Multiple Myeloma: Treatment when you're first diagnosed

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Introduction: Example Patient Case

- A 60 year-old woman was seen by her primary care physician for new onset low back pain. She was found to be anemic with a high calcium level in her blood and worsening kidney function.
- Her astute primary care physician checked an SPEP, which revealed a large M-spike.
- A follow-up PET scan showed multiple bone lesions, and a bone marrow biopsy showed 60% plasma cells.

Introduction: Example Patient Case

- She is referred to see Dr. Myeloma in initial consultation.
  - What factors does Dr. Myeloma use to decide what to treat with her?
  - How should Dr. Myeloma monitor her response to treatment?
  - What other issues are important for Dr. Myeloma to consider?

Your Personal Treatment Plan: Partnering With Your Health Care Team

Your Overall Health and Characteristics of Your Myeloma

- Age and general health
- Other conditions
- Test results
- Symptoms

+

Your Preferences and Personal Goals

- Eliminate vs control disease
- Willingness to tolerate side effects
- Symptom relief
- Personal lifestyle/situation

No one treatment plan is right for everyone.

If you are comfortable with it, consider a clinical trial if available.

If you are not comfortable, consider a 2nd opinion

Goals of Therapy

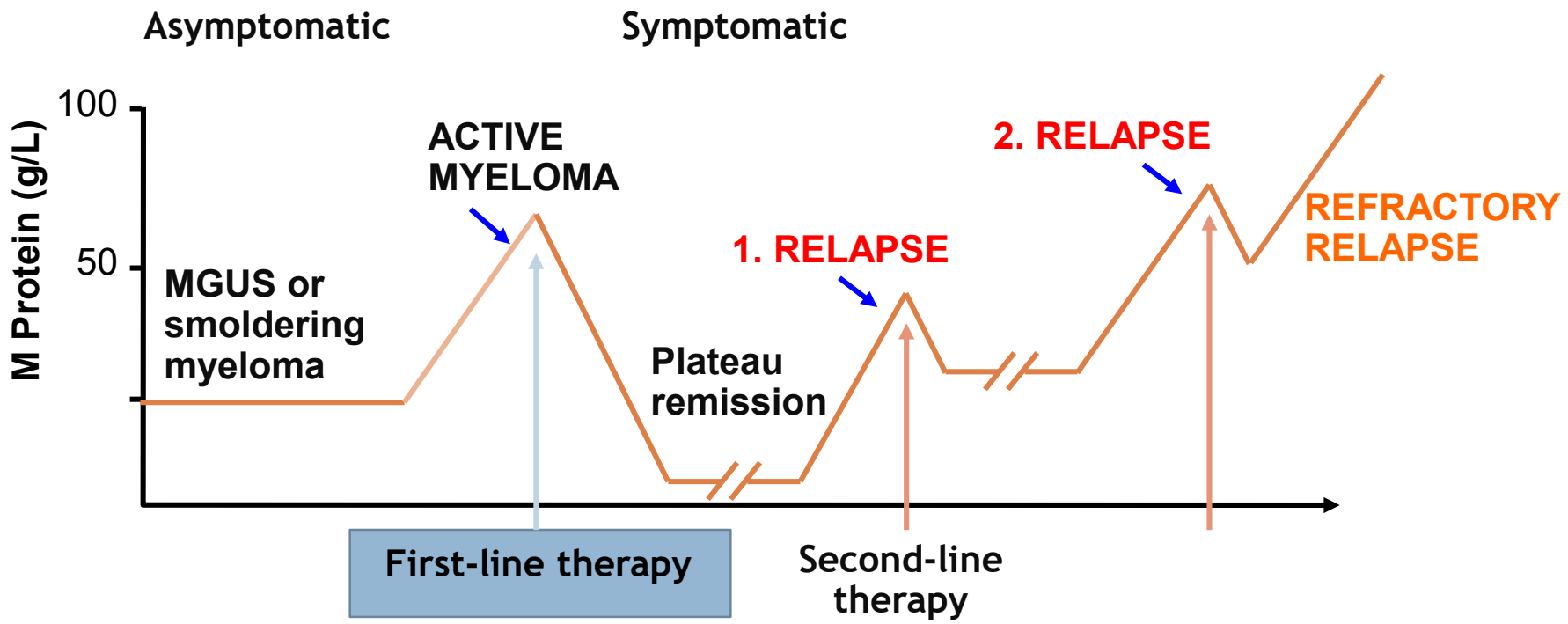
Achieving good response (≥VGPR)

High response rate; rapid response

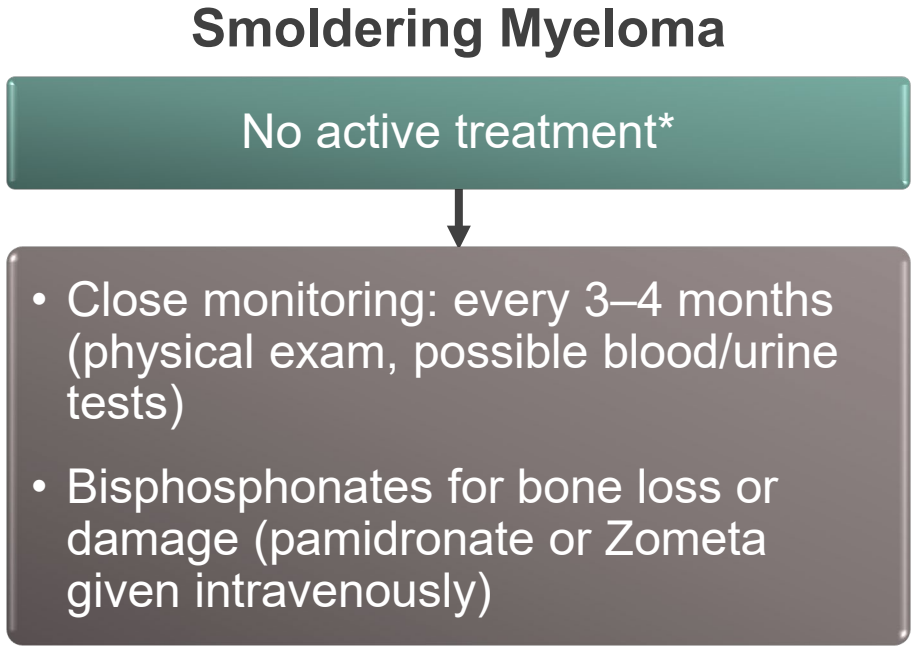
Improve performance status

Minimal side effects

Natural History of Multiple Myeloma



Current Treatment Approaches: Smoldering Myeloma



Promising but limited studies to date.

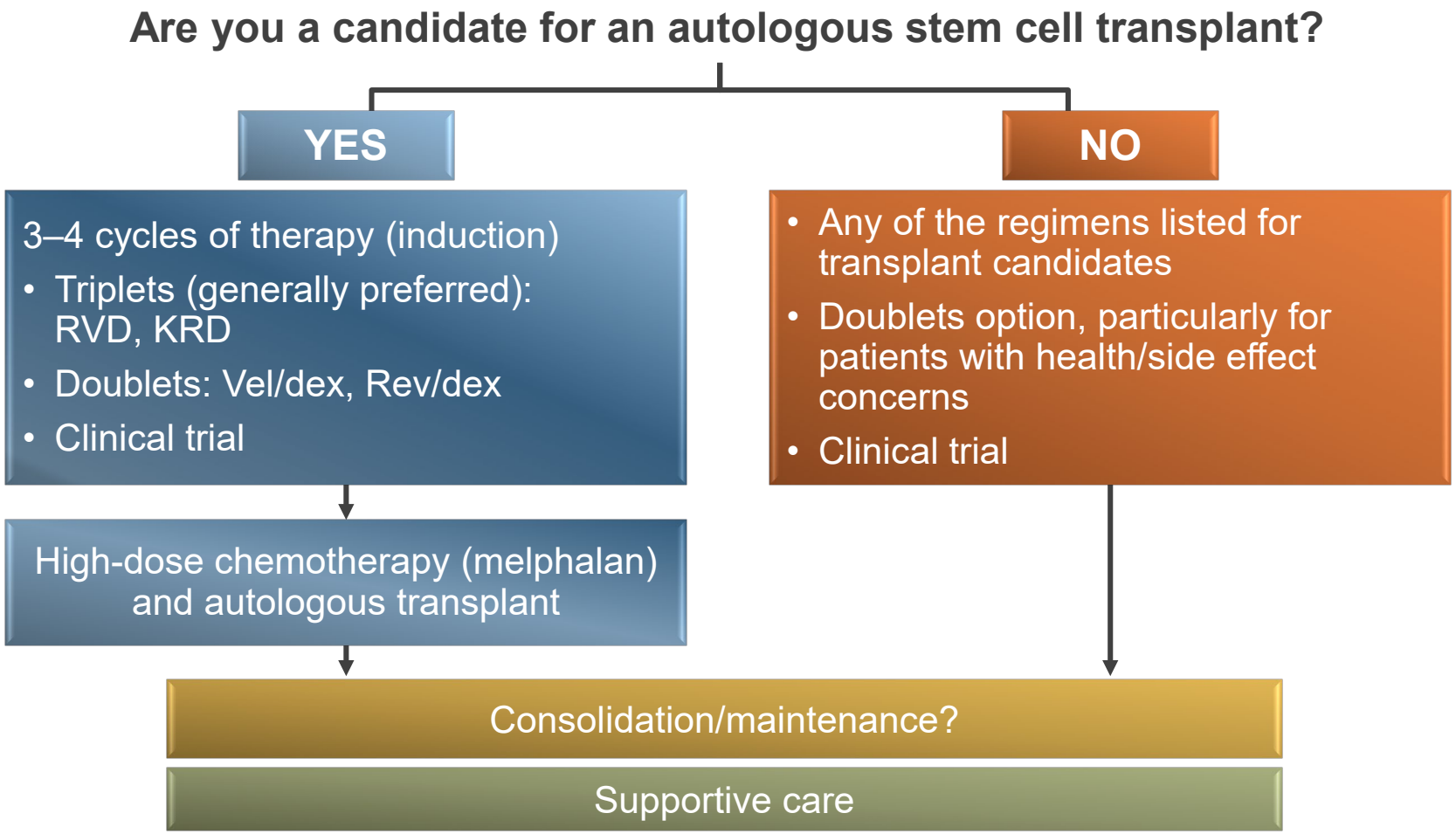
One phase 3 study of Revlimid + Dex followed by Revlimid maintenance in patients with high-risk SMM suggests a benefit; ongoing studies are under way.

Ask your doctor if you are a candidate for a clinical trial.

Frontline Therapy: Standard Drug Overview

Class	Drug Name	Abbreviation	Administration
IMiD (immunomodulatory drug)	Revlimid (lenalidomide)	R or Rev	Oral
	Thalomid (thalidomide)	T or Thal	
Proteasome inhibitor	Velcade (bortezomib)	V or Vel or B	Intravenous or subcutaneous injection (under the skin)
	Kyprolis (Carfilzomib)	K or Carf	Intravenous
Chemotherapy	Cytoxan (cyclophosphamide)	C	Oral or intravenous
	Doxil (liposomal doxorubicin)	D	
	Evomela (melphalan)	M or Mel	
Steroids	Decadron (dexamethasone)	Dex or D or d	Oral or intravenous
	Prednisone	P	

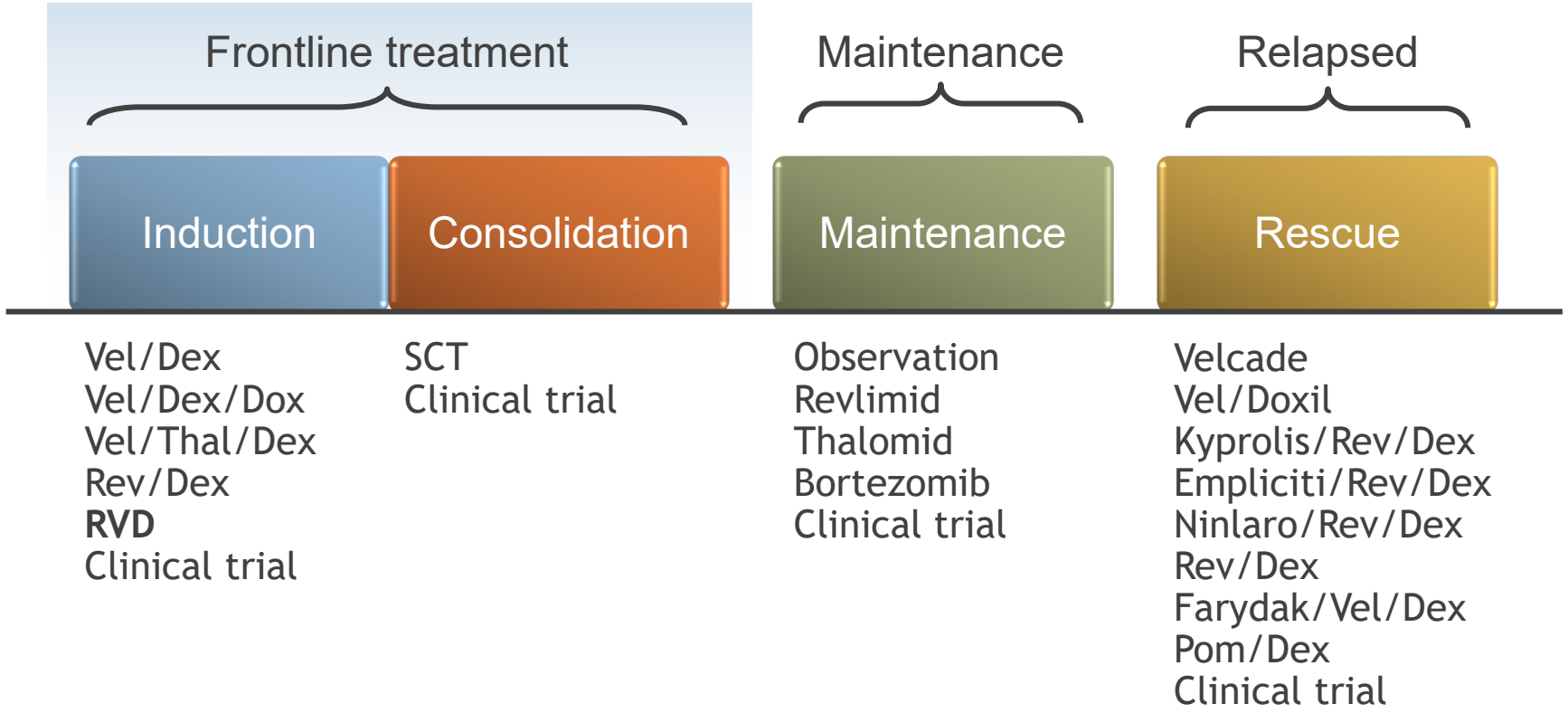
Current Treatment Approaches: Active Myeloma



For t(4;14): combination including Velcade (V) is critical.

Treatment Sequence for Active Myeloma

NCCN Category 1* Recommendations

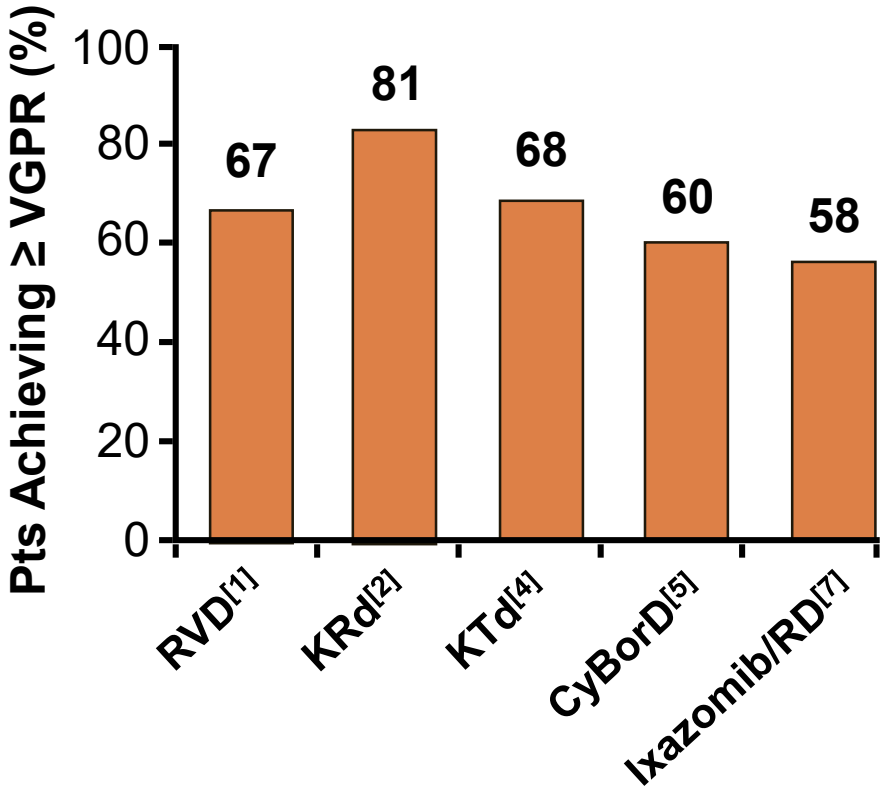


*Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

National Comprehensive Cancer Network. The NCCN Clinical Practice Guidelines in Oncology Multiple Myeloma (Version 3.2016). http://www.nccn.org/. Accessed April 12, 2016.

Induction Regimens for Transplant-Eligible Patients: 3 is Better Than 2

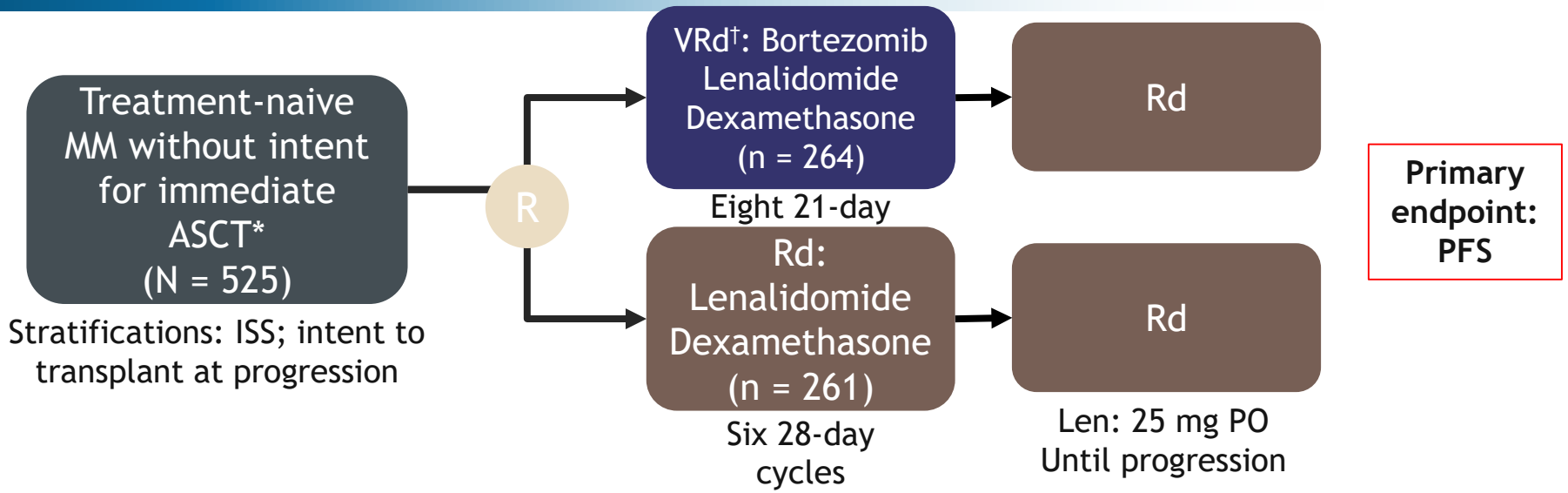
Regimens	Survival
Bortezomib/lenalidomide/ dexamethasone (RVD)[1]	18-mo PFS: 75% 18-mo OS: 97%
Carfilzomib/lenalidomide/ dexamethasone (KRd)[2,3]	12-mo PFS: 97%[2] 24-mo PFS: 92%[2] 3-yr PFS: 79%[3] 3-yr OS: 96%[3]
Carfilzomib/thalidomide/ dexamethasone (KTd)[4]	3-yr PFS: 72%
Bortezomib/ cyclophosphamide/ dexamethasone (CyBorD)[5]	5-yr PFS: 42%[6] 5-yr OS: 70%[6]
Ixazomib/lenalidomide/ dexamethasone[7]	12-mo PFS: 88% 12-mo OS: 94%



1. Richardson, PG et al. Blood. 2010;116:679-686. 2. Jakubowiak A, et al. Blood. 2012;120:1801-1809. 3. Jasielec J, et al. ASH 2013. Abstract 3220. 4. Sonneveld P, et al. Blood. 2015;125:449-456. 5. Reeder CB, et al. Blood. 2010;115:3416-3417. 6. Reeder CB, et al. ASH 2013. Abstract 3192. 7. Kumar SK, et al. Lancet Oncol. 2014;15:1503-1512.

VRd vs Rd: SWOG S0777 Data

3-Drug Regimen as Initial Induction



	VRd	Rd	HR; *P* Value
Median PFS, mo	43	30	0.712; .0018 (1-sided)
Median OS, mo	75	64	0.709; .025 (2-sided)

VRd showed better PFS in patients with high- or standard-risk vs Rd‡

- *All patients received aspirin (325 mg/d). †Patients received HSV prophylaxis. ‡High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.
- Durie BG, et al. *Lancet*. 2017;389:519-527.

Key Steps to Take on Your Journey

1. Weighing your therapy options
2. What to expect on therapy
3. Assessing your response to therapy
4. Maintenance options
5. Consider clinical trials

Revlimid in Frontline Therapy

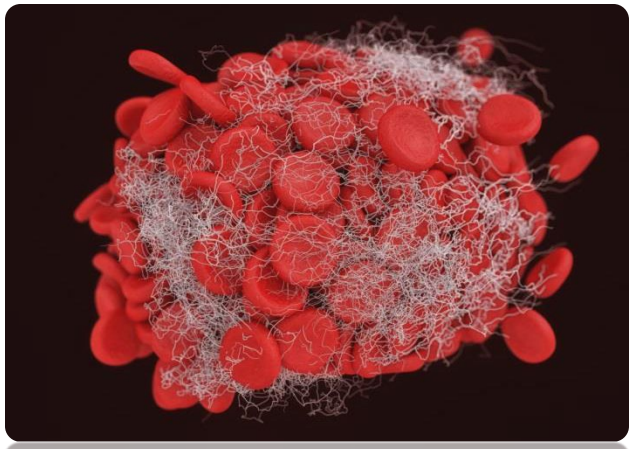
How is Revlimid administered?	• Capsule; usually taken once daily for 21 days out of a 28-day cycle (3 weeks on, 1 week off) • Blood thinners (for example, aspirin or low-molecular-weight heparin [LMWH]) are given along with Revlimid to reduce the risk of blood clots

What are the possible side effects?	• Potential for blood clots
	• Reduced blood counts
	  − Low white blood cells (neutropenia): infections
	  − Low red blood cells: anemia
	  − Low platelets (thrombocytopenia) blood clotting problems
	• Rash
	• Fatigue
	• Muscle pain (myalgia)
	• Diarrhea
	• Small chance of second new cancers when given with melphalan

Patients Taking Revlimid: Some Patients Are More Susceptible to Blood Clots

Key Risk Factors for Blood Clots

- Newly diagnosed active myeloma
- Taking other medications:
  - Chemotherapy (melphalan, cyclophosphamide, Doxil)
  - Dexamethasone
  - Red blood cell growth factors for anemia (erythropoietin)
- History of previous blood clots



Other Risk Factors

- High level of myeloma cells
- Older age
- Other medical conditions such as infections or disease of the lung or kidney
- Obesity
- Family history
- Thrombophilia, a condition where clots form easily
- Orthopedic procedures, such as hip or knee replacement
- Being immobilized (for example, confined to bed, long airplane trips)
- Presence of central venous catheter (a special catheter often used to administer cancer drugs)

What Can You Do To Prevent Blood Clots?

Risk of Blood Clots*	Medication
Low risk	Aspirin
High risk†	LMWH (for example, Lovenox)

Talk to your doctor to see what treatments are best for YOU.

*Also applies to other IMiDs (ie, Thalomid, Pomalyst).
†Patients with many risk factors may receive other drugs, including Coumadin, Xarelto, Pradaxa, or Eliquis (ongoing phase 3 clinical trial evaluating the use of Eliquis in the prevention of thromboembolic disease in patients with myeloma treated with IMiDs).

Velcade in Frontline Therapy

How is Velcade administered?

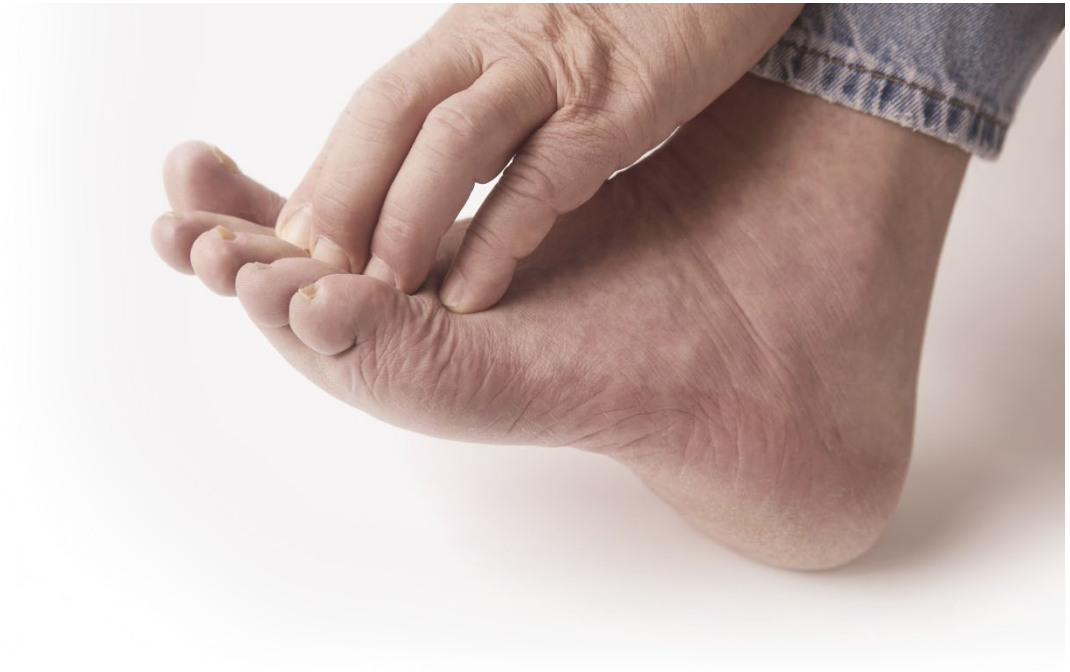
- Options:
  - Injection under the skin (subcutaneous), once or twice weekly
  - Intravenous once or twice weekly – NO MORE!

What are the possible side effects?

- Peripheral neuropathy (numbness, tingling, burning sensations and/or pain due to nerve damage)
  - Occurs less often when subcutaneous or once weekly dosing is used
- Low platelets (thrombocytopenia): blood clotting problems
- Gastrointestinal problems: nausea, diarrhea, vomiting, loss of appetite
- Fatigue
- Rash

Understanding Peripheral Neuropathy

- Peripheral neuropathy is nerve damage that causes pain, tingling, burning sensations, and numbness in the hands and feet
  - Typically improves or resolves after treatment dose is reduced or treatment is stopped
- Risk of peripheral neuropathy varies
  - Greater risk if you have pre-existing neuropathy
  - Velcade dose and type of administration



Be sure to discuss the benefits and risks of taking Velcade with your doctor if you have severe pre-existing neuropathy.

Managing Peripheral Neuropathy

- Managed by reducing the Velcade dose (with no impact on effectiveness)
- Other possible ways to prevent or reduce symptoms (less proven):
  - Vitamins and other supplements*
  - Certain medications such as gabapentin (Neurontin)

Your health care team will check for peripheral neuropathy before treatment and prior to each dose of Velcade.

Be sure to tell your health care team about any symptoms you experience.

*Do not take any supplements without consulting with your doctor.

Measuring Response to Therapy

Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a complete response

Standard Tests to Measure Response

- Blood and urine tests: M-protein, free-light chains
  - Electrophoresis: M-protein levels
  - Immunofixation: sensitive test that measures type of M-protein
  - Freelite™: free light chains
- Bone marrow: plasma cells (antibody producing cells)

Frequency of Testing

- Patients on active treatment
  - Blood/urine tests: monthly
  - Bone marrow: best response, relapse
- Not on active treatment: blood/urine tests every 3-6 months

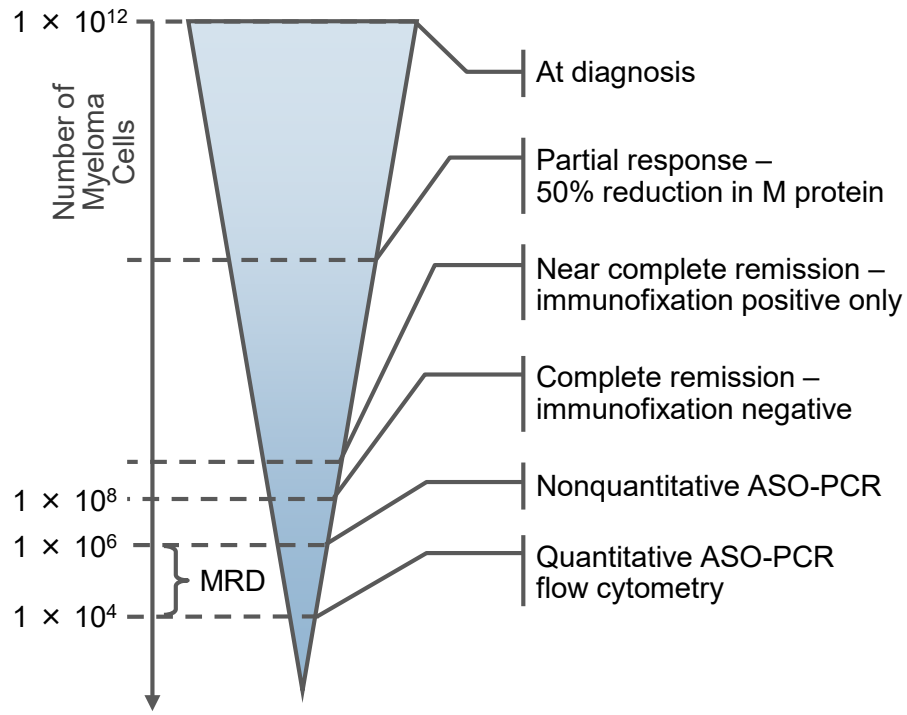
Measuring Response to Therapy

Response Type	M Protein	Plasma Cells in Bone Marrow/	Other
Stringent complete response (sCR)	None (blood/urine)	No abnormal plasma cells	No free light chains
Complete response (CR)	None (blood/urine)	Less than 5%	Disappearance of soft tissue plasmacytomas*
Very good partial response (VGPR)	Greater than 90% reduction (blood)	NA	NA
Partial response (PR)	Greater than 50% reduction in blood + Greater than 90% reduction in urine	NA	Greater 50% reduction in the size of soft tissue plasmacytomas
Minimal response (MR):	25%-49% reduction in blood and reduction of 50%-89% in urine	NA	25%-49% reduction in the size of soft tissue plasmacytomas and no increase in size/ number of bone lesions
Stable disease (SD)	Does not meet criteria for response or progressive disease		
Progressive disease (PD)	Greater than 25% increase (blood or urine)	Greater than 10%	Other changes: bone lesions, soft tissue plasmacytomas, high calcium levels

*Soft tissue plasmacytomas: collection of plasma cells outside the bone

Testing for Minimal Residual Disease (MRD): An Emerging Approach

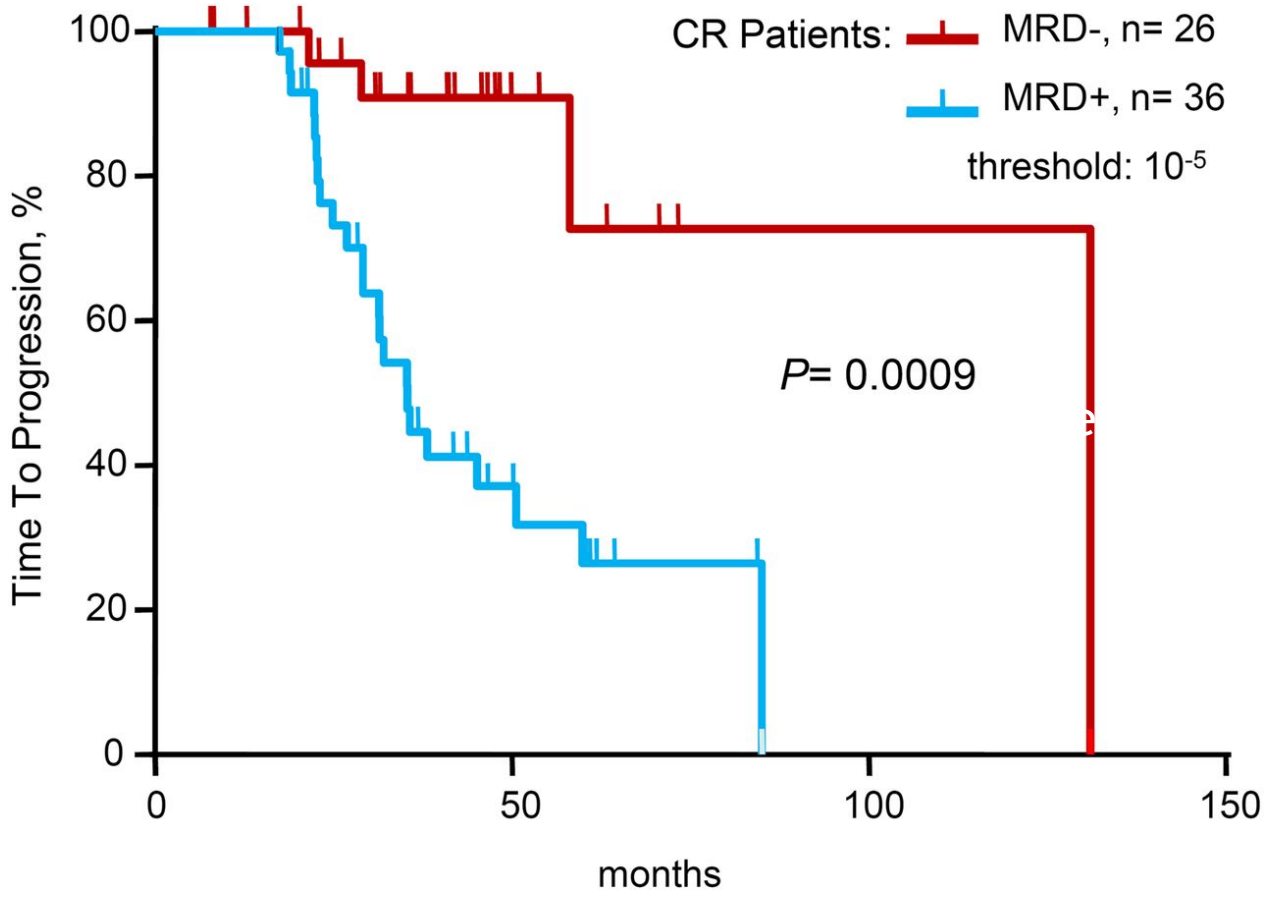
- Small amounts of myeloma cells despite CR (as measured by standard tests)
- Patients who are MRD negative may have better outcomes
- More-sensitive tests/newer technologies to detect and monitor MRD are now available
  - Flow cytometry
  - Molecular tests
    - Polymerase chain reaction (PCR)
    - Sequenta ClonoSIGHT*: novel, highly sensitive test
- New response types incorporating use of new technologies
  - Immunophenotypic CR
  - Molecular CR



Talk to your doctor about types of tests available in your area.

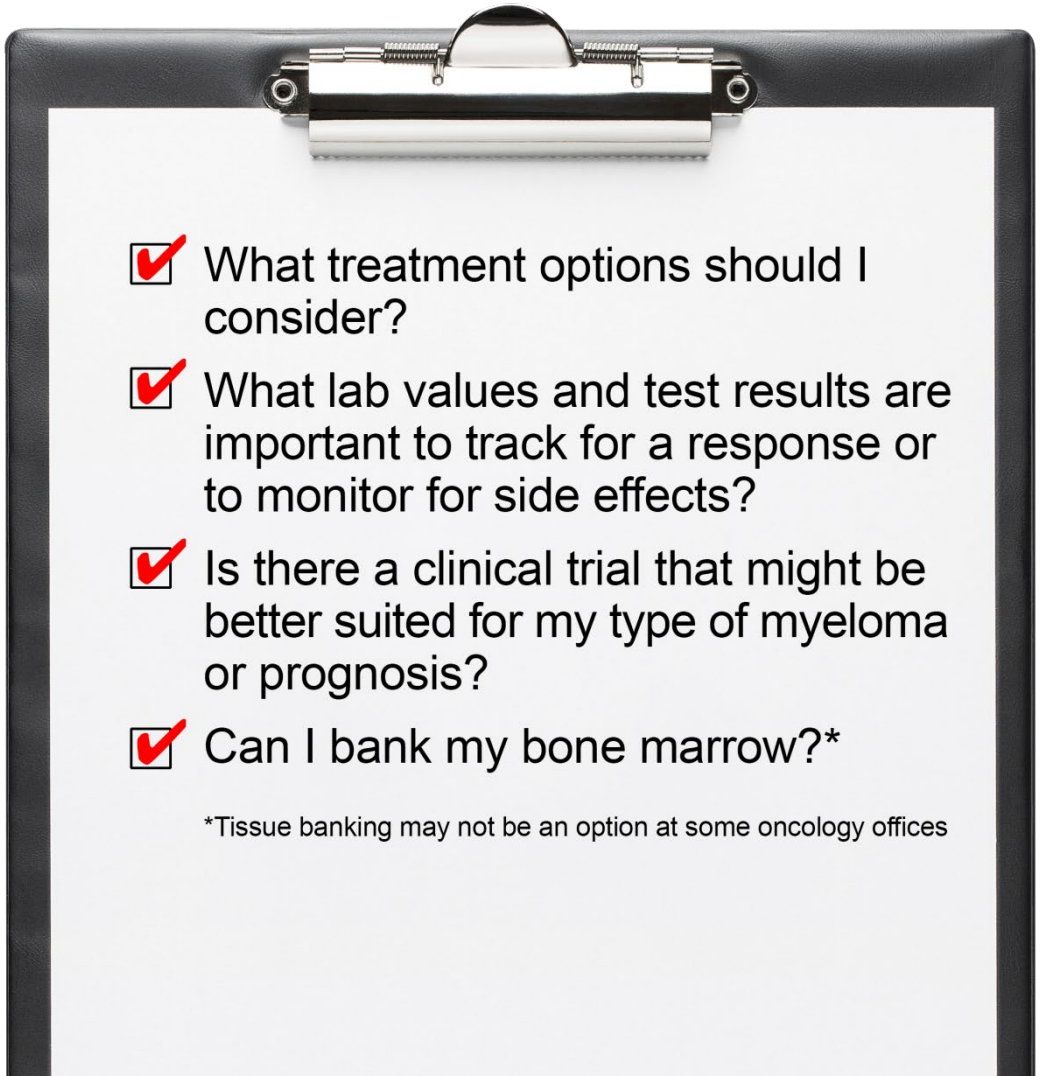
*The Multiple Myeloma Research Foundation is using the Sequenta ClonoSIGHT test in the CoMMpass research study.

Time to Progression for Patients in Conventional CR who are either MRD Positive or Negative by Deep Sequencing



Martinez-Lopez J et al. Blood 2014;123:3073-3079

When Considering a Treatment Regimen, Find Out From Your Doctor…



Conclusion: Example Patient Case

- Dr. Myeloma determines that the patient is an excellent transplant candidate
- RVd is given for 5 cycles, and the patient achieves a CR. The patient has mild fatigue and calf cramps which are relieved by hydration and electrolyte repletion.
- The patient undergoes autologous stem cell transplant followed by low-dose Revlimid maintenance for 2 years.
- Three years later, the patient remains in a CR, with active surveillance of her myeloma labs every 3 months

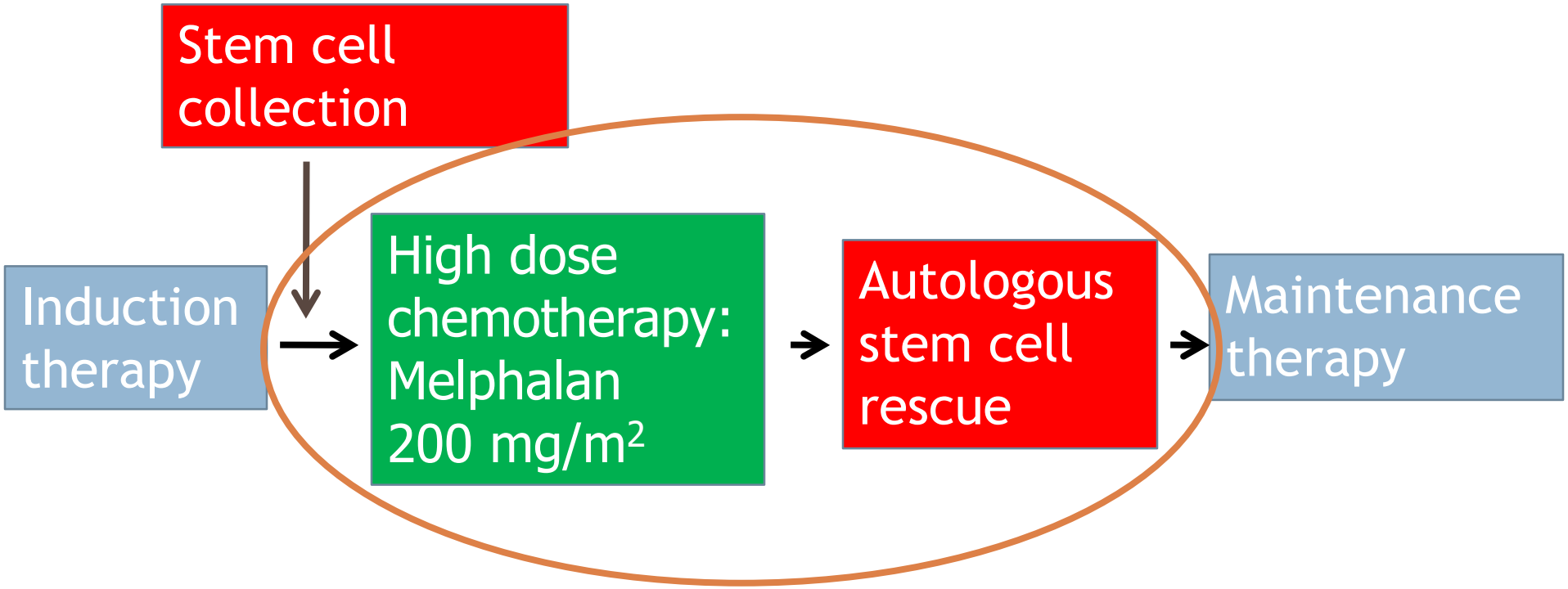
Summary:
Treating Newly Diagnosed Patients

- Smoldering multiple myeloma (SMM):
  - Close monitoring plus bisphosphonates for bone loss
  - Potential for treatment for high-risk patients; clinical trials ongoing
- Symptomatic (active) myeloma:
  - Combination therapies including Revlimid and/or Velcade, along with other drugs (triplets or doublets)
  - Autologous stem cell transplant
  - Maintenance
- Side effects of therapy can be managed
- Research to improve up-front outcomes is ongoing

Partner with your health care team to select the treatment plan that is right for you.

TRANSPLANT??

Treatment Schema for Myeloma



High-Dose Chemotherapy and Stem Cell Transplantation

- Offers best chance for durable remission based on current data
  - Outcomes improving with the use of newer drugs prior to transplantation
  - New trials comparing novel drugs vs transplant
- Can be done as part of frontline therapy or at relapse (or both)
- More patients considered candidates than in the past
  - Based on overall health and age
  - Criteria varies by cancer center
  - Talk to your doctor to see if you qualify

High-Dose Chemotherapy and Stem Cell Transplantation

- NEJM 2017, IFM2009 study: Auto-SCT improves PFS (versus continued chemotherapy)[1] – 50 months vs 36 months
  - Increased likelihood of MRD negativity with ASCT
  - No difference in how long you'll live – TOO SOON?!

- 2014 Italian study: Auto-SCT improves PFS and OS[2]

- American study is in progress

1. Attal, NEJM 2017
2. Palumbo et al, NEJM 2014

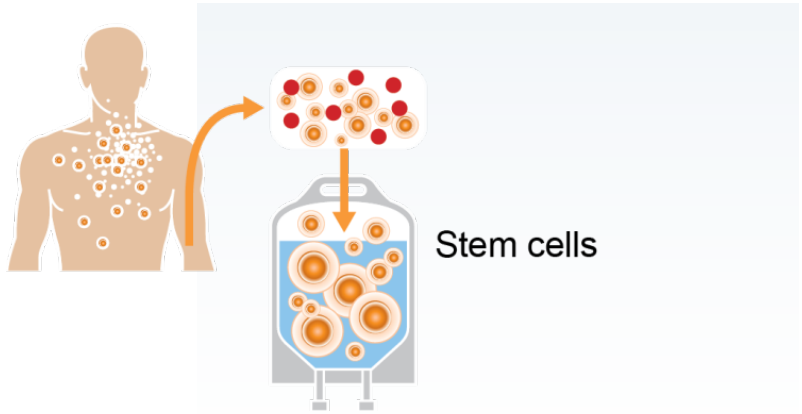
Types of Stem Cell Transplantation

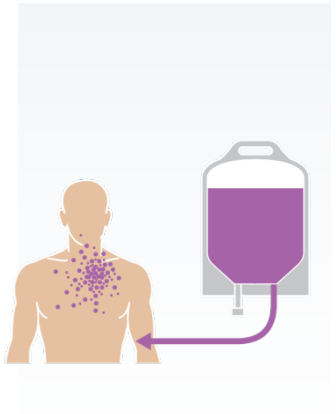
Transplant Type	Stem Cell Source	Transplant Process

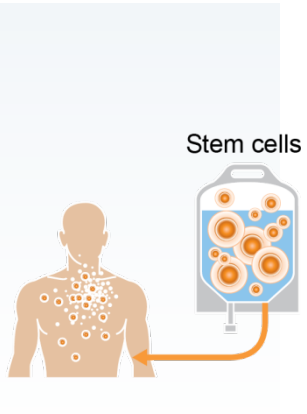
• Autologous*
  – Your own cells
• Allogeneic
  – A donor's cells (requires a match)
	• Peripheral blood	• Mini-allo
		• Tandem
		• Single autologous

*Most common

Overview: ASCT







Induction therapy

~4–6 cycles

Collection of stem cells from the bloodstream

Stem cell mobilization

- Neupogen
- Neulasta
- Leukine
- Cytoxan
- Mozobil

Freezing of stem cells

High-dose chemotherapy

- Evomela (melphalan)

Thawing and infusion of stem cells

“Should I get a transplant?”

“Should I get a transplant?”

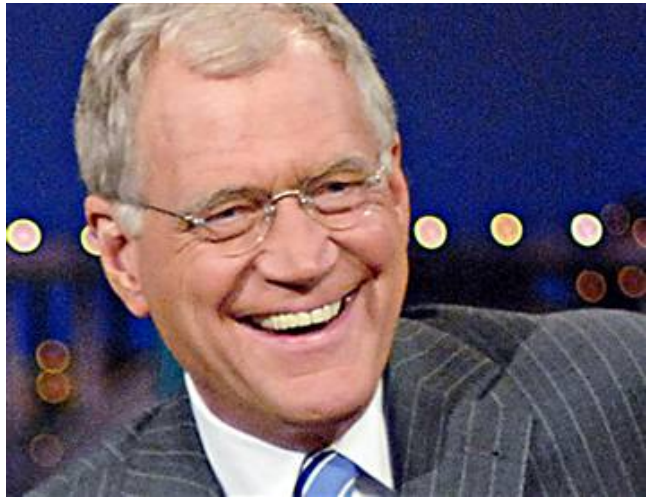
Questions To Ask Your Doctor

- Am I a candidate for high-dose chemotherapy and stem cell transplantation?
- What are the pros and cons of stem cell transplantation in my case?
- When is the best time for me to undergo transplantation?
- Does your center do stem cell transplants? How many transplants has your center performed in multiple myeloma in the last year? Is procedure performed as an inpatient or outpatient?
- How long will I be in the hospital?
- What is the recovery period?
- What kind of changes in my lifestyle will I need to make?
- When do I go back to you for follow-up?

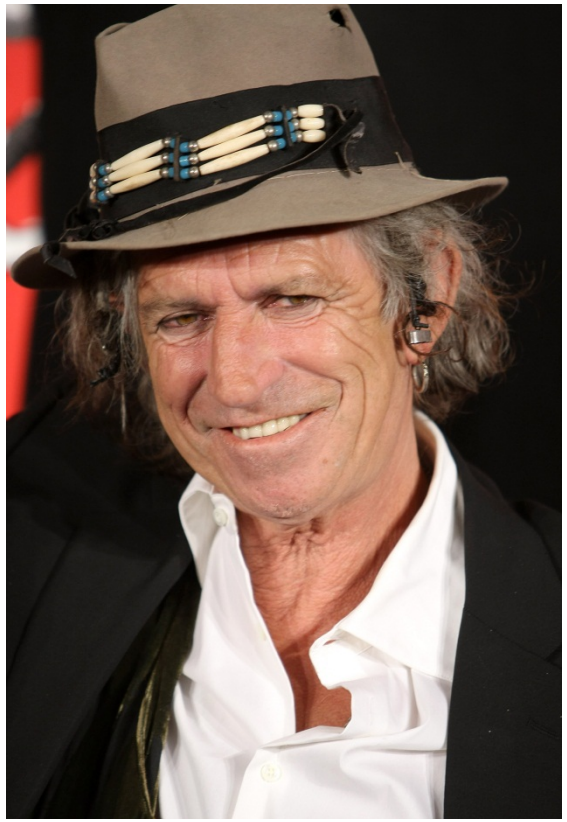
Example transplant schedule

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
	1	2	3	4	5 GCSF	6 GCSF
7 GCSF	8 GCSF	9 collection	10 collection	11 collection	12	13
14	15	16	17 melphalan	18	19 Stem cell infusion	20
21	22	23	24	25	26	27
28	29 egraftment	30	May 1	2	3	4
5	6 Discharge (if in patient)	7	8	9	10 Release to clinic	11

OK but am I too old to get a transplant ??



"60 is the new 50!"



"70 is the new 60!"

Data for older patients

- CIBMTR Analysis of Trends in MM-SCT[1]
  - 1995-1999; 200-2004; 2005-2009
  - More people are being referred to SCT
  - But still not same proportion of older patients as younger patients
- However, age alone does not appear to predict poor outcome from process of SCT
  - No difference in death, TRM, PFS and OS for patients < or > 60[2]
  - Patients ≥ 70 undergoing SCT have similar response and OS compared with younger patients[3]
  - Patients even up to age 80 can undergo SCT safely[4]

1. Costa et al, ASH abstract 596, 2012
2. Reece et al, BMT 2003
3. Kumr et al, Am J Hematol, 2008
4. Bashir et al, Leuk Lymphoma, 2012

Summary: High-Dose Chemotherapy and Stem Cell Transplantation

- Offers best chance for long-term remission for eligible patients based on current data
- Research questions:
  - Given the availability of the novel agents, what is the role of high-dose chemotherapy and stem cell transplantation?
  - Which patients achieve the greatest benefit?
  - When is the best time to undergo transplantation?
  - What is the role of maintenance therapy? How long should patients remain on maintenance therapy?

Thank you !