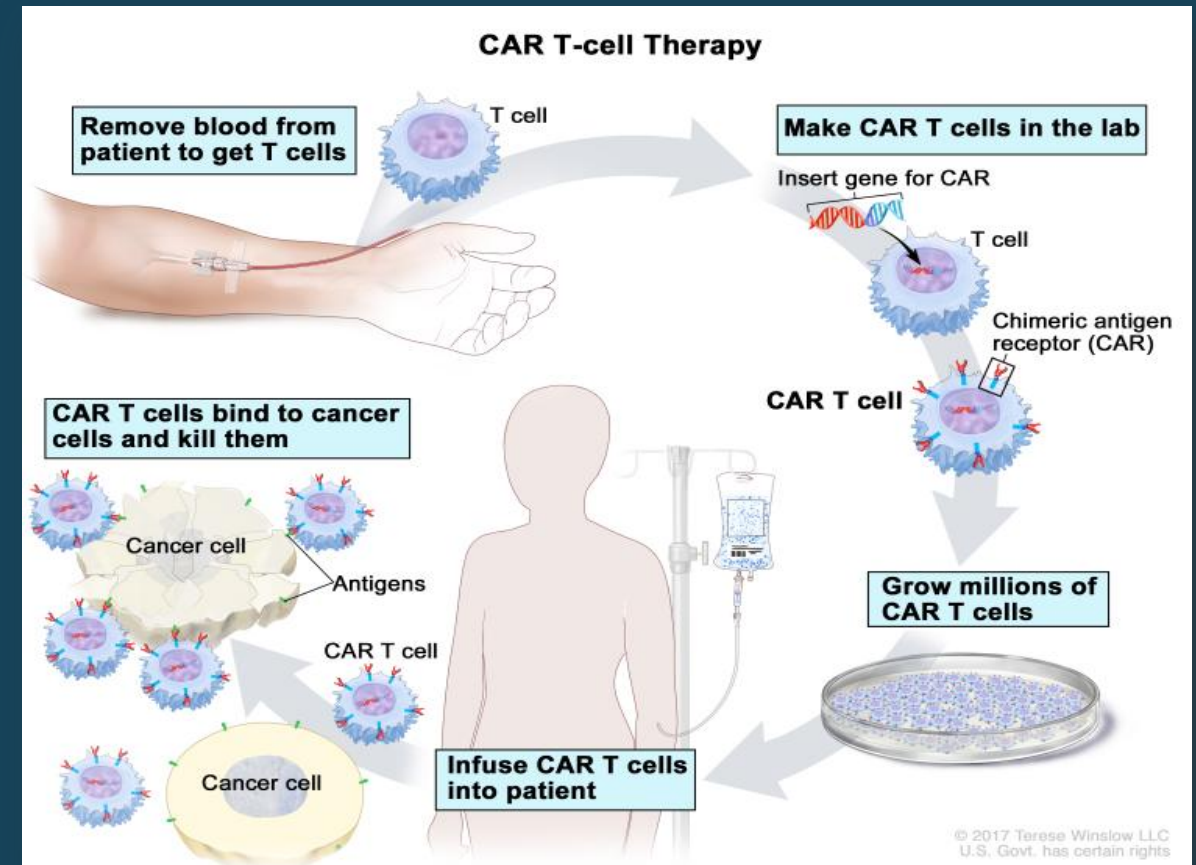
New Drugs

- BiTEs – bispecific antibodies
- Early in development
- Can be administered over and over
- Blinatumomab, approved for acute lymphoblastic leukemia, is a BiTE
- Many companies are developing BiTEs



New “Living” Drug

- CAR T cells
- Possibly will be approved for myeloma in 2020
- Administered once only at this time
- Many companies are developing CAR T cells



bb2121

- 33 patients
- Hematologic toxic effects were the most common events of grade 3 or higher, neutropenia (85%), leukopenia (58%), anemia (45%), thrombocytopenia (45%)
- 25 patients (76%) had cytokine release syndrome, grade 1-2 in 23 patients (70%) and grade 3 in 2 patients (6%)
- Neurologic toxic effects occurred in 14 patients (42%) and were of grade 1 or 2 in 13 patients (39%)
- One patient (3%) had a reversible grade 4 neurologic toxic effect
- Response rate 85%, 15 patients (45%) had complete responses
- Six of the 15 patients who had a complete response have relapsed
- Median PFS 11.8 months
- CAR T-cell expansion was associated with responses, and CAR T cells persisted up to 1 year after the infusion

Next-Generation Immunomodulatory (IMiD) Drugs

- First generation: thalidomide; second generation: lenalidomide; third generation: pomalidomide
- **Iberdomide** under study
- Cereblon E3 ligase modulator
- Phase 1/2 study presented at the IMW in Boston in Sept. 2019 of 27 patients with RRMM (all RR to daratumumab and pomalidomide), ORR was 29.6%, comprising a 3.7% VGPR and a 25.9% PR

More Questions?

Come see us at Booth #829 (next to the APSHO Booth) in the Exhibit Hall from 12:10 to 1:00 today

SMARTIE

This has been a SMARTIE presentation.

To access your post-session questions, you can:

- Click on the link that was sent to you via email
- Visit the SMARTIE station
- Go to jadprolive.com/smartie2019