

WELCOME AND INTRODUCTION



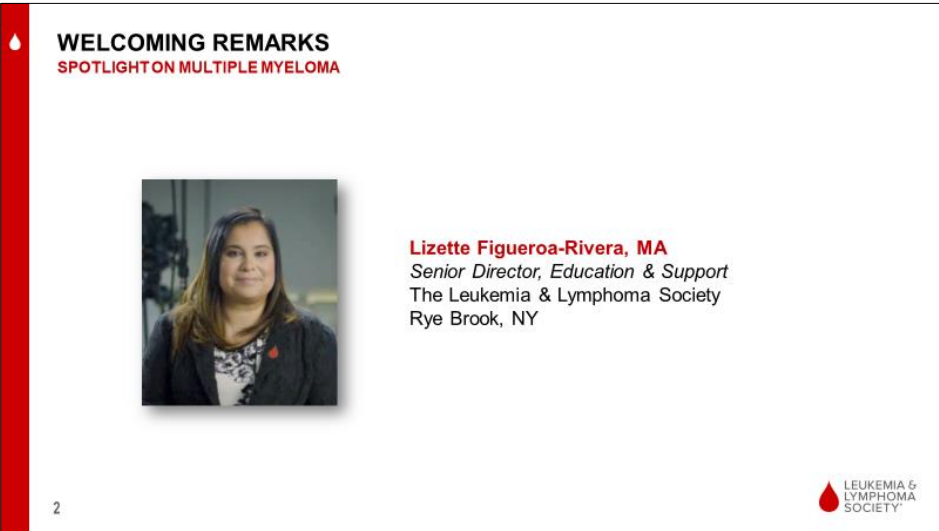
The graphic features a white background with a faint hexagonal molecular structure pattern. On the left, there are three overlapping hexagonal images: a scientist in a lab coat and mask, a young girl smiling, and a man in a blue shirt. The Leukemia & Lymphoma Society logo is in the top right corner. The text 'SPOTLIGHT ON MULTIPLE MYELOMA' is prominently displayed in the center-right.

**SPOTLIGHT ON
MULTIPLE MYELOMA**

Craig Emmitt Cole, MD
*Assistant Professor, Division of Hematology and Oncology
Michigan State University College of Human Medicine
Karmanos Cancer Institute at McLaren Greater Lansing
Lansing, MI*

Lizette Figueroa-Rivera, MA

Hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you and special thanks to Dr. Craig Emmitt Cole for volunteering his time and expertise with us today.




The graphic has a white background with a faint hexagonal molecular structure pattern. On the left, there is a portrait of Lizette Figueroa-Rivera. The text 'WELCOMING REMARKS' and 'SPOTLIGHT ON MULTIPLE MYELOMA' is in the top left. The Leukemia & Lymphoma Society logo is in the bottom right corner. The number '2' is in the bottom left corner.

WELCOMING REMARKS
SPOTLIGHT ON MULTIPLE MYELOMA

Lizette Figueroa-Rivera, MA
*Senior Director, Education & Support
The Leukemia & Lymphoma Society
Rye Brook, NY*




2


 LEUKEMIA &
LYMPHOMA
SOCIETY®

We have over 2,300 people participating in today's program from across the United States as well as other countries, including Australia, Canada, Columbia, Iraq, Ireland, Kuwait, Nigeria, and the Philippines.

WELCOMING REMARKS
SPOTLIGHT ON MULTIPLE MYELOMA


This program is supported by

4 


We would like to acknowledge and thank Bristol Myers Squibb, GSK, and Karyopharm Therapeutics for their support for today's program. Thank you for joining us for this important update on multiple myeloma.

WELCOMING REMARKS
SPOTLIGHT ON MULTIPLE MYELOMA



[LLS.org/EducationVideos](https://www.lls.org/educationvideos)

Gregory O. Proctor
Myeloma Patient
Honored Hero, Visionaries of The Year San Antonio
Executive Leadership Team, Light The Night San Antonio
The Bloodline with LLS, Podcast Guest
Making Good Food Choices, Recipes for Health Series, LLS Video Series

3 

Before we begin, Gregory O. Proctor, a myeloma patient as well as an LLS volunteer, will make some remarks.

Gregory O. Proctor

Hello, my name is Gregory O. Proctor, and I'd like to extend a warm welcome to all the patients, caregivers, and healthcare professionals for attending today's program.

In 2021, my battle with multiple myeloma started. I first felt lower back pain while recording an episode of my audio podcast called *Cut to the Chase*. I could not move when I woke up the following morning and immediately realized this was a critical situation because of the severity of the pain.

Somehow, I climbed out of the bed, slipped on a pair of sweats, and went down the stairs to hop into our vehicle. After getting into the spine manager specialist's office, he quickly scheduled me for two MRIs (magnetic resonance imaging), which led to me being referred to an oncologist. Both my wife and I terrified out of our minds after finding an oncologist, she quickly ordered several tests, including a bone marrow biopsy, I would learn the heartbreaking news that I had multiple myeloma, and that chemotherapy would shortly begin because I had been identified as a high-risk patient. That day we left the oncologist's office in shock. Went home crying. We were utterly taken back, overpowered and distressed on the inside, not knowing what to do or what to anticipate or how to plan for what was yet to come. When you hear the words cancer, everything else is muted in your conscious.

I underwent five days a week of chemotherapy for the next few months before acquiring remission in October of 2021. I had a stem cell transplant in February of '22. Although it's only been a year since my SCT, I am thankful that I am doing much better. As of right now, I've been MRD (minimal/measurable residual disease) negative since October of 2021, and I've been in remission for over 1.3 years. I appreciate the physicians, my family and friends who helped me survive.


The Leukemia & Lymphoma Society has also helped with their Copay Assistance Program and providing crucial educational support for which I am grateful. I'm now devoting my time to assisting others and inspiring them. I give my time to LLS in several ways, including as their Visionary of the Year Adult Honored Hero and as a member of the Executive Leadership Team for Light The Night. I have also appeared on some LLS PearlPoint Nutrition episodes, which aims to provide free nutrition education and consultation services to patients and caretakers of all cancer types.

I want you to remember cancer cannot cripple love, shatter hope, conquer your spirits. Don't give up if you are a cancer patient. Thank you very much.

Lizette Figueroa-Rivera, MA


And thank you, Gregory, for sharing your story with us, and we really look forward to learning more about your journey through your new book that will be coming out soon.

PRESENTATION




The slide features a red vertical bar on the left side with a small white drop icon at the top. The text 'PRESENTATION' is in bold black, and 'SPOTLIGHT ON MULTIPLE MYELOMA' is in red. A portrait of Dr. Craig Emmitt Cole, MD, is shown on the left. To the right of the portrait is his name and title in red, followed by his affiliation in black. The Leukemia & Lymphoma Society logo is in the bottom right corner, and the number '5' is in the bottom left corner.

PRESENTATION
SPOTLIGHT ON MULTIPLE MYELOMA



Craig Emmitt Cole, MD
Assistant Professor, Division of Hematology and Oncology
Michigan State University College of Human Medicine
Karmanos Cancer Institute at McLaren Greater Lansing
Lansing, MI

5



Lizette Figueroa-Rivera, MA

I'm now pleased to introduce Dr. Craig Emmitt Cole, Assistant Professor in the Division of Hematology and Oncology, Michigan State University College of Human Medicine and Karmanos Cancer Institute at McLaren Greater Lansing in Lansing, Michigan.

Dr. Cole, I'm now privileged to turn the program over to you.

Craig Emmitt Cole, MD

Thank you so much and thank you to the LLS for inviting me. I've been working with the LLS, gosh, for over 10 years, and the incredible work that they have done to bring patients and providers, and everyone forward to conquer this disease has just been amazing. So, it's a true honor for me.

DISCLOSURES

SPOTLIGHT ON MULTIPLE MYELOMA

Craig Emmitt Cole, MD

- Consultation and Speaking: Sanofi
- Consultation and Speaking: Abbvie
- Consultation and Speaking: Pfizer
- Consultation: Genentech
- Research Support: GlaxoSmithKline

6

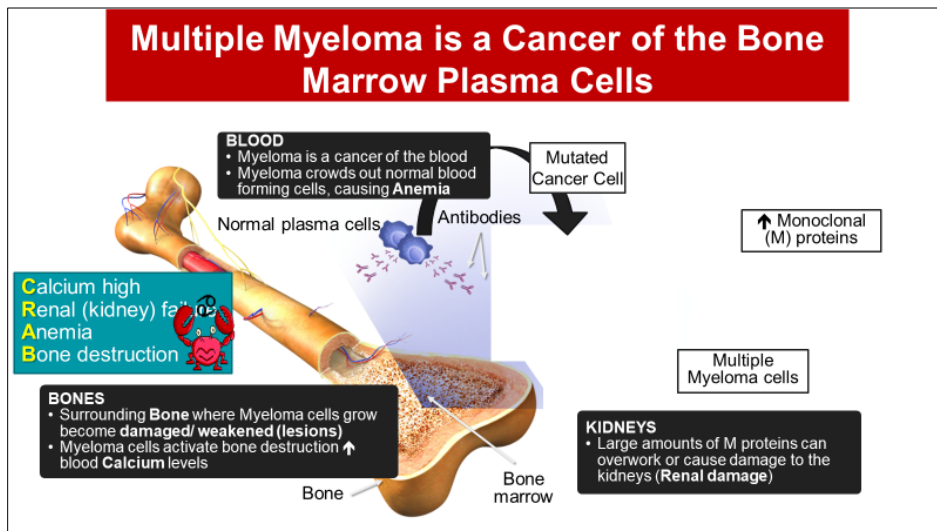


And here are some of my disclosures.

Today's Discussion

- Multiple Myeloma -101
- How to treat myeloma using new therapies
 - Newly diagnosed myeloma
 - Tools of the trade
 - Side effect management
 - Relapsed Refractory MM
 - CAR T-cell therapy for myeloma
 - Bi-specific antibodies
- Patient empowerment: how to communicate with your doctor
- Questions

And what we're going to talk about today is for some of the new patients, we'll talk about myeloma 101, how we treat myeloma with new therapies, including discussion about newly diagnosed myeloma, the tools of the trade and side effect management. Then we'll talk about relapsed/refractory myeloma and all the incredible things that are happening in the relapsed arena, including defining what relapsed is, talking about CAR T (chimeric antigen receptor T cell) and all the bispecifics. Then we'll talk about how to communicate to your doctor and then we'll hit some questions.

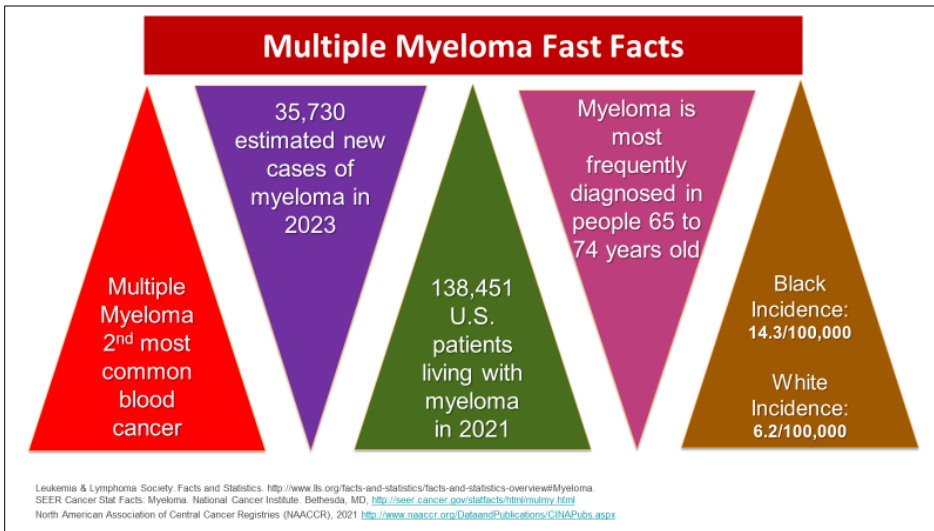


So, myeloma is a cancer of the plasma cells, and plasma cells produce antibodies to help us fight infection. When those cells become mutated, when the plasma cells become mutated, those are myeloma cells, so they're no longer part of the immune system. And they also produce antibodies, but those antibodies are nonfunctional. We call it monoclonal proteins.

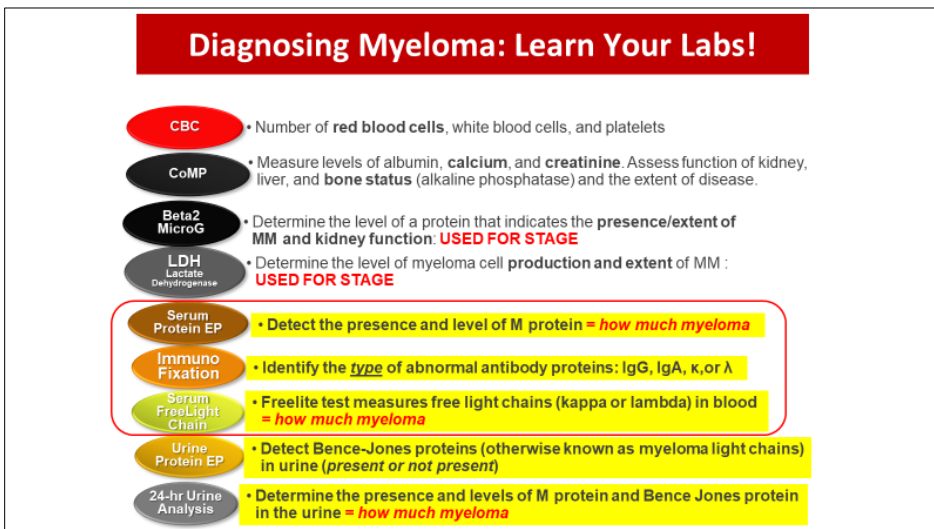
Myeloma is a cancer of the blood, and it crowds out the normal blood-producing organ, which is the bone marrow which causes anemia. Those plasma cells not only squeeze out those bone marrow cells but they also hijack the cells which dissolve bone to release calcium. And that dissolving bone cells cause the bones to weaken and cause lytic lesions and can raise the blood calcium level to dangerous levels.

Then, finally, those myeloma cells, you know, those protein-producing factories can produce large amount of M protein and light chains, we'll talk about in a second, which can overwork the kidneys, get stuck in the kidneys, the bodies' filter, and cause kidney damage.

And that brings us to the mnemonic of the signs and symptoms of myeloma, the CRAB (calcium, renal insufficiency, anemia, and bone disease) criteria. We'll talk about how we use that to diagnose myeloma.



So, some fast facts. Myeloma is the second most common blood cancer behind the lymphomas, the lymph node cancers. This year we predict about 35,000 people will be diagnosed with the disease and about 138,000 people are living with it, which is double the number from about 15, 20 years ago. It's a cancer of adults. It's usually diagnosed between the ages of 65 and 75. And interesting enough, it is a higher incidence of people of African descent. Not just African Americans but people of African descent have double the incidence of myeloma compared to people of European descent. And despite a lot of research that we've done to try and figure that out, we still haven't unlocked the key to why people of African descent have a higher incidence of multiple myeloma.



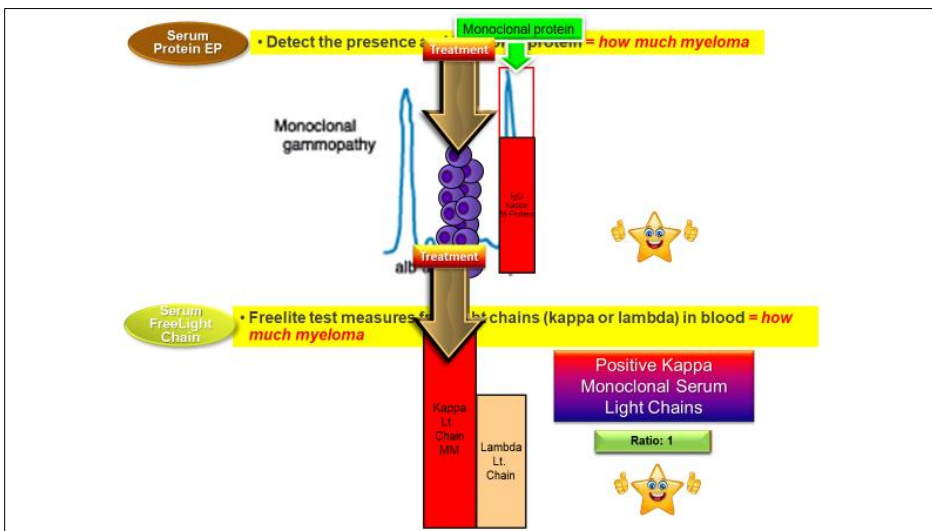
So, the labs. The CBC (complete blood count) is the main test that we do to help us diagnose myeloma by checking for anemia and the other blood counts as well as following patients when they're on therapy.

The comprehensive panel is a test to help us measure the calcium, the kidney function or creatinine and assess the bone status by looking at the alkaline phosphates test. And it's really important to note these labs. It empowers you to know them so you can have a conversation with your doctor about anemia or high calcium or kidney function problems.

The beta-2 microglobulin and the LDH (lactate dehydrogenase) are two tests that we use to stage myeloma, so they're usually used just once at the time of diagnosis for staging. The beta-2 microglobulin's this little protein that's on top of plasma cells that shed into the bloodstream and gives you another idea of how many plasma cells there are, and the LDH is a chemical that's released when cells are dividing quickly, and it gives an idea of the production or how many myeloma cells are reproducing at any particular time.

The main test to tell us about how much myeloma, and we use to follow it, the serum protein electrophoresis (SPEP), which tells us how much myeloma protein there is; the immunofixation, which tells us the type of protein; and the serum-free light chains because about a third of myeloma patients will only produce free light chains and not produce whole antibodies so use a free light chain assay to tell us how much myeloma those patients have.

We don't really use the urine protein electrophoresis or the 24-hour urine anymore because they're just bulky tests to use. Usually those are the big three, the SPEP, immunofixation and the free light chain assay.




So, the serum protein electrophoresis (SPEP) tell us how much myeloma. If you break down the blood serum into different components, you'll see that there are different amounts of different proteins, including in the gamma region, that very end region, is a broad region and that's where all the antibodies hang out. When patients have myeloma and those plasma cells are producing only one type of antibody, they all stack up on top of each other. And that is a monoclonal protein or M protein and that gives us a reasonable idea of how many plasma cells there are. So, instead of doing bone marrow biopsies every month on a patient, we can test the SPEP, and it tells us how much protein there is.

In the same breath with treatment, it reduces the number of cancer cells down and the M protein goes down. So, it tells us an idea of when to celebrate. Tells us how many plasma cells have been reduced by therapy.

Again, some patients only produce light chains, and we normally produce small amounts of kappa or lambda light chain in our blood, so it's normal to have small amounts. And the ratio between the two is about 1:1. However, if someone has multiple myeloma, for instance kappa light chain myeloma, the kappa will be high, and the lambda will be low. If they have lambda light chain myeloma, it'll be just the opposite. And, again, that gives us an idea of how many plasma cells are produced in that kappa light chain. And through treatment, the kappa light chain will go down, the lambda light chain will come up and the ratio returns to normal. This gives us an idea, again, of when to celebrate when someone has a good response to therapy.

Diagnosis of Multiple Myeloma

- Conventional X-rays reveal punched-out lytic lesions, osteoporosis, or fractures in 75% of patients.
- FDG PET/CT appears to be more sensitive (85%) than skeletal survey for the detection of small lytic bone lesions.
- **Diagnosis is confirmed with bone marrow demonstrating greater than 10% involvement by malignant plasma cells with either CRAB or SLiM**



Malignant Plasma cells seen on biopsy
AND ≥1 "CRAB" feature

C: Calcium elevation (>11 mg/dL)
R: Renal- low kidney function; (serum creatinine >2 mg/dL)
A: Anemia -low red blood count (Hb <10 g/dL)
B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET-CT)

OR have ≥1 SLiM "high risk" features:

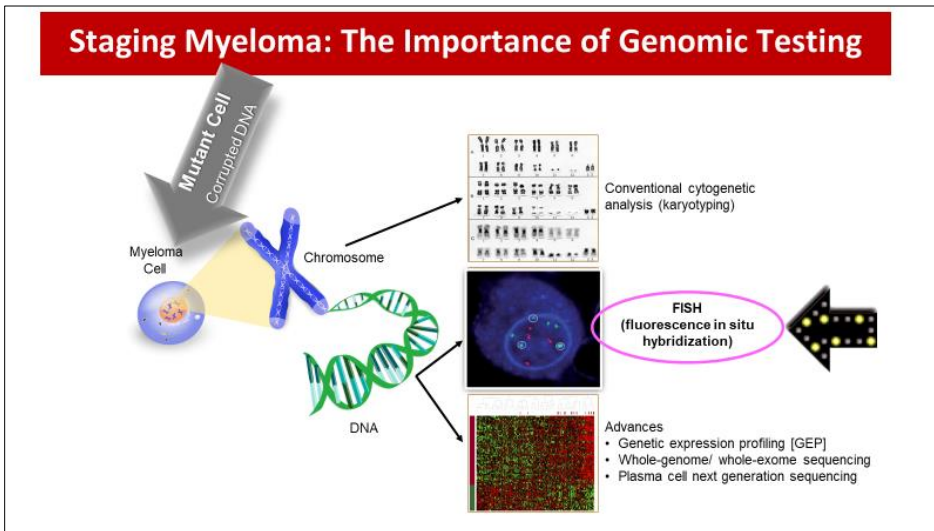
S: >60% Plasma Cells on Bone Marrow biopsy
Li: Serum light chain ratio >100
M: >1 lytic lesions on MRI (or PET/ CT scan)

About 10% to 20% of patients with newly diagnosed myeloma will not have any symptoms.

Kjell RA et al. Mayo Clin Proc. Jan;70(1): 2003. Nanni C et al. European Journal of Nuclear Medicine and Molecular Imaging Vol. 33:2006 Dimopoulos MA, et al. Leukemia. 2009

The diagnosis of myeloma, they used to use x-rays to pick up the lytic lesions or the holes in the bones. And they still use that test occasionally but now the PET (positron emission tomography) scan is a really powerful test and about 85% more sensitive of picking the lytic lesions than the skeletal survey and really is our main way of telling of the B in the CRAB (calcium, renal insufficiency, anemia and bone disease) about lytic bone disease. The diagnosis is confirmed when we do a bone marrow biopsy and find more than 10% plasma cells in the bone marrow and the normal amount of plasma cells is 1%. So, if you have the CRAB criteria plus 10% in the bone marrow, you make the diagnosis myeloma.

In 2014, we found that if patients have greater than 60% plasma cells in their marrow or if they have a free light chain ratio greater than 100, or if they have more than one lytic lesion on sensitive skin, those patients are imminently at risk of developing CRAB symptoms, so now we treat patients with the SLiM (Sixty % plasma cells, Light chains, and MRI lesions) criteria. But about 10% to 20% of myeloma patients won't have any symptoms at all and we use that SLiM criteria or sometimes we call those patients smoldering myeloma.



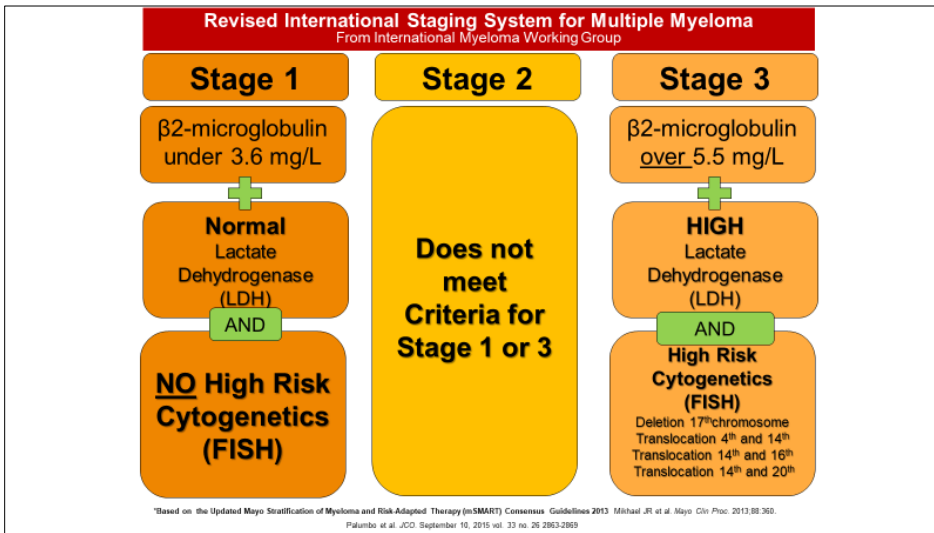
After we've done that bone marrow biopsy, one of the important tests is to see what mutations caused the myeloma in the first place. The main test that we use to detect the mutations is a FISH (fluorescence in situ hybridization) analysis. It's got the arrow pointing the wrong way, that's technology. *(Please note: the arrow is pointing in the correct direction above.)* But the FISH test tells us what mutations occurred in the bone marrow.

| Staging Myeloma: FISH Testing helps to Assign Risk in Myeloma | | |
|--|---|---|
| Risk Category | High Risk | Standard Risk |
| Findings on Chromosome (FISH) Analysis Results in the Bone marrow | <p>FISH:</p> <ul style="list-style-type: none"> • Deletion 17th chromosome • Gain of chromosome 1q • Translocation 4 and 14 • Translocation 14 and 16 • Translocation 14 and 20 <p>NGS: p53 mutation (on chrom 17)</p> <ul style="list-style-type: none"> • Double Hit Myeloma: 2 high risk genetic abnormalities • Triple Hit Myeloma: 3 or more high risk genetic abnormalities | <p>FISH:</p> <ul style="list-style-type: none"> • Hyperdiploid: <i>More than 1 pair of chromosomes (Trisomies)</i> • Translocation 11 and 14 • Translocation 6 and 14 • Others • Normal |

*Based on the Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013. Michael JR et al. Mayo Clin Proc. 2013;88:359.

And that divides patients into high risk or standard risk. High risk is more difficult to treat, more difficult to maintain those remissions and that's classified by deletions of the 17th chromosome, gain of the first chromosome or 4;14, 14;16 and 14;20 translocations.

Standard risk patients, which are two-thirds of patients, they can have either normal cytogenetics, more normal FISH studies, or they can have more than one copy. So usually, we have two copies of chromosomes in our body and some of those myeloma cells will have three different copies. And, again, we call that standard risk, a bit easier to treat.



And we then pull all that information together for the stages of myeloma. And I'll show you in a bit why that's important. But Stage I is when the beta-2 microglobulin is slow, the LDH is normal and there's no high-risk cytogenetics. And Stage III is when you have those adverse features present, and Stage II is when it doesn't meet either one. And I'll show you in a bit why that's important.

SCIENCE

AND OTHER NOVEL THERAPIES:
Selinexor (Xpovio)
Idecabtagene vicleucel or Ide-cel (Abecma)
Ciltacabtagene autoleucel or Cilta-cel (Carvykti)
Teclistamab (Tecvayli)
More to come...


Immunomodulatory (IMiDs):
Thalomid (Thalidomide), Revlimid (Lenalidomide), Pomalyst (Pomalidomide)

Proteasome Inhibitors (Pis):
Velcade (Bortezomib), Ninlaro (Ixazomib), Kyprolis (Carfilzomib)

Antibodies Against Myeloma (Immunotherapy):
Darzelex (Daratumumab), Sarclisa (Isatuximab), Emluciti (Elotuzumab)

So, how do we treat myeloma in 2023? Well, we use science. And back when I had hair, we were using chemotherapy, and now we have incredible new therapies to treat myeloma using immunomodulatory drugs, so the IMiDs, like thalidomide-Revlimid® (lenalidomide) and Pomalyst® (pomalidomide). We use a proteasome inhibitor such as Velcade® (bortezomib), Ninlaro® (ixazomib) and Kyprolis™ (carfilzomib). And now we use the antibodies, and we'll talk about each of these in a bit, but really, it's been an incredible past just five years and we've had so many novel therapies that have come out. We have many more to come, and we'll go over those at the end of the talk.

IMiDs for Multiple Myeloma

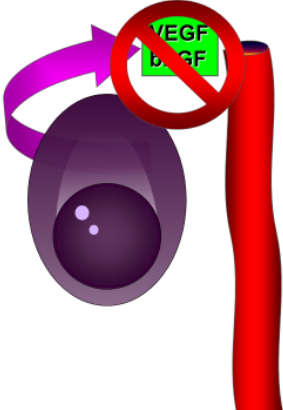


How does it work? -SCIENCE!

- Direct inhibition of DNA synthesis of myeloma cells.

So, how do those IMiDs (immunomodulatory drugs) work? Well, they use science. They inhibit DNA (deoxyribonucleic acid) synthesis to a small degree where the cells have a hard time reproducing.

IMiDs for Multiple Myeloma



How does it work? -SCIENCE!

- Direct inhibition of DNA synthesis of myeloma cells.
- Inhibition of blood vessel synthesis in the bone marrow.

And they do inhibit blood vessel production to a small degree by inhibiting fast synergy of growth factor and basic fibroblast growth factor.

IMiDs for Multiple Myeloma

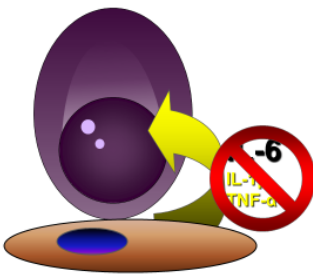


How does it work?—SCIENCE!

- Direct inhibition of DNA synthesis of myeloma cells.
- Inhibition of blood vessel synthesis in the bone marrow.
- Inhibition of adhesion between the myeloma and bone marrow stromal cells.

But one thing it really does; the myeloma cells are very dependent on those bone marrow cells. That's why you find myeloma only in the bone marrow. Myeloma cells can't live without the bone marrow stromal cells and the IMiDs (immunomodulatory drugs) break that connection between the bone marrow stromal cells and the myeloma cells.

IMiDs for Multiple Myeloma

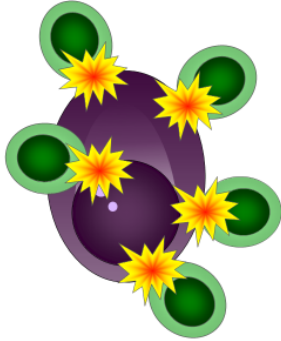


How does it work?—SCIENCE!

- Direct inhibition of DNA synthesis of myeloma cells.
- Inhibition of blood vessel synthesis in the bone marrow.
- Inhibition of adhesion between the myeloma and bone marrow stromal cells.
- Inhibition of the release of the cytokines IL-6, TNF- α , and IL-1 β .

It also starves the myeloma cells to death that they need interleukin-6 or IL-6 in order to grow and proliferate. It stops the production of that so the myeloma cells can't feed.

IMiDs for Multiple Myeloma



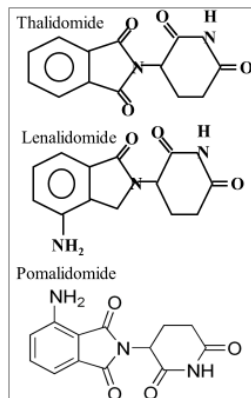
How does it work?-SCIENCE!

- Direct inhibition of DNA synthesis of myeloma cells.
- Inhibition of blood vessel synthesis in the bone marrow
- Inhibition of adhesion between the myeloma and bone marrow stromal cells.
- Inhibition of the release of the cytokines IL-6, TNF- α , and IL-1 β
- Activation of the body's natural killer cells (T-cells) which attack the myeloma cells.

And one of the most important mechanisms is that it gets those T cells, those cancer-fighting cells activated to go after the myeloma cells and clear it, so it gets your own immune system to destroy those myeloma cells.

Evolution of the IMiD Biologic Therapies

- 1990s, several thalidomide analogs were synthesized to increase efficacy and minimize toxicity.
- 2006 FDA approves Lenalidomide (Revlimid).
- Revlimid is felt to be 50 to 2000 more potent than thalidomide.
- Phase 2 trial 91% new myeloma achieved responses with Lenalidomide plus dexamethasone.
- 2013 FDA approves Pomalidomide.
- Pomalyst and dexamethasone given to multi-refractory myeloma with response rates of 35 to 65%.
- Combination of pomalidomide, bortezomib, and dexamethasone in relapsed MM response rates of 72%.
- **CELMoDs are the next class of IMiD with Iberdomide (CC-220) is now in clinical trials**
- **Second generation CELMoD is Mezigdomide (CC-92480) felt to be more potent than iberdomide**



Blood. 2005;106:4050-4053. Blood. 2013;Jan 14. [Epub ahead of print]. Exp Hematol Oncol. 2012; 1:27. J Clin Oncol. 2009;27(30):5008-5014. Blood. 2022; 140 (Supplement 1): 1366-1368.

In 1990, thalidomide (Thalomid®) was the very first IMiD (immunomodulatory drug) that came out and showed some efficacy, but then lenalidomide (Revlimid®) came out in 2016. It was about 2,000 times more potent than thalidomide. Then pomalidomide (Pomalyst®) came out in 2013 and now we have the CELMoDs (cereblon E3 ligase modulator), which are really incredible drugs. CC-220 (Iberdomide) and MEZI (Mezigdomide), CC-92480, very powerful drugs to treat myeloma, the IMiDs to come.

IMiD (Revlimid) Side Effects

Hematologic Side Effects:

- Neutropenia (ANC <1000) was reported in 26% of patients treated with lenalidomide–dexamethasone (Rd) for 18 cycles and in 28% of those on continuous Rd in the FIRST trial (RD vs MPT)
- Thrombocytopenia (platelets <50,000) occurred in 8% of patients
- Higher risk of blood clots requires use of prophylaxis
 - Daily aspirin vs. other oral anticoagulants (Eliquis, Xarelto, etc..)

Non-Hematologic side effects:

- Infections (22%), fatigue (9%), cardiac disorders (7%), venous thromboembolism (6%), and asthenia (6%)
- Low risk of secondary cancers
 - Cumulative incidence of 0.7% at 1 yr., 2.3% at 2yrs, and 3.8% at 3 years, with the highest incidence in elderly patients.

Leukemia 32, 1542–1560 (2018). N Engl J Med. 2014 Sep 4;371(10):906-17.

There are some significant side effects with the IMiDs (immunomodulatory drugs) that can cause low blood counts like low neutrophil counts and low platelet counts. It can cause blood clots, and so we use some type of way to prevent that, either a daily aspirin or sometimes if patients have had blood clots in the past, we'll use some anticoagulants.

And some of the nonhematologic side effects, we definitely have to watch for infection for patients. Fatigue is not an uncommon side effect that you should discuss with your provider and there's a low chance of secondary cancers, including myelodysplastic syndromes (MDS) or mutations inside the normal bone marrow function is about 2% to 3%. So, it's not very common, but we do have to watch for those secondary cancers.

IMiD (Revlimid) Side Effects: Diarrhea

- Long-term therapy with lenalidomide may result in a specific form of diarrhea, the so-called **bile salt malabsorption syndrome**
 - Which seems to result from damage of the lining of the intestine causing accumulation of bile acids in the small bowel
- Treatment of Revlimid bile salt malabsorption syndrome
 - Hold Revlimid
 - Imodium
 - Dietary fat intake should be reduced (to 20% of total calories)
 - Treatment with bile acid binders: colestipol or cholestyramine

Leukemia 32, 1542–1560 (2018). N Engl J Med. 2014 Sep 4;371(10):906-17.

One of the biggest side effects, especially when patients are on Revlimid® (lenalidomide) for a long time is diarrhea, and it's a specific type of diarrhea, bile salt absorption syndrome. So, bile salts are secreted when there's fat in our diet and it comes because Revlimid® causes some damage to the

lining of the intestine so that we have difficulty in absorbing bile salts. One way to alleviate that diarrhea is to make sure it's the Revlimid®, so you hold the Revlimid®. The diarrhea goes away, you know, it's the Revlimid®. Using Imodium® I think helps most patients. Decreasing dietary fat, and if that doesn't work, then we use a bile acid binder such as cholestyramine. That's what I frequently will prescribe to my patients. But make sure you talk to your doctor. If you're having diarrhea with Revlimid®, there are solutions for that diarrhea.

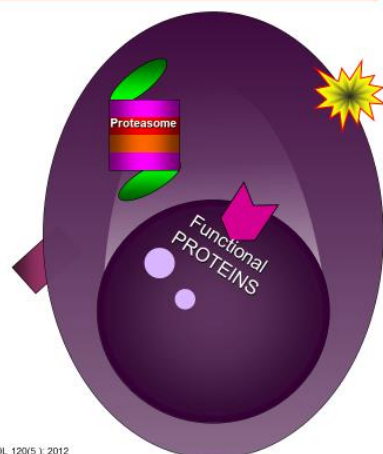
Revlimid Side Effects: Others

- Fatigue:
 - Sleep hygiene, good fluid intake, regular exercise, dose reduction
- Cramps:
 - L-glutamine, fluid hydration, normalizing magnesium and potassium levels, use of muscle relaxants, and moving and stretching the affected areas
- Rash:
 - Hold Revlimid, antihistamines or topical steroids are recommended, occasional low-dose oral prednisone
 - Consider restart after rash has resolved

Leukemia 32, 1542–1560 (2018). N Engl J Med. 2014 Sep 4;371(10):906-17.

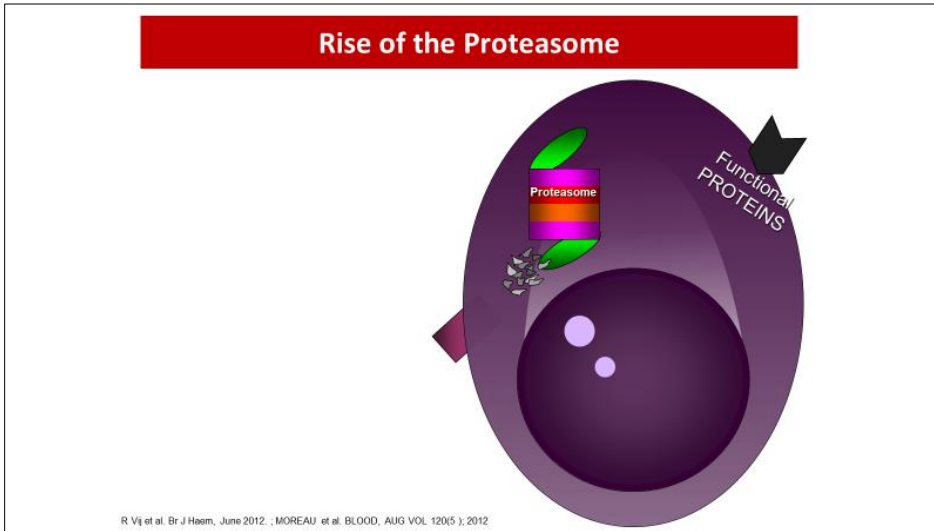
Fatigue is a common side effect, so good sleep hygiene. Some of those patients need to take the Revlimid® (lenalidomide) in the morning instead of at night. Regular exercise for cramps, L-glutamine (an amino acid), hydration is critical, normalizing the magnesium phosphorous potassium levels. Sometimes patients use pickle juice in order to help with that. And use of muscle relaxants and stretching. And then rash, frequently when patients first start Revlimid®, they'll have a rash. We usually tell patients to hold the Revlimid® and then restart after the rash has gone away. And antihistamines can help with that, but that's usually not an allergic rash.

Rise of the Proteasome



R Vij et al. Br J Haem, June 2012. ; MOREAU et al BLOOD, AUG VOL 120(5), 2012

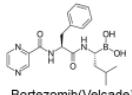
So, on to the proteasomes, the other main therapy that we talked about. So, inside myeloma cells, there are these little organelles called proteasomes. And what they do is that they help to remove proteins from the cells. And so, once a protein has done its job, it goes inside the proteasome, gets chewed up and then the rest gets spit out, so it helps us remove proteins from our cells.



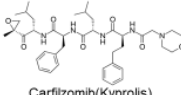
Myeloma cells are packed full of proteasomes. Now if you can inhibit the proteasome, then what will happen to these myeloma cells, these protein-producing cells it's like putting a cork inside the myeloma cell. These proteins then build up and build up and build up and they build up to a degree that the cell begins to literally pop open because they can't get those proteins out.

Rise of the Proteasome

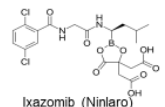
- Bortezomib(velcade) approved by the FDA in 2003 in patients with relapsed refractory myeloma.
 - Several phase 2 trials in newly diagnosed myeloma with bortezomib-dexamethasone induction.
 - Responses 66% to 90%, including 15% to 21% Complete Responses!
- 2012 FDA approves Carfilzomib(Kyprolis); second-generation **irreversible** Proteasome inhibitor
 - In refractory myeloma with 48% response rates. Higher in combination
- Ixazomib (Ninlaro) is an oral boronated reversible proteasome inhibitor currently approved by the FDA in 11/2015
 - Clinical trials showing use in relapsed and newly diagnosed MM



Bortezomib(Velcade)



Carfilzomib(Kyprolis)






Ixazomib (Ninlaro)

R Vij et al. Br J Haem, June 2012; MOREAU et al. BLOOD, AUG VOL 120(5); 2012; Blood 2014;124(7):1047-1055; Cancers 2020, 12, 265, doi:10.3390/cancers12020265

The bortezomib, Velcade®, was the first one that was released in 2003. There were several trials that showed its benefit. Carfilzomib (Kyprolis®) then came out in 2012 which is an irreversible proteasome inhibitor, so, again, those proteins build up in the cells and they can't get out which kills the myeloma cells. And then ixazomib (Ninlaro®), the oral version of bortezomib, came out in 2015 and that's still in

clinical trials showing results in relapsed, and very exciting new trials and using it in newly diagnosed myeloma.

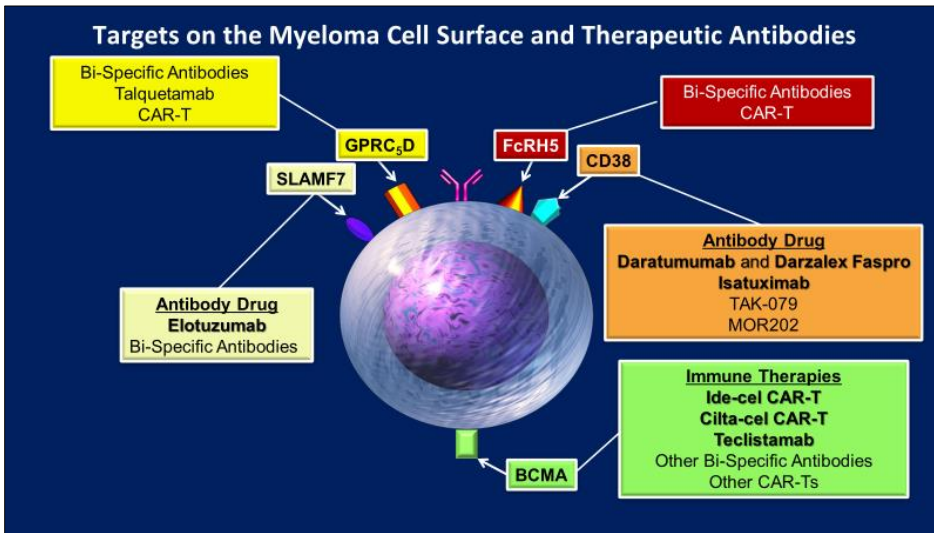
Side Effects of Proteasome Inhibitors

| | | |
|--|--|--|
| <div style="background-color: #333; color: white; padding: 5px;">Neurologic</div>  <ul style="list-style-type: none">• Peripheral neuropathy side effect that affects the nerves, resulting in pain, tingling, burning sensations, and numbness in the hands and feet• Peripheral neuropathy may be caused by Velcade• Risk is lower with subq dosing vs. IV and weekly vs. 2x weekly dosing• Treated with medications and ↑ activity | <div style="background-color: #ccc; padding: 5px;">Cardio-vascular</div>  <ul style="list-style-type: none">• Cardiovascular side effects including high blood pressure or congestive heart failure can occur with Kyprolis• Risk is lowered with good BP control | <div style="background-color: #f96; padding: 5px;">Gastro-intestinal</div>  <ul style="list-style-type: none">• Velcade and Ninlaro may cause a variety of gastrointestinal problems, such as constipation, diarrhea, and nausea/vomiting• Using nausea medications and/or stool softeners before dosing |
|--|--|--|

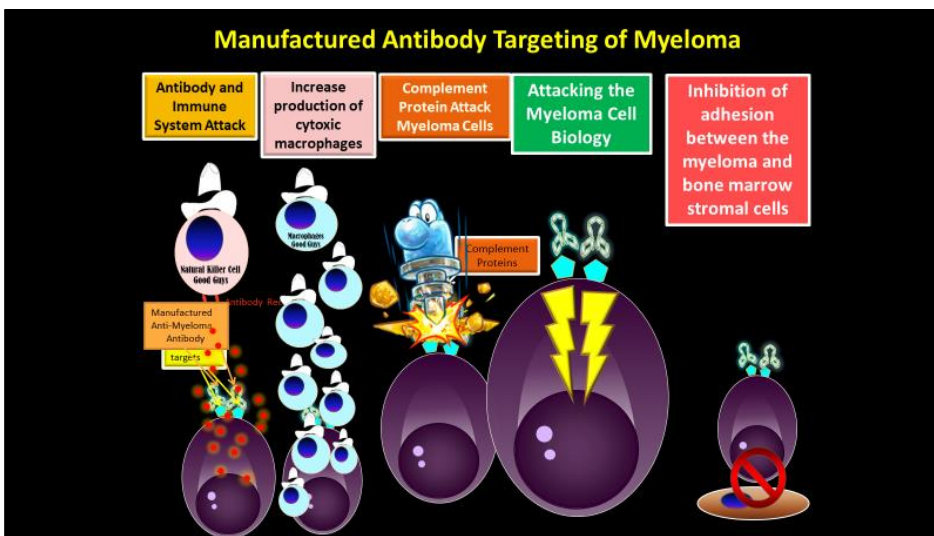
Similar side effects to the proteasome inhibitors is peripheral neuropathy. That's one of the big side effects and the risk of that is really a Velcade® (bortezomib) issue. It's reduced by using the Velcade® as a subcutaneous or under the skin injection and usually using it once weekly versus twice weekly. And if patients have neuropathy, we can reduce the dose of the Velcade® or hold the Velcade® using medications such as gabapentin to help treat that neuropathy.

Another side effect are cardiovascular symptoms or heart problems can occur especially with carfilzomib, or Kyprolis®. It can induce high blood pressure inside the heart which can cause congestive heart failure, so it's really important to have good blood pressure control and to coordinate with your primary care provider.

And then Ninlaro® (ixazomib) and Velcade® (bortezomib) can cause constipation or diarrhea and stool softeners can help with that. One little point about the proteasome inhibitors is that flavonoids such as green vegetables and green tea in the laboratory can inhibit the proteasome activity. So, one thing I tell my patients is to on the day that they have their therapy to just don't drink any green tea on that day or eat green leafy vegetables on that day. They can eat them all day long any other day except for the one day that they get their therapy.



So, on to the antibodies or the immune therapy. So, the myeloma cell has a very specific number of proteins on top of it that identify it as multiple myeloma – SLAMF7, GPRC5D, CD38, and BCMA. That is what identifies a myeloma cell as a myeloma cell. Because patients don't make antibodies against their own myeloma cells, we've made antibodies against them so that we can identify those myeloma cells and kill them off. Against SLAMF7 we have elotuzumab (Empliciti®), against CD38 we have daratumumab (Darzalex®) and isatuximab (Sarclisa®). And we'll talk a lot about BCMA only on plasma cells and we can identify that and kill them with the CAR Ts (chimeric antigen receptor T cell) and the bispecific antibodies. And actually, besides reducing the immune system, these antibodies and therapies don't have a lot of side effects, but we'll talk about some of the side effects of the BCMA-related proteins.



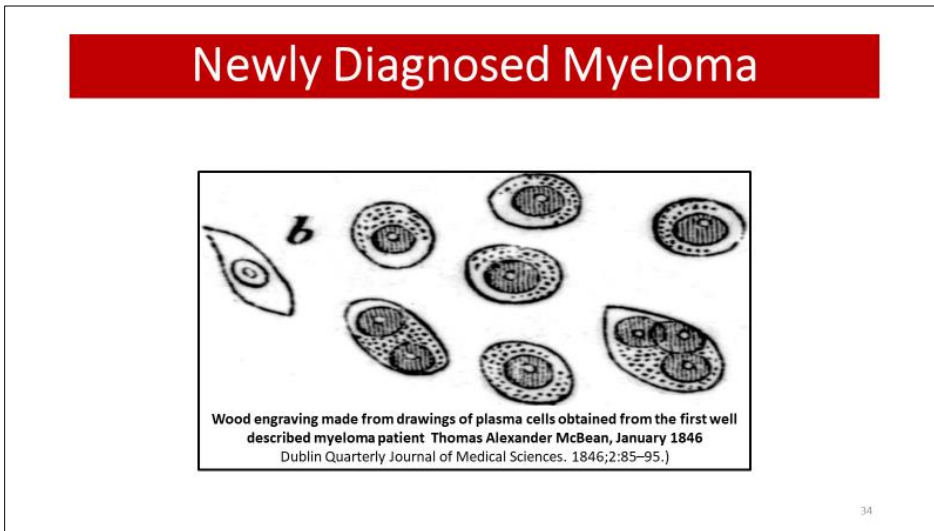
How does Darzalex® (daratumumab) and isatuximab (Sarclisa®) and elotuzumab (Empliciti®) work? Well, again, we identify those targets on the myeloma cells and those antibodies attached to the myeloma cells get the immune system to kill them off which then causes the immune system to attack

them, but also causes another protein called, complement, to come in and destroy the myeloma cells. And then, finally, when antibodies attach to those myeloma cells, they will be kicked out of the bone marrow compartment and, again, those myeloma cells need to have those bone marrow stromal cells to attach to. Without those bone marrow stromal cells, they starve to death so the elotuzumab and daratumumab-isatuximab get the immune system to kill the cells as well as disturbing their microenvironment.

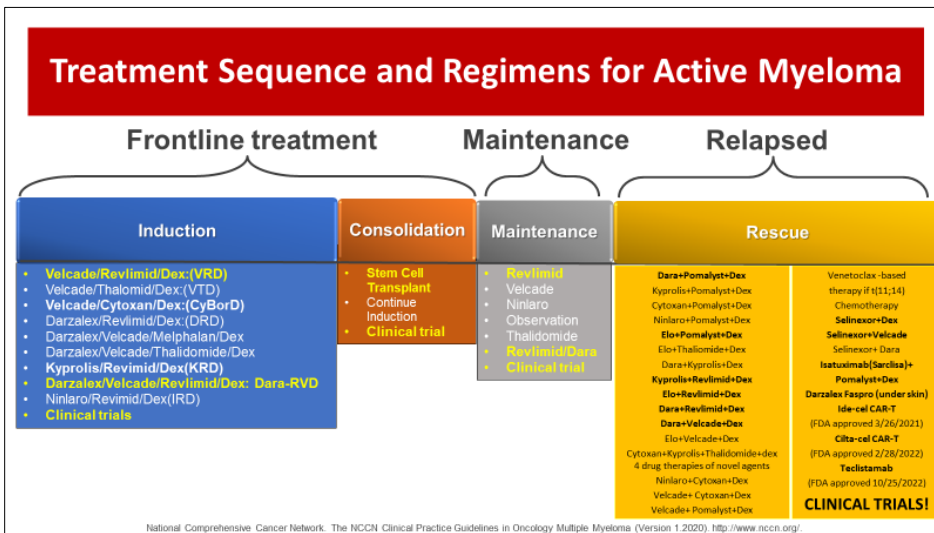
| Side Effects of Steroids (dexamethasone) | | | | |
|--|--|--|---|---|
| Insomnia | Fluid retention | Mood changes | Dyspepsia–heartburn | Elevation in glucose |
| <ul style="list-style-type: none">• Healthy sleep habits• Timing of dosing• Medication to assist with sleeping as needed | <ul style="list-style-type: none">• Monitor for swelling of extremities and “puffy” face• Monitor weight changes/gain• Reduce dose | <ul style="list-style-type: none">• Irritable, anxiety, difficulty concentrating• Severe cases of depression• Coordinate treatments with primary care provider | <ul style="list-style-type: none">• Dietary modifications (spicy, acidic foods)• Avoid NSAIDs• Acid-blocking medications• Take with food | <ul style="list-style-type: none">• Monitor glucose and refer/treat as needed• Coordinate with primary care provider |

And then, finally dexamethasone (Decadron®), the therapy that we've been using for almost 50 years to treat myeloma and probably has the most side effects of anything because they can cause insomnia. Usually, we give the dexamethasone on a weekly basis so patients can have insomnia for one night. The timing of the dosing is key. Sometimes patients take it in the morning because it can be very activating; it can change patients' moods in the morning. Sometimes it's activated after about eight hours so sometimes patients take it at night but try to find your best time to take it for insomnia. Fluid retention and mood changes are very frequent so always talk about reducing the dose of dexamethasone if you can and coordinate with your other providers for mood changes and heartburn and elevated glucose. Again, coordinating with primary care providers is key.

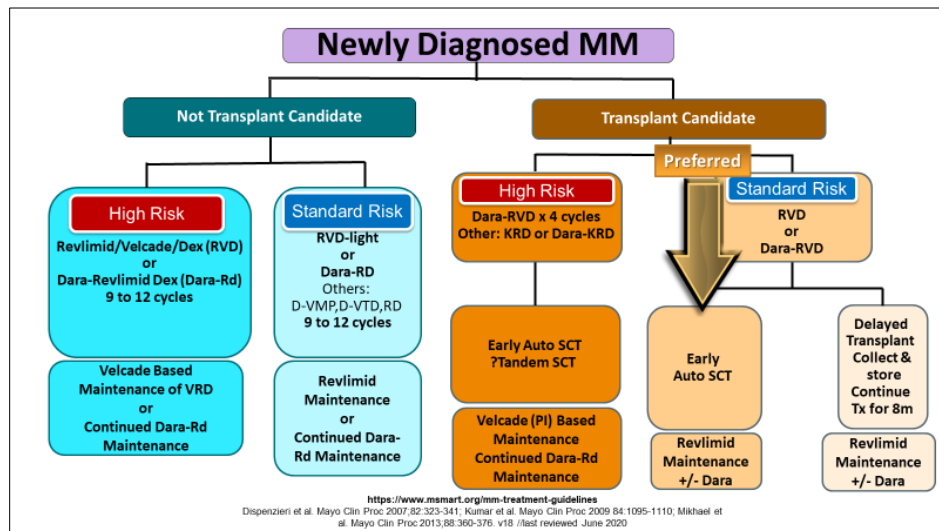
And one thing that has been one of the most exciting things that we've seen in myeloma, is that in a couple studies that have been done by the International or French Myeloma Group is reducing and eliminating dexamethasone (Decadron®). It's really been the mission of myeloma is to try and get rid of dexamethasone in our therapy. We're not there yet but really these clinical trials are very encouraging.



So, now we'll talk about newly diagnosed myeloma.



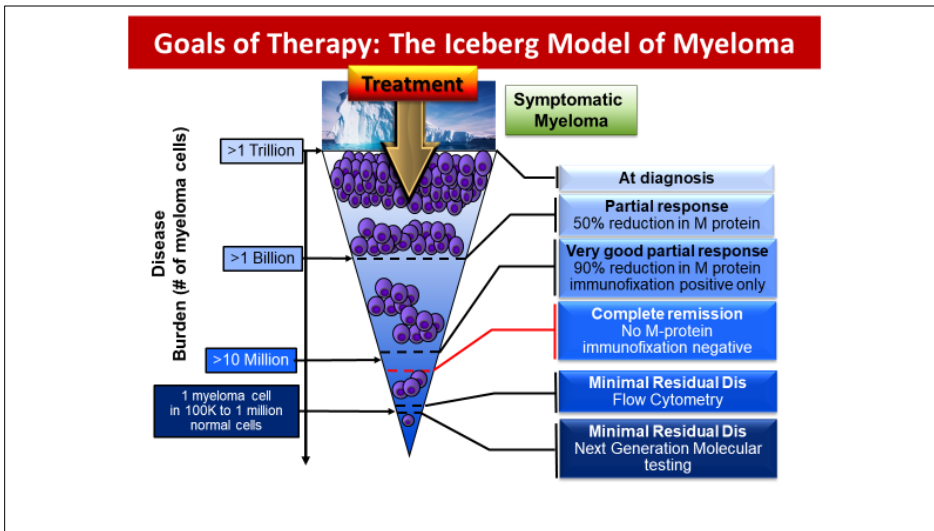
So, frontline therapy in the sequence of myeloma therapy is to start with induction therapy. And there's lots of choices for induction therapy, including daratumumab (Darzalex®), Revlimid® (lenalidomide), Velcade® (bortezomib), -dex (dexamethasone/Decadron®), RVD or VRD Velcade® - Revlimid® and dex, and then the quads, Darzalex®-Velcade®-Revlimid® and dex but, also, always we're interested in clinical trials. Induction is followed by consolidation either stem cell transplant continuing induction and then some type of maintenance therapy, so we'll talk about all three of those in a bit, and then relapse therapy. So, we haven't cured myeloma yet, and so when it comes back, we have a number of rescue regimens and that's when the playbook really opens, and clinical trials become key.



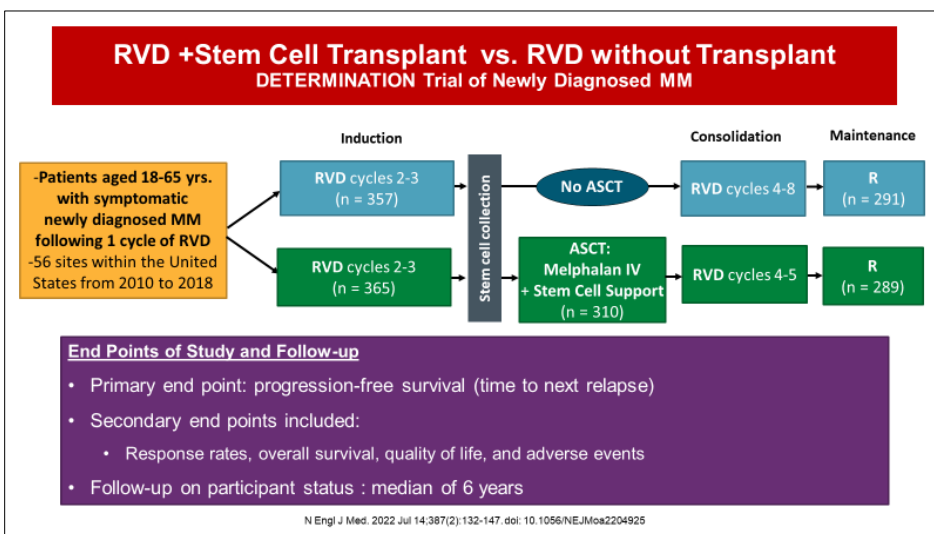
So, in newly diagnosed myeloma, the first question is, “Is the patient a transplant candidate or not a transplant candidate?”. Not transplant candidate is not based on age but more based on other medical problems. And if somebody has lots of heart problems and lung problems, they may not be a transplant candidate. If they have a hard time getting around and functioning independently, then they may not be a transplant candidate. The best person to decide that is a transplant doctor.

If you're not a transplant candidate, then the question is, “Is it high risk?,” like Stage III myeloma, those high-risk cytogenetics, or standard risk, or Stage II or Stage I? For high-risk patients, we need to treat it aggressively, again, to try because they don't stay in remissions very long, so we use either RVD (Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]) or dara (daratumumab [Darzalex®]-RVD (Darzalex®, Velcade® and Revlimid®, Decadron®) or dara-Rev-dex (Darzalex®, Revlimid® and dexamethasone/Decadron®), and then we may add on the Velcade® a bit later. For standard risk patients then, one of the main regimens these days has been using daratumumab-Rev (Revlimid®)-dex for a year then to go on maintenance.

For those patients that are transplant candidates, then, again, we divide high risk or high-stage myeloma where we're definitely using a quad, the dara (daratumumab) -RVD (Darzalex® [daratumumab], Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]) for four cycles followed by transplant. And there's a lot of new data coming about using dara (daratumumab)-KRd (Kyprolis® [carfilzomib] Darzalex® [daratumumab], Decadron® [dexamethasone]) for newly diagnosed high-risk patients or for early transplantation and then a three-drug maintenance therapy. For standard-risk patients, use RVD (Revlimid®, Velcade®, Decadron®) or dara (daratumumab/-RVD has become very common, I'll show why that in a second, followed by transplant and maintenance. Sometimes we can delay transplant for a future date, and usually I tell my patients that really we can coordinate transplant when it's really good for you. But the first thing is to get that really good response, but our preference is early transplantation.



And the goal of therapy is always to reduce the disease down as much as you possibly can. To shrink that iceberg down to the lowest that we can possibly shrink it. And so, when patients start out with myeloma, many times it's obvious. They have lytic bone disease, or they have, like Mr. Proctor had talked about, pain and low blood counts, and they have over a million myeloma cells. And then with treatment you start to reduce that down. And when the M protein, and this is why it's important to know your M protein, which you had a 50% reduction in M protein. So, you go from a protein of four to a protein of two, or a light chain of 100 to a light chain of 50. And then you keep going down and you shrink that iceberg down to the lowest you possibly can to 90% reduction in the protein and, eventually, possibly having a complete remission where there's no M protein, you're immunofixation negative. And there are more and more studies coming out the value of minimal residual disease (MRD) where we use molecular methods in order to look for one myeloma cell and 100,000 or a million normal cells work much better than what those protein tests can possibly do to shrink the myeloma down as much as we can.



So, how can we shrink the myeloma down as low as we can? One of the most important studies that came out in 2022 was the DETERMINATION study. It's been going on for a long time since 2010 and it enrolled patients between 18 and 65. And the reason they set it at 65 is that there's a companion study in Europe that also set it at 65, so that's not a hard stop for transplant, that is just how the study was designed. The patients everyone got RVD (Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]). They all got the stem cells plugged, but then they were divided into no stem cell transplant versus getting the stem cell transplant. Then they had consolidation and then maintenance. And the question was, "Do we still need transplant in 2023?"

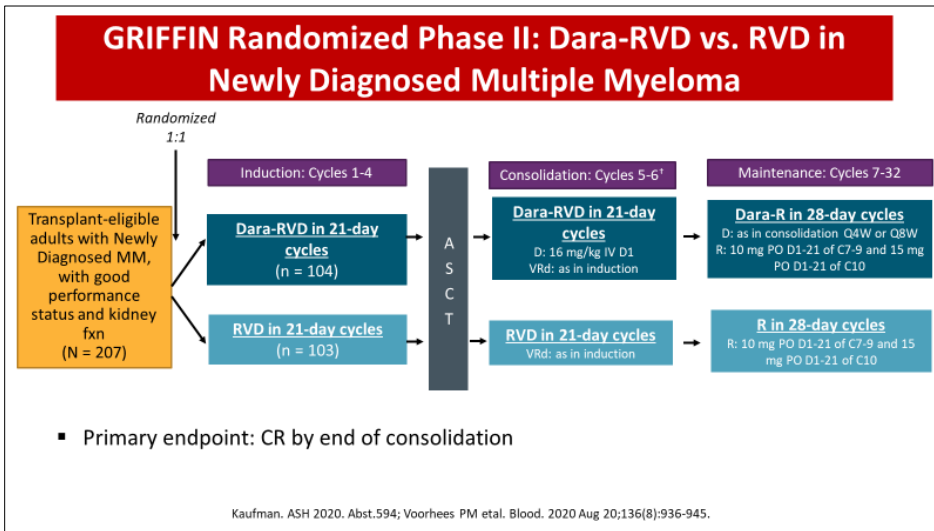
| RVD +Stem Cell Transplant vs. RVD without Transplant DETERMINATION Trial of Newly Diagnosed MM RESULTS | | | |
|---|---------------------------------|---|----------------------------------|
| Parameter | RVD- No Transplant (n = 357) | RVD with Up Front Transplantation (n = 365) | P Value Is it Significant? |
| Grade 3 or 4 toxicities | 78 | 94 | YES! P<0.001 |
| <ul style="list-style-type: none"> At a median follow-up of 76.0 months, the risk of disease progression or death was 53% higher in the RVD-alone group than in the transplantation group (P<0.001) | | | |
| OVERALL SURVIVAL at 5 years (%) | 79.2 | 80.7 | NO |
| Median duration of Partial Response or better, mo | 38.9 | 54.4 | YES! .003 |
| Negative MRD | 39.8 | 79 | |

N Engl J Med. 2022 Jul 14;387(2):132-147. doi: 10.1056/NEJMoa2204925

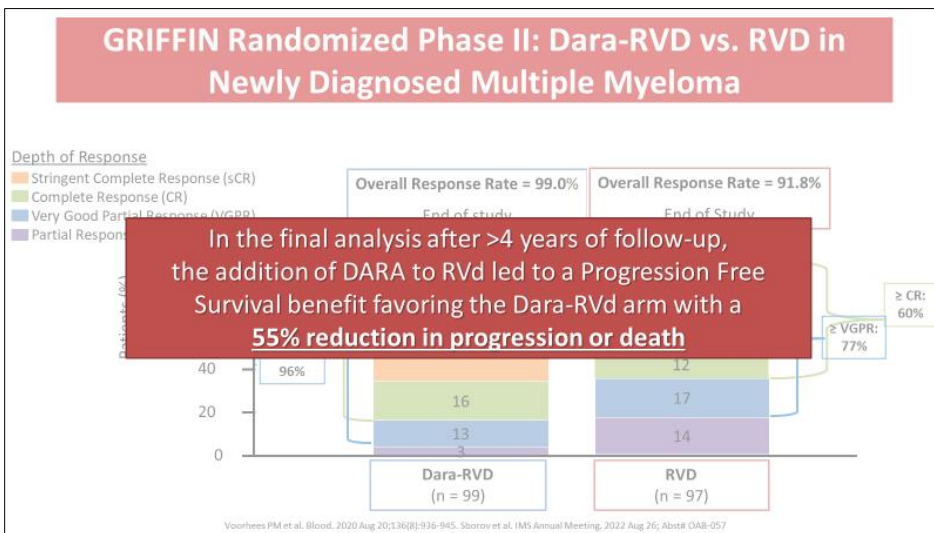
And what that study showed is between no transplant in green and transplant upfront in yellow, for toxicities like anemia, thrombocytopenia, nausea, transplant won. But a lot of those symptoms happen in the hospital and patients usually don't go home with a lot of those symptoms. When it came to time to relapse, transplant won. There was a longer time it took for patients to relapse than it was without transplant. But transplant wins in delaying the time to relapse.

That was really strong in the high-risk patients; again, that's why it's so important to know your risk. High-risk patients really benefited from getting a stem cell transplant. However, the overall survival was the same and between no transplant and transplant. That's why because we have so many good options to treat patients when they relapse, or we can delay the transplant for a later date.

When you look at duration of those deep responses better with transplant, MRD negativity, really, really deep responses, shrinking that iceberg to an ice cube, better with transplant. And at 76 months the risk for progression, primarily progression, was 53% higher without transplant than with transplant, and that's why we recommend transplant to patients.



How else can we reduce the disease down? The other important study that came out was the GRIFFIN trial. And this randomized patients between the standard of care, which is RVD (Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]) versus dara-RVD (Darzalex® [daratumumab], Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]). Everyone got transplanted and then everyone got consolidation and maintenance.



And the important thing about this study is RVD (Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]) super good response rate, 91% response rate, but it was better with dara-RVD (Darzalex® [daratumumab], Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]), 99% response rate at the end of consolidation. Now at the end of the study, those responses got even deeper because of maintenance therapy. And where the VGPRs (very good partial response) are deeper than RVD alone and the complete remissions were better. And in this study after four years of follow-up, they definitely favored dara-RVD (Darzalex® [daratumumab], Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]) versus RVD

(Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]) alone with a 55% reduction in progression. Very important trial. It really has become the standard of care.

Maintenance Therapy

- Maintenance is to prevent disease progression for as long as possible while maintaining favorable quality of life
- Data from 4 randomized trials of Revlimid (lenalidomide) maintenance vs. no maintenance
 - The results of the analysis showed that Revlimid maintenance therapy is associated:
 - Significant **improvement in progression-free survival**
 - **Modest improvement in overall survival**
- **Duration of maintenance is unknown**

Disease Response Before and After Maintenance

| Response Category | Before Maintenance | During/After Maintenance |
|-------------------|--------------------|--------------------------|
| MRD negative | 37 | 72 |
| CR | 57 | 49 |
| VGPR | 34 | 14 |
| sPR | 11 | 4 |


Alonso R et al. Blood Adv. 2020;4:2163.

Maintenance therapy, we use maintenance therapy after induction and possibly transplant to prevent disease progression. And the big thing is there have been four big trials that looked at this showing that there's a benefit to using a maintenance therapy for our myeloma patients. And you can see the graph to the right how those responses get deeper, MRD negative deeper, complete responses and VGPRs (very good partial response) transform into CRs (complete responses) and MRD negativity. But we still don't know how long we should have patients on maintenance. So, our usual theorem is to have patients stay on maintenance as long as they can until the disease relapse.

Bone Support & Control of Bone Pain

Multiple myeloma can cause weakened areas in the bone called osteolytic lesions which can compress the spinal cord or cause bone destruction.

- Bone strengthening drugs: bisphosphonates (**pamidronate & Zometa**) or monoclonal antibodies (**Xgeva**) are given at diagnosis and continued for at least 2 years
- **Vitamin-D and Calcium supplements to help bone healing**
- Orthopedic support
 - Physical therapy, physical medicine consults, orthopedic/neuro surgery, radiation therapy, etc.
- Minimally invasive procedures: kyphoplasty or vertebroplasty
- Use of medication to control pain
- Anticonvulsants and antidepressants for treat relieve pain from nerve damage or numbness

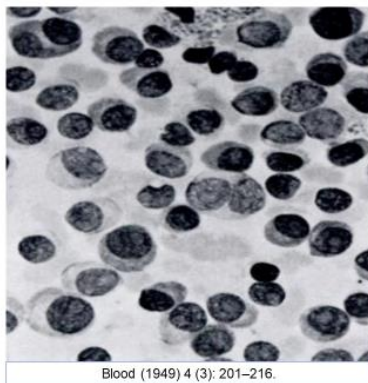


And one other important point is bone disease. Again, myeloma bone disease occurs in about 70% of patients which can cause, of course, incredible pain, so we need to make those bones strong again. And we can make those bones strong again by using drugs like pamidronate (Aredia®), Zometa®

(zoledronic acid) or Xgeva® (denosumab) which help to put the calcium back in the bones, but you also need vitamin D and calcium supplements to help the bone heal. But you do get there. Especially after three months of using the bone strengtheners and control the myeloma, then the number of bone events decreases dramatically.

Similar to other orthopedic support is our physical therapy, physical medicine colleagues, and also watching for osteonecrosis of the jaw (ONJ). So, you don't want to get any teeth pulled while you're on these therapies, so you usually try and get as much of your dental care done upfront and then you can get the Zometa® (zoledronic acid) or Xgeva® (denosumab) uninterrupted. If you're on these drugs, I stop it for two weeks before any dental procedures.

Relapsed Refractory Myeloma



Blood (1949) 4 (3): 201-216.

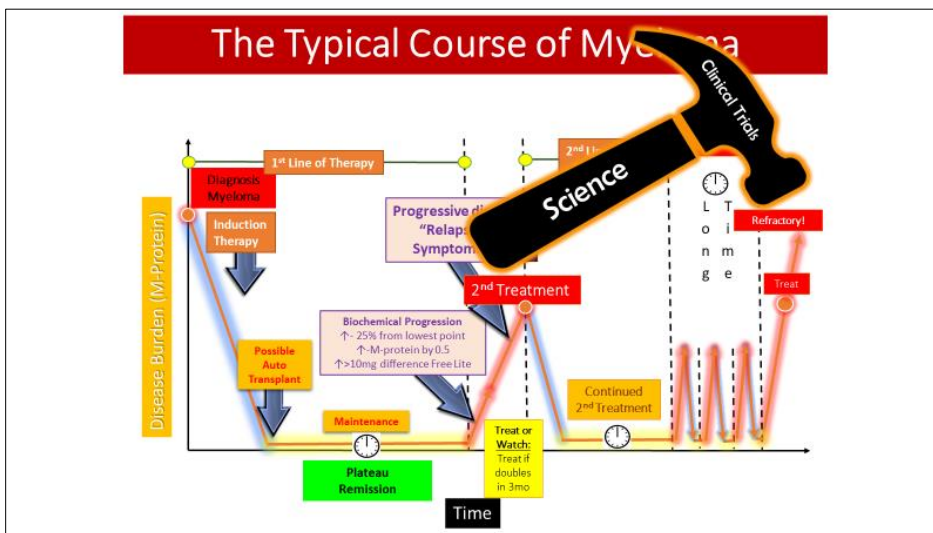
So, now on to relapsed myeloma, and this is actually a photograph from 1949 and using urethane for relapsed myeloma.

What is Relapsed Multiple Myeloma ?

- Relapsed multiple myeloma is when the cancer returns after treatment
 - Usually after a period of remission or response.
- Since multiple myeloma does not have a cure, it is likely that at some point patients will have a relapse
- With therapy, relapsed myeloma patients can achieve a [second response](#)
- **Refractory** myeloma is when myeloma is not responsive to therapy.

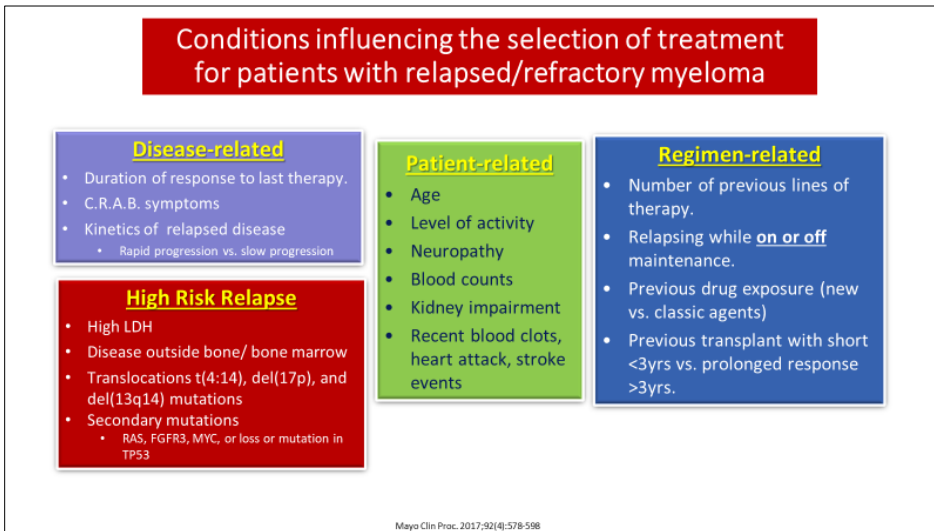
“RRMM” = Relapsed Refractory Multiple Myeloma

So, what is relapsed myeloma? I get this question quite a bit. It's when the myeloma returns after treatment. So, when you first get diagnosed, when it comes back while patients are frequently on maintenance therapy, we call that relapsed or sometimes we call it recurrent, or we call it progressive myeloma. And since we haven't cured myeloma yet, most patients will have some type of relapse. But with therapy and with all the new drugs that we have, we can put patients in a second response and sometimes even deeper responses than they first had. But when the myeloma isn't responsive to therapy anymore, we call that refractory myeloma. And RRMM, I'll use those throughout the talk, is relapsed/refractory myeloma.

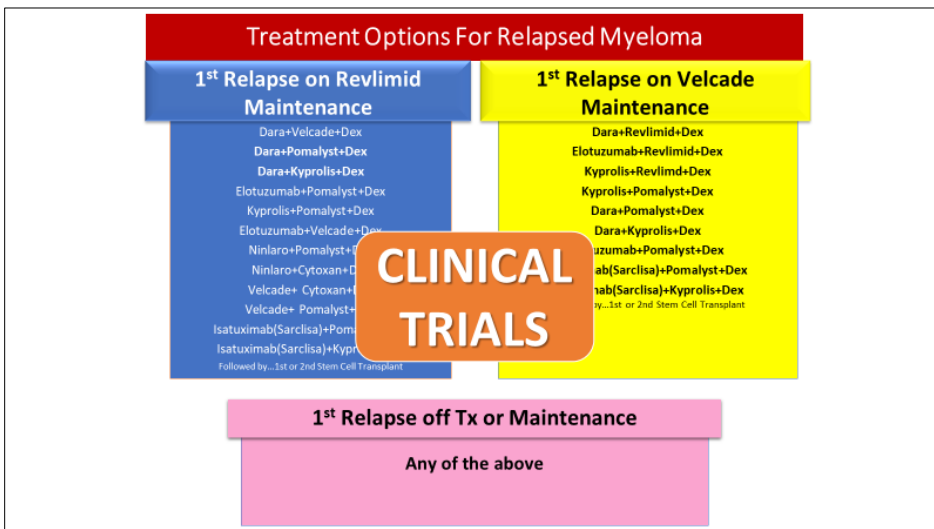


So, how does it work? Well, at the time of diagnosis, the M protein is pretty high. We do an induction therapy like dara-RVD (Darzalex® [daratumumab], Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]) or RVD (Revlimid® [lenalidomide], Velcade® [bortezomib], Decadron® [dexamethasone]) and then consolidate with transplant and then patients are in maintenance therapy. And, hopefully, they're on maintenance therapy for a long time and the myeloma is reduced down to very, very low levels. That's the first line of therapy.

When the M protein tends to go up again, and specifically a 25% increase from this lowest point where the M protein goes up by 0.5, we call that biochemical progression where the myeloma cells are active again, there are more of those cells and they're producing protein. We watch those patients very closely and frequently we'll do a PET (positron emission tomography) scan to make sure there's no bone disease or any of those CRAB (calcium elevation, renal insufficiency, anemia, and bone lesions) criteria. And if the protein continues to go up or if there's any of those CRAB, including looking for lytic lesions on the PET scan, then we treat again, and they have a second treatment. And then they have a very good response, hopefully, and they continue that therapy for, hopefully, a long time, and that's a second line of therapy. And then the myeloma comes back. We treat again. And then it goes down and on and on, and then you talk about third-, fourth-, fifth-line therapy, and, hopefully, that's a long time. And then when the myeloma comes back and we treat and it doesn't work, we call that refractory disease. And that's where the science and the clinical trials beats that down, and it has done a fantastic job in doing that.

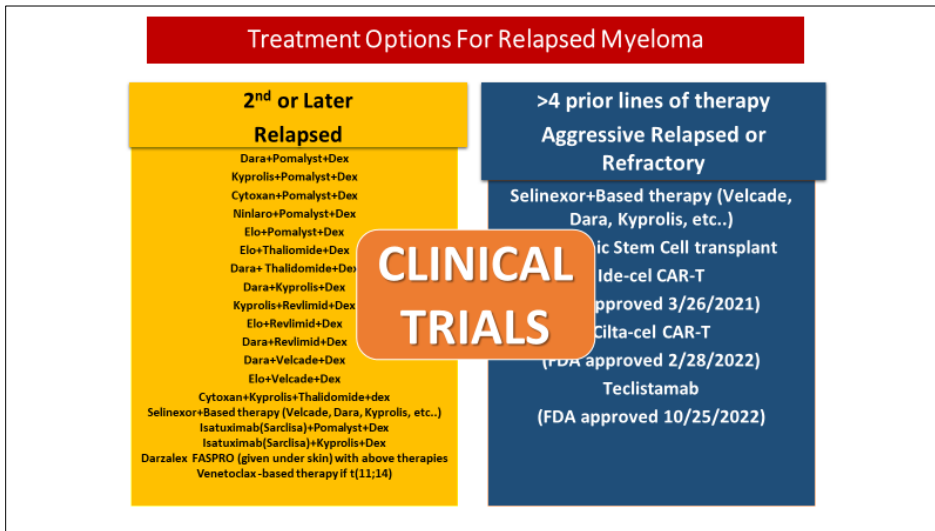


How to decide on which therapies to use? Well, we look to see what was the last therapy they used because we don't want to repeat what they had before at the time of relapse. How bad is their relapse or do they have immediate symptoms and bone lesions or is it just a biochemical relapse? Is that relapse high risk? Are the cells producing faster and have more translocations that are more difficult to treat? And, also, age, level of activity, what side effects they had with their previous therapy helps us make a decision of which therapy to use. And then one of the most important things is what were they on at the time of relapse and what did they previously have and what drugs are present. Sometimes we'll repeat the transplant if they've had a long period of remission with a transplant.

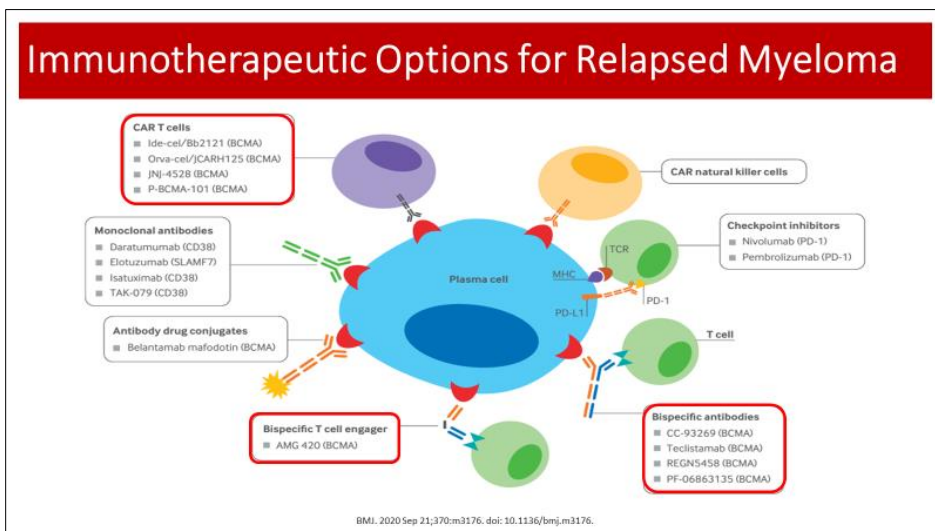


If you're relapsing off Revlimid (lenalidomide), then there's an open playbook with dara-pom-dex (daratumumab [Darzalex®], pomalidomide [Pomalyst®] and Decadron® [dexamethasone) and dara (daratumumab)-Kyprolis® (carfilzomib)-dex (dexamethasone [Decadron®] being one of the most frequent therapies used for relapsed myeloma while patients are just on Rev (Revlimid® [lenalidomide]) maintenance. If they're on Velcade® (bortezomib) maintenance, we use Revlimid®-

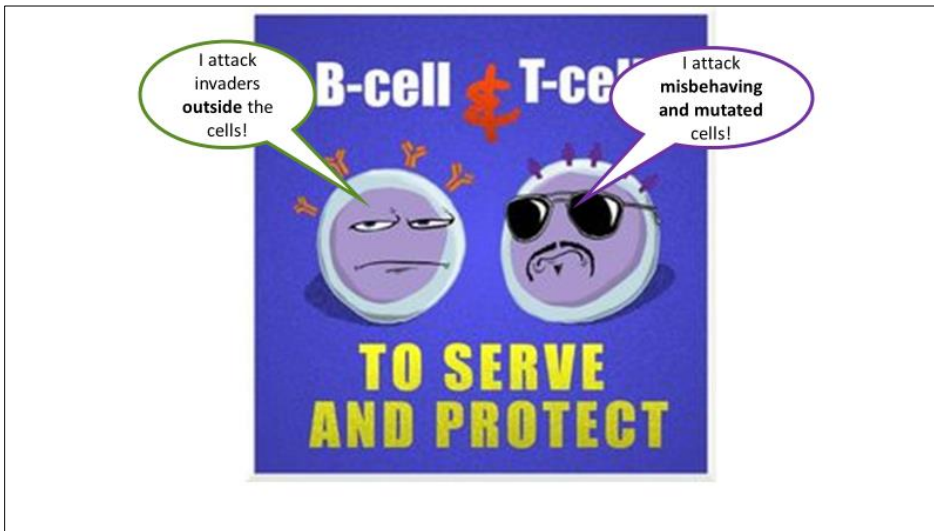
based therapy, so we don't repeat the same therapy over again. And if you're not on any maintenance therapy, then, again, you have an open playbook of which therapies to use. And, again, if you have a high-risk relapse, we may decide on a different therapy than if you have a standard risk relapse, but clinical trials are the mainstay that we should definitely look at when patients relapse.



If there's a second-line relapse or later, again, open playbook with lots of new therapies available for those patients. And after four or more lines of therapy, that's when the newest things, the things that we have approved in the past couple years become important, such as Selinexor (Xpovio®)-based therapy and we'll talk about the CAR Ts (chimeric antigen receptor T cell) and bispecifics in a bit. And, again, clinical trials the pointy end of the myeloma armamentarium.



And really what's been exciting are the immunotherapies. The CAR T (chimeric antigen receptor T cell) therapies, which we'll talk about in a bit, the bispecific T-cell engagers which get the T cells to attack the myeloma cells and get rid of the disease.



So, I get frequently asked, "Well what's CAR T (chimeric antigen receptor T cell)?" Well let's talk about CAR T. So, B cells are the cells that help attack bacteria and viruses. T cells destroy mutated cells and cancer cells, but our patient's T cells aren't doing that.

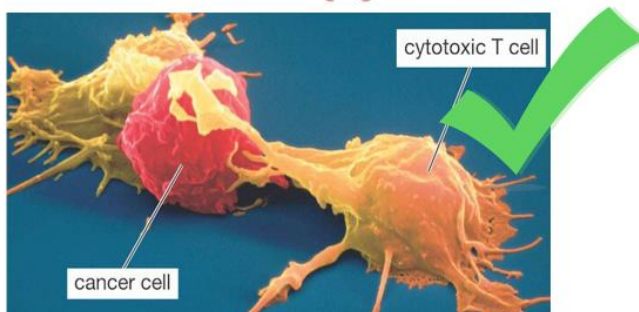
CAR –T Immune Therapy



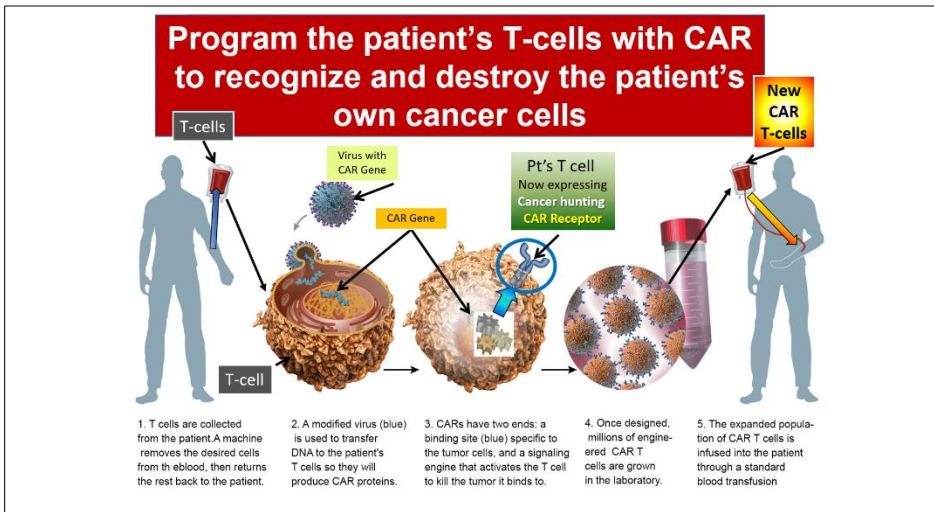
CAR –T Immune Therapy



CAR –T Immune Therapy

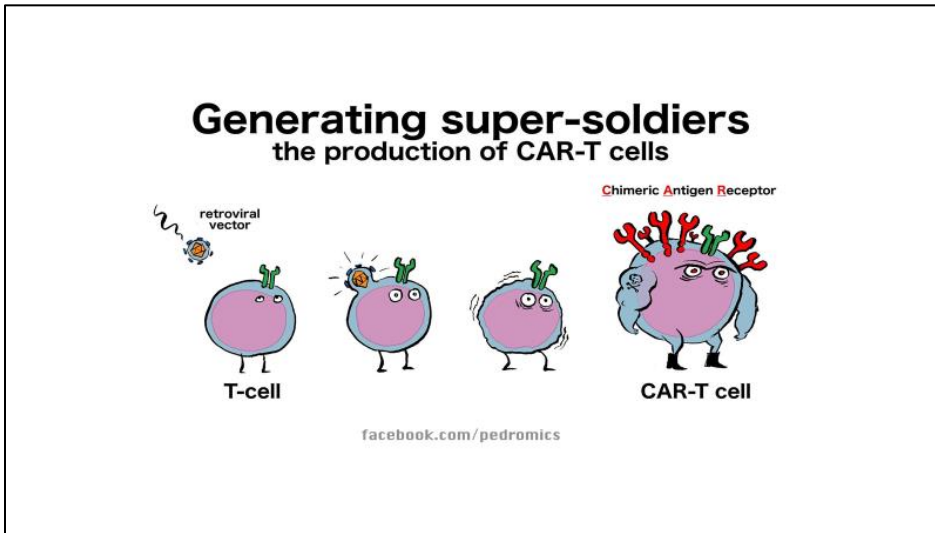


So, here's a CAR T, model T, I'm from Detroit so I can say that. This is my favorite slide Mr. T and a CAR, there's CAR T for you right there, but what we're really talking about is getting cytotoxic T cells to go after cancer cells.



And how do we do that? Well, again, T cells are those white blood cells that help identify cancer cells, and they use it to chimeric receptor antigens help to recognize the cancer cells. So, what if we can get your own T cells to recognize cancer cells? Well, they're not doing that right now. The way to do that is we harvest the T cells the same way we would harvest stem cells, through pheresis, and then we get a virus, we get a lentivirus that has that man-made gene, that CAR (chimeric antigen receptor) gene inside of it that helps identify cancer cells. And we incubate the patients T cells with this retrovirus. The retrovirus puts that gene into the T cells that engineers those T cells to now become cancer-hunting cells by reading that gene that was inserted into them and now your T cells are cancer-hunting cells. We then grow those in cultures so that there are about 400 million of them and then infuse it back into the patient, and now those T cells are hunting cancer.





The easy way to show that is here's a little T cell. Retrovirus inserts that gene into it and turns that T cell into a cancer-hunting T cell that's angry and ready to kill some myeloma cells.

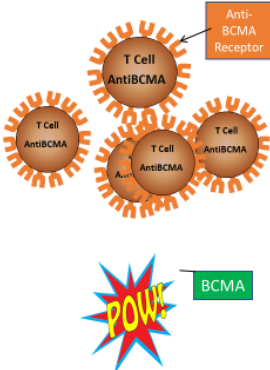
CAR-BCMA T-Cells in Myeloma: Background

- B-cell maturation antigen (BCMA) is expressed myeloma cells and is a potential target for CAR T-cell therapy for MM.
- T cells can be genetically modified to express chimeric antigen receptors (CARs) specific for BCMA or other proteins associated with cancer.
- The patient's own T-cells are stimulated, transduced with BCMA retroviruses, and cultured for 9-14 days before re-infusion.

J Clin Oncol 35, 2017 (suppl abstr LBA3001); 22nd EHA Congress, June, 2017; Abstract 5142; Cohen AD, et al. ASH 2017, Abstract 505

CAR-BCMA T-Cells in Myeloma: Background

- B-cell maturation antigen (BCMA) is expressed on myeloma cells and is a potential target for CAR T-cell therapy for MM.
- T cells can be genetically modified to express chimeric antigen receptors (CARs) specific for BCMA or other proteins associated with cancer.
- The patient's own T-cells are stimulated, transduced with BCMA retroviruses, and cultured for 9-14 days before re-infusion.
- The CAR-T cells engage myeloma cells through BCMA.
 - T-cells are activated and then kill the myeloma cells
 - The CAR-T cells also have another built-in switch which causes the CAR-Ts to expand in number and potency



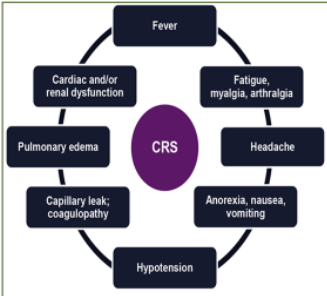
J Clin Oncol 35, 2017 (suppl. abstr. LBA3001); 22nd EHA Congress, June, 2017; Abstract S142; Cohen AD, et al. ASH 2017 Abstract 505

So, again, we use BCMA (B-cell mutation antigen) as the target, so that's a gene that we insert into those T cells. So, we get the T cells and now they're anti-BCMA-hunting T cells and then they find those myeloma cells and go and kill them. It takes about two weeks to make the CAR T cells (chimeric antigen receptor T cell) for myeloma; sometimes a little bit longer, but once those cells get in, then you hold those cells that reproduce in the body and continue to destroy those myeloma cells through BCMA.

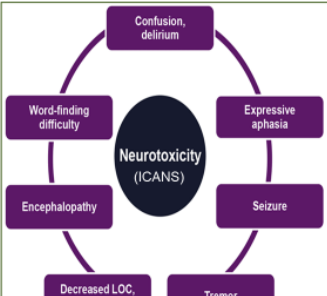
Toxicities of CAR-T:

Cytokine Release Syndrome and Neurotoxicity

- Cytokine Release Syndrome (CRS) is a severe inflammation reaction related to T-cell engagement to the target
- CRS can be mild (grade 1) to severe (grade 4) causing multisystem organ failure
- Immune effector cell-associated neurotoxicity syndrome ICANS is the neurologic toxicity of CAR-T
- The cause of the neurotoxicity is unknown



1. Lee DW et al. Blood. 2014;124:189-195.



The cytokine release syndrome (CRS) is the main side effect that we see with CAR T (chimeric antigen receptor T cell). This is a severe inflammatory reaction that can occur when all those T cells go out to kill cancer cells all of a sudden which can cause fever, pulmonary edema or fluid leaking, low blood pressure, sometimes fatigue. And then the ICANS or neurotoxicity, the immune effector cell-associated neurotoxicity syndrome. Long name to say that you can get confused, word-finding difficulty, sometimes seizure with infusions of CAR T and T-cell-related therapies.

Idecabtagene vicleucel (Ida-cel) BCMA-directed CAR T-cell therapy

- Multicenter KarMMa Phase II trial in pts with R/R MM who received ≥ 3 prior lines of therapy.
- Treatment approach:


```

            graph LR
            A[T-cell apheresis to collect cells to construct bb2121 CAR-T] --> B[3 days of Chemo with Fludarabine and Cyclophosphamide]
            B --> C[50 x 10^6 bb2121 CAR T-cells]
            B --> D[150 x 10^6 bb2121 CAR T-cells]
            B --> E[450 x 10^6 bb2121 CAR T-cells]
            
```

- 128 consecutive patients who received Ida-cel (bb2121) infusion were reported
 - The median age was 61 years (range, 33 to 78)
 - 35% had a high-risk cytogenetic profile
 - Median number of previous regimens was 6
- The manufacturing of Ida-cel was successful for 99% of the patients
- Anti-BCMA CAR was expanded over a period of 10 days

Raje N et al. N Engl J Med 2019;380:1726-1737

The Ida-cel BCMA KarMMa trial is one of the most important trials that has been published in the past few years with myeloma where T cells were collected from patients. They were given three days of chemotherapy that we still do today to make room for those new CAR T cells (chimeric antigen receptor T cell). Then we infuse the CAR T cells in the patient.

Ida-cel CAR-T : Overall Response Rate

| Outcome | Ide-cel 150 x 10 ⁶ (n = 4) | Ide-cel 300 x 10 ⁶ (n = 70) | Ide-cel 450 x 10 ⁶ (n = 54) | All Ide-cel Patients (n = 128) |
|---------------|--|---|---|-----------------------------------|
| ORR, n (%) | 2 (50) | 48 (69) | 44 (81) | 94 (73) |
| CR/sCR, n (%) | 1 (25) | 20 (29) | 21 (39) | 42 (33) |

| Outcome by Prior Lines | 3 Lines Tx (n = 15) | ≥4 LinesTx (n = 113) | All Ide-cel Patients (n = 128) |
|------------------------|------------------------|-------------------------|-----------------------------------|
| ORR, n (%) | 73 | 73 | 73 |
| CR/sCR, n (%) | 53 | 30 | 33 |
| VGPR | 0 | 23 | 20 |
| PR | 20 | 20 | 20 |

- Median follow-up: 24.8 mo (range: 1.7-33.6 mo)
- Median Duration of response 10.9 mo (9.0-11.4)
- Median PFS at 300 x 106 CAR T-cells was 5.8 mo vs 12.2 mo with 450 x 106 CAR T-cells

Anderson. ASCO 2021. Abstr 8016.

And for patients that have failed multiple lines of therapy where their survival is normally about three months, the overall response rate is 73%. And when you look at by lines of outcome, it didn't matter if you're three lines, four lines refractory, it all worked the same. Incredible response rates.

Idecabtagene vicleucel (Ida-cel) BCMA-directed CAR T-cell therapy

- Idecabtagene vicleucel BCMA-directed CAR T-cell therapy FDA approved for R/R MM **after ≥4 previous lines of therapy**, including an IMiD, a PI, and an anti-CD38 mAb
- In patients with R/R MM, use of idecabtagene vicleucel CAR T-cell therapy in KarMMA trial continued to result in durable responses, regardless of number of prior therapy lines
 - Median follow-up of 24.8 mo: ORR in all patients, 73%; CR/sCR, 33%
 - Median DoR: 10.9 mo; median PFS: 8.6 mo
 - Median OS: 24.8 mo, and >20 mo in most subgroups at high risk of progression

Chari. NEJM. 2019;381:727. Lonial. Lancet Oncol. 2020;21:207. Raje. NEJM. 2019;380:1726. Anderson. ASCO 2021. Abstr 8016

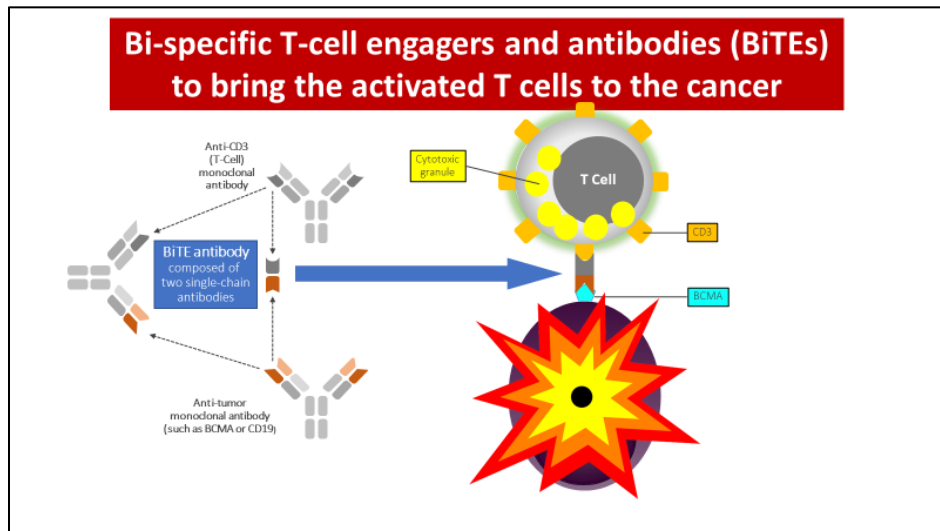
And, again, the duration of response way longer than anything we had seen before which then had this drug approved by the FDA (United States Food and Drug Administration) for patients that have relapsed/refractory myeloma after four prior lines of therapy. Again, incredible response rates and overall survival two years in patients that otherwise had a very hard time.

Safety and Efficacy Data of the 2 FDA approved CAR-Ts

| | Idecabtagene vicleucel KarMMA trial | Ciltacabtagene autoleucel CARTITUDE 1 trial |
|------------------------------|---|---|
| Phase of Trial (pts infused) | 2 (128) | 1b/2 (97) |
| Follow-up, median (range) | 13.3 mo (0.2-21.2) | 21.7 mo (not reported) |
| Prior lines, median (range) | 6 (3 to 16) | 6 (3-18) |
| LD chemotherapy | Fludarabine 30mg/m ² × 3 d Cyclo 300mg/m ² × 3 d | Fludarabine 30mg/m ² × 3 d Cyclo 300mg/m ² × 3 d |
| Efficacy | | |
| ORR, n (%) | 94 (73) At dose: 450 × 10 ⁶ (n=54): 44 (81%) | 95 (97.9) |
| CR or sCR, n (%) | 42 (33) At dose: 450 × 10 ⁶ (n=54): 21 (39) | 82.5% (sCR) |
| DOR, median (95% CI) | 10.7 mo (9.0-11.3) 8.8 mo (5.6-11.6) | Not reported NR (16.8-NE) |
| PFS, median (95% CI) | At dose: 450 × 10 ⁶ : 12.1 mo (8.8-12.3) | 2-y PFS: 60.5% (48.5-70.4) |
| OS, median (95% CI) | 24.8 mo (19.9-31.2) | NR (27.2-NE) |
| CRS, n (%) | | |
| Overall | 107 (84) | 92 (95) |
| Grade 3-4 | 7 (5) | 4 (4) |
| Neurotoxicity, n (%) | | |
| Overall | 23 (18) | 20 (21) |
| Grade 3-4 | 4 (3) | 9 (9) |
| Infections, n (%) | 88 (69) | 56 (58) |
| Grade 3-4 infections, n (%) | 28 (22) | 19 (20) |
| Death, n (%) | 44 (34) | 14 |

Modified from Hematology Am Soc Hematol Educ Program 2022; 2022 (1)

There are now two products available. Ida-cel I just mentioned and cilta-cel. So, ida-cel has one BCMA-binding motif. Cilta-cel the newest one has two, so it's extra sticky to those myeloma cells. The overall response rate is very comparable, maybe tending a bit more to the cilta-cel and the overall duration of response ten months with ida-cel. Not reported yet with cilta-cel. They're both, again, very, very effective therapies.

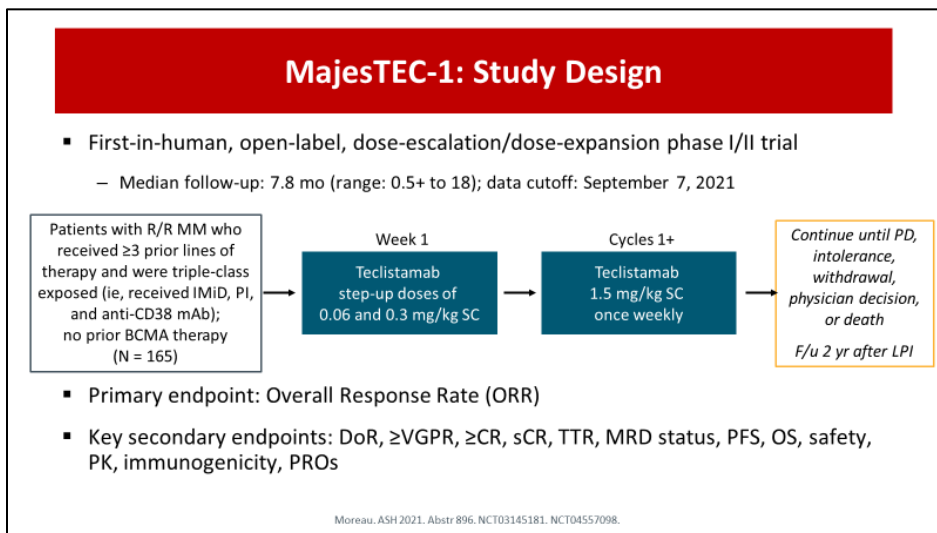


And then on to the bispecific antibodies. And this, at the last American Society of Hematology [ASH Annual] meeting, this class of therapies really took the stage. And what a bispecific antibody is, is you build an antibody against a T cell, so you have an anti-CD3 T-cell-hunting antibody that doesn't destroy the T cell, but it just finds the T cell. And then you have an antitumor antibody, a BCMA antibody, anti-BCMA which finds plasma cells. Well, what if you can reengineer the sticky part of the anti-T cell and the sticky part of the anti-myeloma cell, what if you pull those two together for a bispecific T cell engager, or you build a whole new antibody that has sticky parts for T cells and myeloma cells?

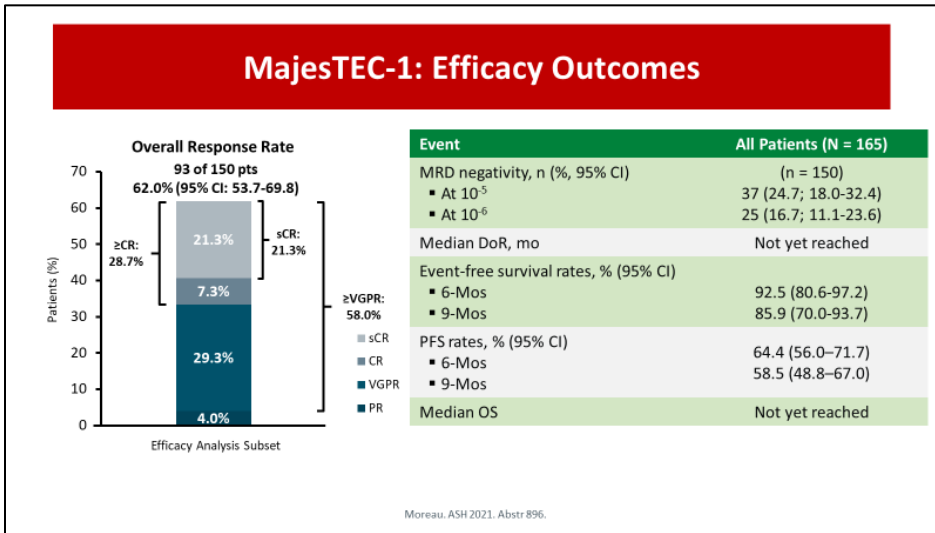
What you do, that's a bispecific antibody or bispecific T-cell engager. And when you infuse that in a patient, it gets those T cells and brings those myeloma cells together. It activates those T cells, makes them angry and they degranulate and go and kill the myeloma cell. And that's what we want. In the same way that it kills a myeloma cell by engineering them with CAR T (chimeric antigen receptor T cell), these T cells are reengineered, but they're brought in close proximity, and they go and kill those myeloma cells.



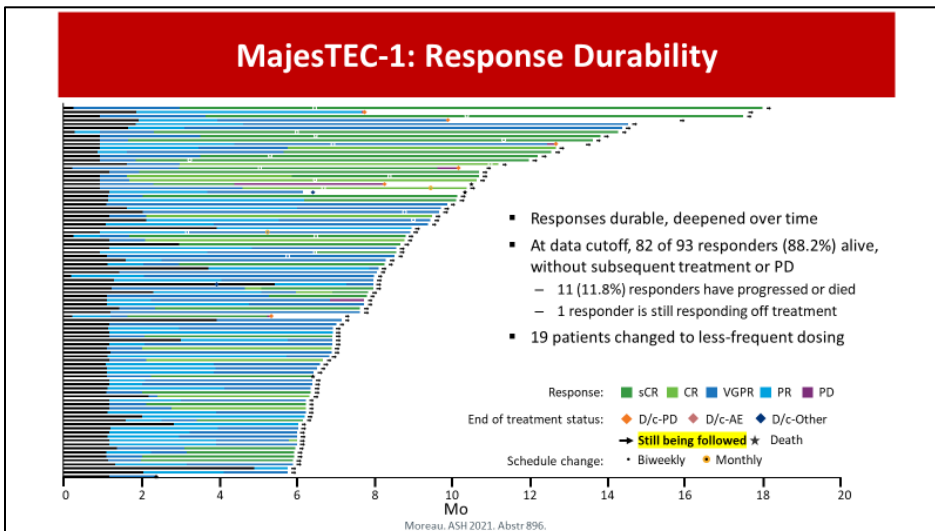
What was really exciting is this year teclistamab (Tecvayli™) was approved by the FDA (US Food and Drug Administration) in October, and that was because of the MajesTEC trial, a very important trial that came out.



This is patients that have had relapsed/refractory myeloma, have failed all the conventional therapies, and gave them tiny doses of teclistamab (Tecvayli™) over a weeks' time, and then gave them a weekly teclistamab until relapse.



What did it show? Again, remarkable response rates. And these patients were sick because they didn't have to wait around for three or four weeks to a month in order to start therapy. They could start therapy because teclistamab (Tecvayli™) was off the shelf. MRD negativity incredible for really sick patients. Overall response rates 62% including a lot of deep responses. VGPR (very good partial response) 60%. Still, I think that is incredible. The time it took to relapse, the progression-free survival, again, most patients at six months and nine months still maintained their responses, and the overall survival hadn't been reached so these folks that were otherwise very sick with myeloma doing very well.



This is a swimmers plot and what it shows all the little arrows, each line is a patient that's on teclistamab (Tecvayli™), and all of the arrows are patients that are still on therapy, so most patients are still receiving the drug. Even after 20 months of therapy still on drug, still responding and maintaining those responses, which is, again, I think, incredible results.

MajesTEC-1: Safety

| AEs in ≥20% of Patients, n (%) | All Patients (N =165) | |
|--------------------------------|-----------------------|-----------|
| | Any Grade | Grade 3/4 |
| Hematologic | | |
| ▪ Neutropenia | 108 (65.5) | 94 (57.0) |
| ▪ Anemia | 82 (49.7) | 57 (34.5) |
| ▪ Thrombocytopenia | 63 (38.2) | 35 (21.2) |
| ▪ Lymphopenia | 56 (33.9) | 53 (32.1) |
| Nonhematologic | | |
| ▪ CRS | 118 (71.5) | 1 (0.6) |
| ▪ Injection site erythema | 42 (25.5) | 0 |
| ▪ Fatigue | 41 (24.8) | 3 (1.8) |
| ▪ Nausea | 40 (24.2) | 1 (0.6) |
| ▪ Headache | 36 (21.8) | 1 (0.6) |
| ▪ Diarrhea | 34 (20.6) | 4 (2.4) |

Moreau, ASH 2021. Abstr 896.

- No patients required teclistamab dose reduction; only 1 patient discontinued due to AE (adenoviral pneumonia)
- Serious Adverse Events: 88 (53.3%)
 - Teclistamab-related per investigator: 33 (20.0%)
- Injection-site reactions (all grade 1/2): 58 (35.2%)
- **Infections: any grade, 104 (63.0%); grade 3/4: 35.2%**
 - Opportunistic infections: 9 (5.5%)
- **Hypogammaglobulinemia-Low normal antibody levels: 119 (72.1%)**
 - 41 patients received IVIG at any time during the study (at physician discretion)
- 9 deaths due to AEs; none related to teclistamab
 - 7 COVID-19, 1 pneumonia, 1 hemoperitoneum

It did have some toxicities. It can cause neutropenia. There were some CRS, cytokine release syndromes and ICANS. But probably one of the biggest side effects that we saw was infections. Infections of any grade were about 63% and severe infection about 30% and that's because the teclistamab (Tecvayli™) hunts down myeloma cells and normal immune system plasma cells which then has low antibody levels, so the immune system is a bit reduced. So, we usually use intravenous immunoglobulin to help maintain the patient's immune system and the antibiotics.

Teclistamab Approval

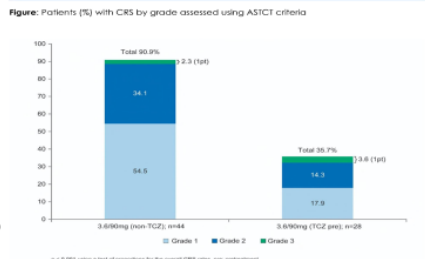
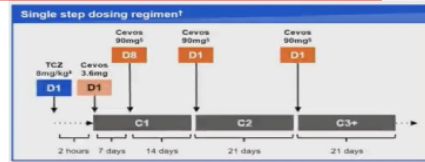
- On October 25, 2022, the Food and Drug Administration granted accelerated approval to teclistamab-cqyv (Tecvayli), the first bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
- Approved for relapsed or refractory multiple myeloma who have received **≥4 prior lines of therapy**, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
- Because of the risks of CRS and neurologic toxicity, including ICANS, teclistamab-cqyv is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), called the Tecvayli REMS
- REMS program requires an inpatient hospital stay for the first 3 step up doses

<https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma>

So, again in October, we were so excited the FDA (US Food and Drug Administration) approved teclistamab (Tecvayli™) after four prior lines of therapy. And, again, because of that cytokine release syndrome and neuro-cytokine release syndrome, we admit patients to the hospital for the first three doses.

Pretreatment with Tocilizumab Prior to Bispecific Cevostamab Showed a Marked Reduction in CRS

- Tocilizumab (TCZ) is a monoclonal antibody which blocks the IL-6 receptor
- TCZ pretreatment arm was added GO39775 Phase I study of cevostamab, an FcRH5xCD3 bi-specific T-cell engager for RRMM
 - To determine whether a single dose of TCZ prior to the 1st dose of cevostamab can reduce CRS
- 35.7% of pts in the TCZ arm experienced CRS as compared to 90.9% in the non-TCZ group
- No negative impact on anti-tumor activity was observed
 - ORR in the TCZ arm was 50% compared to 37.2% in pts receiving 90mg without TCZ pretreatment

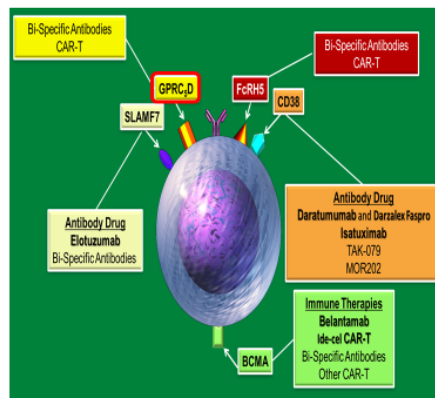


Trudel, ASH 2022, Abstr 567.

One really important study that really changed our practice here at Michigan State (MSU) was of a drug called tocilizumab (Actemra®). Tocilizumab was used a lot for the severe reactions of COVID, and it blocks IL-6, which is the main cytokine that causes a cytokine release syndrome or CRS. So, they pretreat this study with cevostamab, another type of bispecific antibody. They gave patients tocilizumab before they got the bispecific antibody on day one, and it reduced the number of CRS from 90% to 30% with no negative impact on tumor activity. So, our standard here at MSU is that we give toci (tocilizumab) before we give the bispecifics because it reduces the cytokine release syndrome by such a big degree as compared to not giving it at all.

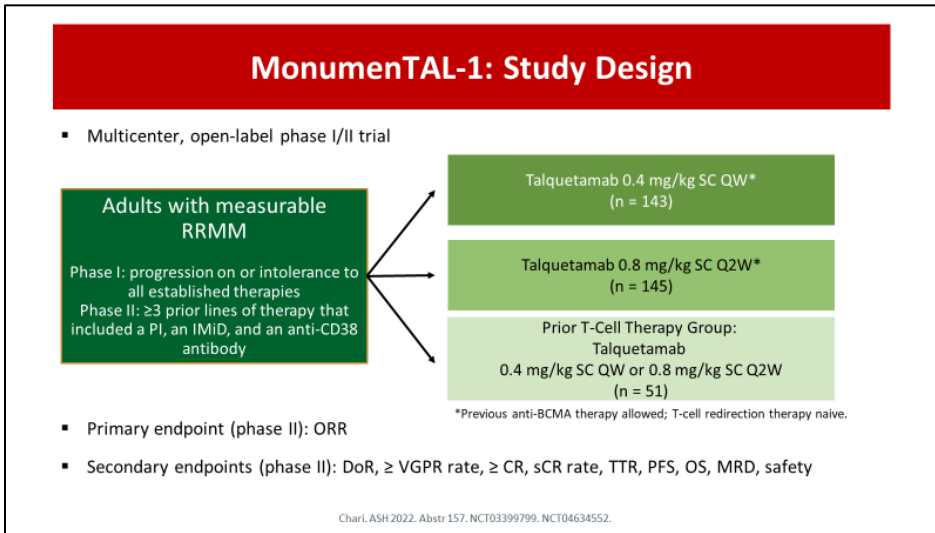
Talquetamab in MM: Background

- GPCR5D: orphan receptor highly expressed on MM cells relative to normal cells
- Talquetamab: first-in-class bispecific IgG4 antibody binding **GPCR5D and CD3 receptors**
- Phase I ORR of 64% to 70% with talquetamab shown with QW and Q2W dosing
- Current analysis reports updated data from pivotal phase II MonumentAL-1 study including

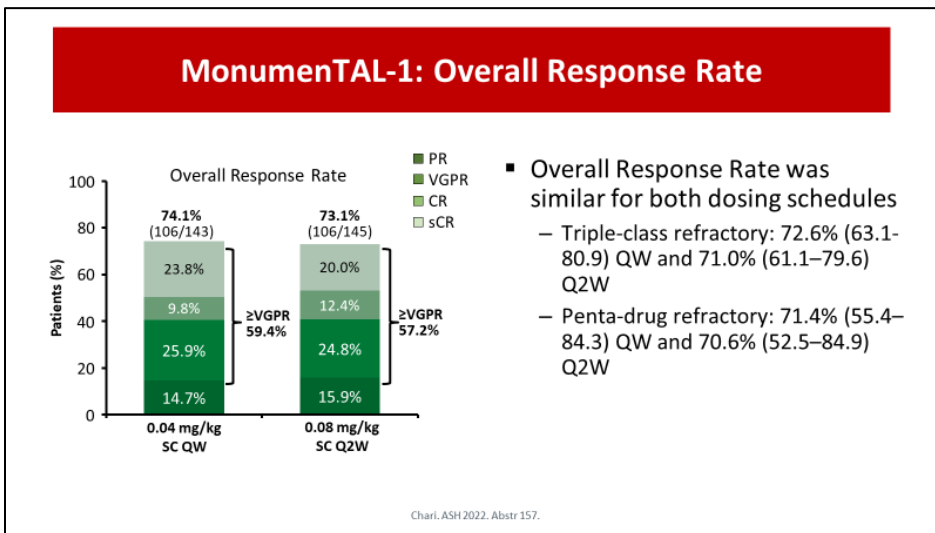


Verkleij, Blood Adv. 2021;5:2196. Pillarisetti, Blood. 2020;135:1232. Chari, ASH 2020, Abstr 290, Minnema, ASCO 2022, Abstr 8015, Chari, NEJM. 2022;387:2232

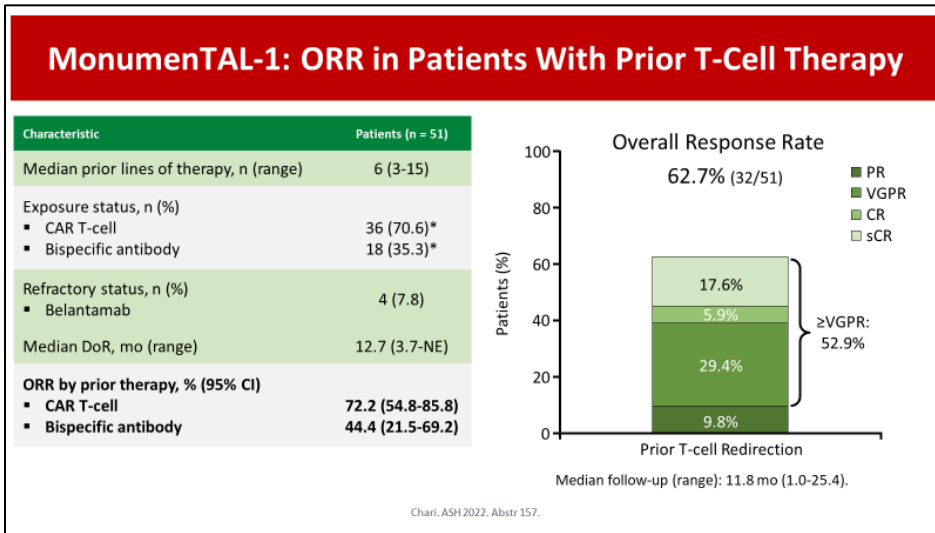
And now I'll end on talquetamab, which is a novel bispecific antibody against GPCR5D, which is in a lot of the therapies I talked over against BCMA, and this is another epitope that identifies those myeloma cells. And the phase I trial showed excellent response rate.



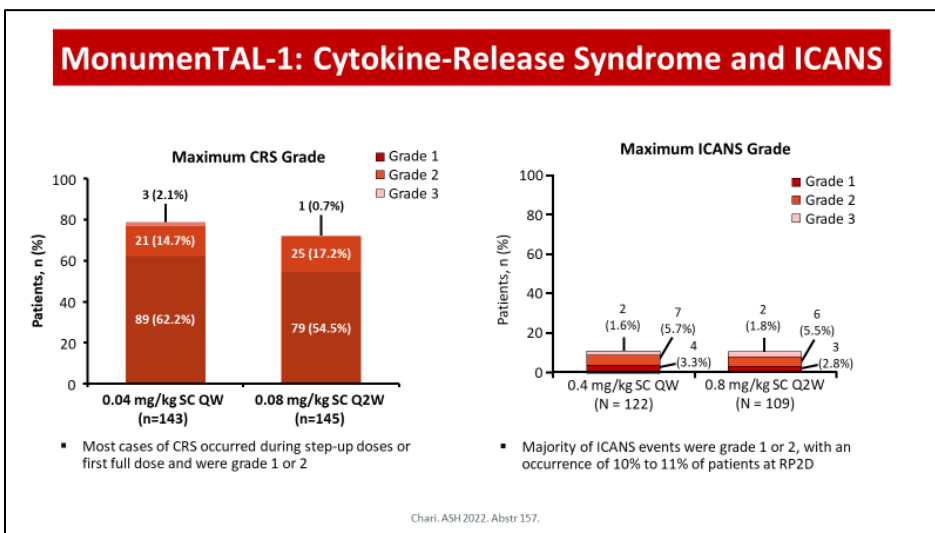
The MonumentAL-1 trial then tested it again. And this is really important because it tested at two different doses, but, more importantly, it tested in patients that are already failed CAR T and other BCMA therapies. This is going to be important to know in the future as we treat more and more patients with BCMA-directed therapies.



The overall response rate was excellent. Excellent overall response rate for triple-class and penta-class refractory, 73% and 74% regardless of the dose.



However, in patients that had prior T-cell redirection therapy, prior CAR T or bispecific antibody, remarkable responses for these patients where we're really worried on what we're going to treat them with is a 62% response rate for these patients in using something besides BCMA as a myeloma target.



Again, there were some CRS' but low-grade CRS for the most part and ICANS.

| Comparison of immunotherapy approaches in myeloma | | |
|---|--------------------------------------|--|
| | Bispecific T-cell engagers | CAR T-cell therapy |
| Advantages | Off-the-shelf therapy (no delays) | - |
| | - | One time treatment Vacation from continuous therapy |
| | Deep responses | Deep responses |
| | Mostly grade 1-2 CRS/ICANS | - |
| | Only initial dosing as inpatient | Only initial dosing as inpatient |
| Disadvantages | - | Administration delays due to manufacturing time |
| | Continuous therapy until progression | - |
| | Weekly or biweekly dosing | - |
| | Significant immunosuppression | Significant immunosuppression |
| | - | Potential for severe CRS/ICANS; prolonged cytopenias |
| | Specialized centers required | Complex infrastructure required |
| | Cost (\$\$) | Cost (\$\$\$) |

Adapted from Hematology Am Soc Hematol Educ Program 2022; 2022(11): 163-172

So, there's some real advantages to the bispecific antibodies as off the shelf there are no delays in giving the therapy, deep responses, and low amount of the CRS and ICANS and there's only one hospitalization associated with it. But with the bispecific T-cell antibodies engager just continuous therapies or you're getting it once every two weeks or once a week and there's significant immunosuppression.

For the CAR T-cell therapies, usually it's a one-time treatment and there are delays. We can take some time to make them, but it's a one-time treatment. So, it's a one and done. Again, deep responses. It does require just one, usually one hospitalization, but it does cause immunosuppression and the potential for severe ICANS and it's really at only specialized centers that will do CAR T.



So, now probably the most important part of the talk is communicating, so I can give you a bunch of different options of treating newly diagnosed refractory myeloma. And the most important person to decide which of those therapies is you. Based on your age or other conditions, your goals of therapy,

your risk profile, your geography, you are the main person that decides what type of therapy among those options.

Choosing Your Health Care Team

- You should feel **respected and listened to** by your doctor, nurse, care extenders, social worker and others on your team
- Ideally you can work with a doctor who's **experienced in treating multiple myeloma**
- You should be able to **talk openly** with your health care team and **trust their advice**



So, it's really important that you feel respect and listened to by your doctor and other people involved in your healthcare team. That you pull your team together and they should all respect and listen to you to have a doctor's experience in treating myeloma because myeloma all in all is a rare disease compared to colon cancer, lung cancer and breast cancer. So, having someone that treats myeloma frequently is really important, so that all these new things and all these opportunities are coming about. You should always talk openly to your healthcare team and trust their advice. If you don't have those features in your physician, then I would strongly recommend that you find someone who does listen to you and that you can trust their advice.

Second Opinion

- **You have the right** to get a second opinion.
- A second opinion can help you:
 - Confirm your diagnosis
 - Give you more information about treatment options
 - Additional chance to hear about your disease
 - Talk to other experts
 - Introduce you to clinical trials
 - Help you learn which health care team you'd like to work with, and which facility

You also have a right to a second opinion. If your doctor doesn't want you to get a second opinion, then you definitely need to find a different doctor because a second opinion can help confirm your

diagnosis, give you more information about treatment options, to hear your disease from a different point of view, from a different provider, and to help introduce you to clinical trials. So, I send my patients for second opinions, and I do lots of second opinions because it's really important for my patients to hear that other opinion.

Open Communication Is Key

- Tell your health care team about:
 - Your **symptoms**, and how they impact your life
 - Any **treatment side effects** you feel, and how they impact your life
 - Financial toxicity of therapy
 - Your **goals for treatment** (they may change over time)
 - **Your questions and concerns**
- It's important to **work together** with your doctor for the best outcome
 - When a doctor recommends a treatment, share your concerns about side effects and ask questions about other options

You tell your healthcare provider about your symptoms, any side effects you're having. Communicate, communication. We did a study looking at communication with patients, and 60% of patients don't speak about their side effects because they don't think we can help them. We can definitely help you with your side effects and let us know and make sure your questions are answered. It's important to work together with your provider.

Preparing For Your Doctor Visit

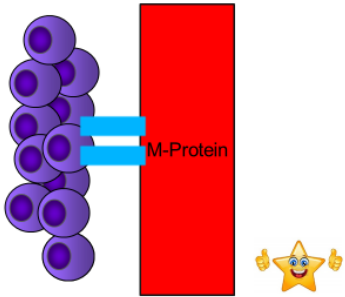
- Write questions down before you go to the doctor; bring them to your appointment and use them to talk to your health care team
 - Write down/ record the answers to these questions.
 - Keep copies of your lab work, x-rays, and biopsies
- **Bring a friend or family member with you**
- Tell your doctor and nurse about all medications you are using, including over the counter medications, vitamins, or supplements

Please always write your questions down before going to your doctor. When I go to my doctor, my head starts to spin, and I forget everything, so I write down my questions before I go to my doctor, and I write down the answers. Always bring somebody with you. Have someone else listening for you

to pick up some of those nuances that you may otherwise miss. And make sure you tell your doctor about other medications that you're taking.

It's important to know...

- What are **YOUR** goals of therapy
- How to read your myeloma protein level
- What is your **MM** risk/ stage
- What are your therapy options
- What is your response to tx
- Know what side effects to expect so you can report them
- Who is on your care team
- Obtain a second opinion
- Ask about clinical trials
- Be informed and empowered in 2023!**



So, it's important to know what your goals of therapy are, how to read your myeloma protein level so that you know when to celebrate when the treatment has worked because the number of myeloma cells equals an M protein or light chain, to make sure that you know your risk and stage because we definitely treat that differently in 2023, what are your treatment options, what's your response to therapy, so, again, you know when to celebrate when the myeloma has gone down and gone to a very good partial response or complete remission, know your side effects and tell us about your side effects, know your team around you, obtain second opinions, ask about clinical trials, the pointy end of myeloma therapy, and be an informed patient in 2023 most important thing. And being at this meeting today makes you informed, makes you empowered ready to tackle this year.



Thank You!

For Your Time and Attention


colecrai@msu.edu  Cancer Research
MICHIGAN STATE UNIVERSITY

And that's it. There's our hospital and there's our laboratory at Michigan State University. So, thank you.

Lizette Figueroa-Rivera, MA

Wow! Well thank you so much, Dr. Cole, for volunteering your time with us today and updating us on the treatment advances for myeloma.

QUESTION-AND-ANSWER SESSION




ASK A QUESTION
SPOTLIGHT ON MULTIPLE MYELOMA

Ask a question by phone:
Press star (*) 1 on your keypad to ask a question
To remove your question press star (*) 2 on your keypad

Ask a question by web:
Type your question in the "Ask a Question" box under the speaker video window

Due to time constraints, we can only take one question per person.
Once you've asked your question, the operator will transfer you back into the audience line.

82



Lizette Figueroa-Rivera, MA

And, as you said, it is time for our Question-and-Answer portion of our program. For everyone's benefit, please keep your questions general in nature without many personal details so Dr. Cole can provide answers that are more general in nature.

So, the first question is from Naomi. She said you mentioned a higher incidence of myeloma in the African American and Black communities and is asking, "Are we trying to find out why?"

Craig Emmitt Cole, MD

Yes. We are really trying to find out why. There are multiple studies that are going on trying to look at the genetics to see what the difference is between Blacks, people of African descent and Caucasians. One of the bigger studies that I would recommend to people is the PRIMA study. So, the PRIMA study is a nationwide study that you can login over your computer and it's for patients' family members. And they specifically want to enrich the population of African Americans. And so, if you're Black and over the age of 50, like I signed up for the PRIMA study, or if you're a family member of someone with myeloma, you can sign up for the PRIMA study. And they do a blood test and a questionnaire for patients with family members. And if they have a monoclonal gammopathy, then

they follow you and they do genomic testing to see what are the genes involved that causes myeloma, period, and why we see those differences between the races.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And we'll take the next question from our telephone audience, please.

Wayne from Wisconsin

My question is about the light chain ratio. I'm 11-months past transplant now and the light chain ratios are increasing each month. Right now, it's at 2.25. Is that something to be concerned about?

Craig Emmitt Cole, MD

Usually, when the light chain ratio goes up or the light chains themselves go up by ten, or if the ratio really begins to expand month after month after month or assessment after assessment, then we have to wonder if it's a biochemical relapse or if those plasma cells are becoming active again. The one thing with the light chain, a lot of things can raise the light chain. So, changes in our immune system, you know, because the light chains can be made by normal plasma cells. So, you have a cold or a flu, that can raise the light chains artificially. The kidney function is low if you're really dehydrated. That can raise the light chains artificially. But if they keep going up and up, and if the light chains are going up by 10 milligrams or the ratio expands by ten milligrams, or the ratio expands by 10, then you have to wonder, and if it's on a consistent basis, if the myeloma is becoming more active.

Lizette Figueroa-Rivera, MA

Thank you for that question. Doctor, our next question is from V. V is asking if myeloma is hereditary.

Craig Emmitt Cole, MD

Oh, they're all super good questions. That's a super good question. And so, myeloma in and of itself is not hereditary. However, the precursor disease to myeloma, the monoclonal gammopathy of uncertain significance (MGUS), of which a small minority of patients with MGUS will become myeloma, MGUS does appear to have a hereditary pattern. So, primary family members to a patient with myeloma have a higher risk of having MGUS, the precursor condition which rarely turns into myeloma. And that is more pronounced in patients of African descent than in Caucasian patients. So, is myeloma itself hereditary? No. But is the precursor condition hereditary? It is. The precursor condition can be hereditary, especially in patients of African descent.

Lizette Figueroa-Rivera, MA

Thank you so much. And our next question, Maria and Joseph are asking about MRD (minimal/measurable residual disease), "Why is it important and how is it tested?"

Craig Emmitt Cole, MD

Yeah. It's a super good question. And so MRD is when we look for very, very small amounts of plasma cells. When you think about it, the SPEP (serum protein electrophoresis) test we've been doing since the 1950s. The light chain test we've been doing since about 2010, so they're pretty old tests. And they were never designed to look for very, very small amounts of myeloma like we're able to achieve today because back in 1970, we didn't have any of these therapies, and we couldn't get anyone down to a complete remission or very good partial response. But now we're able to get people down to very, very low amounts of disease, lower than what the SPEP and light chains are able to detect. So now we need a new test, and the MRD is a way to do that.

There are two ways to measure it. One way is that you use a flow cytometer, and the flow cytometer uses lasers like the checkout machine at the grocery store. And it uses lasers to actually read the proteins on myeloma cells to be able to pick up myeloma versus other cells. And it can count millions of cells by running them through the scanner and able to count those myeloma cells compared to normal cells, that's using flow cytometry.

Even better than that is checking the genetic fingerprint of myeloma cells. The way that's done is that every myeloma cell has a unique fingerprint at the time of diagnosis. So, you get that fingerprint from that initial diagnosis and then you get a bone marrow biopsy at the time of remission, and you can look for one in a million cells by looking for that fingerprint inside the bone marrow, which, again, is way more sensitive than what our lab tests are able to do today.


One of the most important things that MRD allows us to do is able to predict into the future. And we know patients that have sustained MRD when they remain MRD negative for long periods of time, that they usually maintain their remissions for long periods of time. So, the FDA instead of waiting for five or six years for these new therapies that patients relapse, they'll use MRD as a surrogate to approve drugs much sooner.


So, how does MRD fall into decision-making for an individual patient? We're still trying to get a handle on that. There are multiple trials that are now looking at is it possible to start reducing the maintenance therapy for patients based on MRD negativity? Can we deescalate or do we escalate therapies based on MRD? Those studies are still ongoing and, hopefully, in the next few years, they'll show some results where we use MRD in the decision-making process.

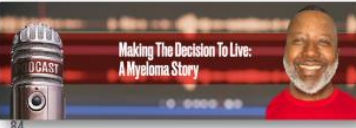
Lizette Figueroa-Rivera, MA


Thank you so much. And we'll take the next question from our telephone audience, please.

LLS EDUCATION & SUPPORT RESOURCES

 **Online Chats**
Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit www.LLS.org/Chat

 **Education Videos**
View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit www.LLS.org/EducationVideos

 **Patient Podcast**
The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org



Debra from New York

My husband has multiple myeloma and has had it for 12 years and has only had an exclusive maintenance therapy of Revlimid®. His oncologist retired and we have a new oncologist who immediately took him off the Revlimid® cold turkey. He said that we had to get a second opinion, but he said that that second opinion had to be on a tertiary level. We're older and we are far, far from central therapeutic centers, and I wonder if that is a common request whether it should be mandatory. What is wrong with a lateral level second opinion? And he said that unless we go to a major center that he's not going to take care of us. And my husband's out of his Revlimid®, and we can't get a new oncologist because they're not sending the records. I don't know what to do.

Craig Emmitt Cole, MD

Yeah. No, I'm sorry to hear that.

Debra from New York

Thank you.

Craig Emmitt Cole, MD

So, you know, the one thing about maintenance Revlimid® is that we really don't know how long patients should stay on maintenance Revlimid®. We know from a study that was published a couple of years ago, called the STaMINA trial, where they had patients stop maintenance Revlimid® after three years. And we know three years may be a bit short. That when patients stopped the maintenance Revlimid® after three years that there was a tendency that some patients started to relapse after three years.

There's another study that was at the last American Society of Hematology [ASH Annual] Meeting that was done in Europe, so a bit different in induction therapy, a bit different in the patient population.

But they found that after five years, that the return on the Revlimid® investment begins to wane a bit. Does that mean we should stop patients after five years? Absolutely not. But it gives us a hint that we should really be looking at these long-term Revlimid® and seeing, and that's where maybe MRD will become important to see if we can discontinue therapy early because when they discontinued therapy in some of these MRD patients, that they were able to maintain their responses. But we need some more American trials to help us tell that.

For second opinions, you know, I think second opinions are usually where a second provider, a person that's experienced in treating myeloma, can then communicate with the provider closer to home. And especially if you have a computer, and the LLS can help finding providers, myeloma providers that do telehealth. And so, I've done telehealth for patients around the country and sometimes in other parts of the world by giving an opinion about myeloma without the patients having to travel long distances. And so, if you have a computer or even a cell phone, because I've done lots of second opinions over cell phones where I get their records and I'm able to communicate to patients through their cell phones by TeleHealth, which has really opened up the opportunity for doing second opinions in people that were otherwise unable to travel long distances.

Lizette Figueroa-Rivera, MA

Thank you so much for that question. Doctor, the next question is from Patricia. Patricia is asking, "Is a bone scan as good as a PET (positron emission tomography) scan?"

Craig Emmitt Cole, MD

Ah! So, a bone scan, a nuclear medicine bone scan is a test that's usually used for patients with breast cancer, lung cancer and prostate cancer because those cancers, what they do is that they activate the bone-forming cells, and that's what the bone scan picks up. The myeloma cells do just the opposite. The myeloma cells get rid of the bone-forming cells and hijack the bone-dissolving cells, the osteoclasts, in order to form holes in the bones. And so actually the nuclear medicine bone scans don't work for multiple myeloma, but they will work for other cancers.

And so, the best test for looking for lytic lesions in myeloma is you can do a skeletal survey. We've been doing skeletal surveys since 1900 for myeloma. It's a bit older of a test and not very sensitive, but the PET scans and the low-dose CT (computerized tomography) scans and MRIs (magnetic resonance imaging) are the best ways to detect lytic bone disease, and the nuclear medicine bone scans are for other cancers.

Lizette Figueroa-Rivera, MA

Thank you so much. And we'll take the next question from the telephone audience, please.

John from British Columbia

I am a survivor of multiple myeloma, and I used two lines of treatment. Firstline treatment was a transplant that I needed, and my oncologist actually told me not to do any continued maintenance

with the Revlimid®. And then I did stop taking all the medications. Yeah. So, after a year and a half the myeloma came back and the numbers started rising up. And at that time, he told me that it was not good for me to repeat the transplant again because the response it was not long enough and if they do repeat, probably it's only going to last six months or less. So, at that particular point he actually put me on the second line of treatment which I am on now for two years is daratumumab combined with Revlimid®. So, I've been on this second line of treatment for two years now, and they did start on IV (intravenous) daratumumab and now they switched to a subcutaneous daratumumab which is an injection which it's much faster. But my question is though I just wonder how long can I be on this line of treatment because when I talk to my oncologist, he just tells me my numbers are in the range and which is good, but my question is just how long can I be on this treatment? How many more years or how long when I start feeling the spike on my light chain?

Craig Emmitt Cole, MD

That's a super good question. And it's good to hear how well you've responded to Darzalex® or sub-Q daratumumab and Rev (Revlimid®). And, I guess, the answer is that it kind of depends. And what I mean by that is, one thing that I learned very early on with myeloma, especially when we started using these immune therapies and these novel therapies is that everyone is different with myeloma. That when we were using chemotherapy and the treatments were not very good, everyone was kind of the same. The outlook was pretty bad back in the late 1990s and early 2000s. And now with the immune therapies, we are really seeing that there's huge differences between patients.

And so, one thing that determines how long that your response would be is if you were high risk or standard risk at the time of diagnosis. Again, higher-risk patients are harder to maintain in a remission and responses and standard risk patients are a bit longer. And that helps determine it and, also, how deep is the response. And I would ask your doctor, you know, "Am I a partial response, a very good partial response, or one of the deeper responses?" because the smaller we can shrink that ice cube, the longer it takes to come back.

I can tell you that to the regimen that you're on, the dara-Rev-dex., I have had patients on for years. And I would say that the standard is two to three years, especially using it as a second-line therapy after a failure of the first-line therapy. But everyone can be very different with that and so the two questions I would ask your provider is, "What was my risk at the time of diagnosis and how deep of a response have I achieved?"

Lizette Figueroa-Rivera, MA

Thank you for that question. Doctor, Alana is asking, "I'm confused by the term remission being used here when there's no cure. I was told that there is no real remission."

Craig Emmitt Cole, MD

So, we tend to use remission and response kind of in the same breath. It's true that we don't have a definition for cure with myeloma. And we use the terms in myeloma very differently because myeloma is different than any other cancer. We use those terms very differently, so a remission in breast

cancer means that you're cured. A remission in myeloma or a complete response myeloma means that we can't see the protein on a test, or someone is MRD negative.

It is true that we haven't cured myeloma yet, but the terms that we use in the way of very good partial response, partial response, complete response, or complete remission, MRD negativity are very, very specific to myeloma and really can't be extrapolated to other types of cancer.

Lizette Figueroa-Rivera, MA

Thank you, doctor. The next question is coming from Ben. Ben is asking, "Is there a risk that bone deterioration can occur while the M protein is stable, for example, during maintenance?"

Craig Emmitt Cole, MD

Yeah. That's also a good question. I'm going to say that every time. So, a couple different things can happen while patients are on therapy. So, when they're on maintenance, or if they're in a really good remission or response, that if they already had osteoporosis before that, if they had osteoporosis before they had myeloma, then they could still have brittle bones after they've attained a response. So, what I'll frequently do is after a patient has achieved their induction therapy, that they have gotten to the recommended two years of a bone strengthener after they've achieved a very good partial response or a complete response, I'll do a bone scan. I shouldn't say bone scan, a DEXA (dual energy x-ray absorption) scan and that looks for osteopenia/osteoporosis because that could still be there. They could've had that at the time of diagnosis, and it could still be there. And I'll check that DEXA bone test to see if they have thin bones to begin with. If they have thin bones, then I will prescribe the bone strengthener as if they were just anybody else with osteopenia and every three months, I mean every six months, sometimes once a year.

Another thing is the medications that you're on. And if you're still on dexamethasone, that could still cause the bones to thin. And then I would really challenge to say, "Do you still need to be on the bone thinner?" And continuing to take calcium and vitamin D can also help continuing to strengthen the bones. But that's a really important question. I think the biggest thing to think about is, is there still some osteoporosis there, some thinning of the bones, that may need continued treatment? But otherwise, if the disease is quiet, the bones are going to be happy.

Lizette Figueroa-Rivera, MA

Thank you. And the next question, doctor is from Paul. Paul is asking, "When is a second stem cell transplant warranted?"

Craig Emmitt Cole, MD

Wow! That's a really good, again, they're all super good questions. But, you know, that's a very fluid answer. It was a much easier answer back in 2010 and 2012 when we didn't have a lot of other options for patients who relapsed, and we would reach for a second transplant. So, the textbook

answer to that question is if you've had a response lasting more than three years, that once you've achieved a second very good partial response, you can then think about a second transplant.

The one thing about a second transplant is they usually last about half as long as the first one. So, we just had someone here that had a 10 year – I think it was longer than that – like 12-year remission from their transplant and, therefore, it made sense to do a second transplant because they would probably get six or seven years out of a second transplant, so that's kind of an easy answer.

If someone has had three years remission with a transplant, then you have to think twice about having a second transplant where it may last a year and a half. And so, as the responses get closer and closer to three years, then the attractiveness of a second transplant begins to go down a bit. And kind of the more competing cause is that we have such good therapies that are available now. The one thing I didn't mention is that I had talked about how the bispecifics and the CAR T-cell (chimeric antigen receptor T cell) therapies are being used in fourth-line therapy, which is they're FDA (US Food and Drug Administration) approval, but there are innumerable clinical trials that are going on with the newest therapies and using it in earlier lines of therapy. And the question that we'll have in the next couple years is, will using CAR T or using the T-cell engager bispecific antibodies as a second-line therapy, will that supplant doing transplant for some patients? And that question is still to be answered, but a very exciting one, which is why I would recommend above doing a stem cell transplant is doing a clinical trial.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And we'll take the next question from the telephone audience, please.

Susan from California

Hello. Dr. Cole, you're always so interesting and so helpful. Thank you. So, my question is about a test I read about recently called the EasyM™ test for monitoring MRD status. Perhaps you're familiar with it. It's a blood test and doesn't require biopsy. And I'm wondering whether this is something that we can now look to, to supplant biopsies as a way of monitoring MRD and whether you need to have a blood sample analyzed at diagnosis in order to be eligible to use this test.

Craig Emmitt Cole, MD

What are the letters again, EVM (EasyM™)?

Susan from California

EasyM™, the FDA just approved it for use in the United States. It's from a Canadian company that I believe is called something like Nuvor, N-U-V-O-R (Rapid Novor, Inc.). And I guess it's been approved for use perhaps in Canada for a while. It's just been approved by FDA here.

Craig Emmitt Cole, MD

They're two super good questions. Thanks for the kind words. So, there are two new monitoring methods for, and really one I think that I hope will be the newest thing to supplant the SPEP (serum protein electrophoresis) and free light chain because, again, those tests have been around for quite a while. And for the SPEP, it's been around since the '50s. And one of them I think this is what you're referring to is the mass spec (mass spectrometry), which is able to look at very, very, very small amounts of myeloma protein in the bloodstream, much smaller than what the SPEP is able to detect and can be used for MRD assessment.

The other one, which is even more exciting, is looking for circulating tumor DNA (deoxyribonucleic acid) because I kind of mentioned earlier that with MRD assessment, with the molecular MRD assessments that you look for that genetic fingerprint. And cancer cells are kind of sloppy. They release a lot of their DNA and RNA into the bloodstream. And you can pick that up during tests to see if there is circulating cancer DNA that they match that fingerprint. Because, of course, if you have cancer cells in your body and you do the DNA fingerprint test and you find the fingerprint, then that means that there are cancer cells there. And that's one of the really emerging to liquid biopsy tests that are being used to help diagnose myeloma to do some of the gene assessment and to monitor for MRD.

Lizette Figueroa-Rivera, MA

Thank you so much for that question. And, doctor, our last question today, Ronald is asking, "What is the best lifestyle I could pursue, including diet, exercise, supplements, along with my treatment to improve my chances?" He's saying, thankfully, that so far, he's done pretty well.

Craig Emmitt Cole, MD

Yeah. With my wife as a dietitian, this is a frequent conversation that we have at home. And probably one of the biggest things is balance. There has been a study that was done in Iceland, there's been a study that was done in Europe looking at limiting processed foods. And, you know, your immune system has to do backflips if you're eating foods with lots of chemicals and strange things in it. And so having a balanced diet of fresh fruits, this is what I recommend to my patients and what my wife had recommended when we used to work together recommended to patients is a balanced diet limiting processed foods. I mean it's okay to go to a burger place once in a while, but I wouldn't live there because those things have lots of chemicals in it. To take supplements, vitamins as needed but really important to try and stay active. Activity helps the immune system. Activity helps the mind. Activity helps the circulatory system. And staying as active as you possibly can help to balance everything. Balance your mind, balance your body, balance your immune system, and keep everything in check, and to help your quality of life.

Lizette Figueroa-Rivera, MA

Well thank you so much, doctor, for that answer and thank you for that question, Ronald, which was the last question today. And thank you all for your questions. Again, Dr. Cole, your continued

dedication to patients, and providing us with this update on myeloma. Thank you for volunteering your time today.

Craig Emmitt Cole, MD

Oh absolutely!

Lizette Figueroa-Rivera, MA

Thank you.

Craig Emmitt Cole, MD

I just love the LLS. It is such a joy for me. And if I can just real quick. And I think of when I first started doing talks for the LLS, the only thing I could talk about was pomalidomide was the newest thing. You can talk about all these exciting things and it's just incredible, so thank you.

Lizette Figueroa-Rivera, MA

It's wonderful. And thank you to all that provided compliments to Dr. Cole as the presentation was going along. Thank you.

CLOSING REMARKS



LLS EDUCATION & SUPPORT RESOURCES

HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials: www.LLS.org/InformationSpecialists

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation

NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLS.org/Consult

83




Lizette Figueroa-Rivera, MA

And, again, if we weren't able to answer your question today, you can contact a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572. And Information Specialists are available to speak to you from 9 AM to 9 PM Eastern Time, or you can reach out to us by email at

LLS.org/ContactUs. They are also available to speak about clinical trials as well as find ways for you to obtain a second opinion.

LLS EDUCATION & SUPPORT RESOURCES


The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers:
www.LLS.org/Finances



To order free materials: www.LLS.org/Booklets


85

Please note that continuing education credit is not being offered for this program.



THANK YOU

This program is supported by



LEUKEMIA & LYMPHOMA SOCIETY®

We have one goal: A world without blood cancers

Again, we'd like to acknowledge and thank Bristol Myers Squibb, GSK, and Karyopharm Therapeutics for their additional support for this program.

Again, Dr. Cole, thank you so much, and to all our patients, caregivers and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you so much for sharing our time with us. We wish you well.