WELCOME AND INTRODUCTION

Lizette Figueroa-Rivera, MA

Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Amrita Krishnan for sharing her time and expertise with us today. And we have over 1,600 people participating in today's program from across the United States and other countries, including Canada, China, France, and India. We would like to acknowledge and thank Bristol Myers Squibb, Genentech, and Biogen and Takeda Oncology for their support for today's program.

Before we begin, Jack Aiello, a myeloma patient and advocate, as well as LLS's volunteer, will take some time to provide some welcoming remarks. Jack:

Jack Aiello, Myeloma Survivor

Thank you, Lizette. Hi, my name is Jack Aiello, and I'd like to welcome, as well, all the patients, caregivers, and healthcare professionals for attending the program today. I've been living with myeloma since 1995 and have volunteered for The Leukemia & Lymphoma Society since 2000 when I was first trained to be a Patty Robinson Kaufmann First Connection volunteer. This is a very cool free service from LLS that matches patients and their loved ones with trained peer volunteers who have shared similar experiences.

My own treatment began in 1995, starting with chemotherapy, followed by a tandem, that's two, autologous transplants. However, with only an 18-month remission in '97, I signed up for the Regional Thalidomide Clinical Trial. While it didn't work for me, about a third of the myeloma patients showed a response. So, results from this trial began a resurgence in the development of many myeloma treatments that we have today, and so I'm quite proud of having participated in that trial.

Finally, in 1998, I had a full allogeneic (allo) transplant where the donor was my sister. Although that caused some side effects, I've been off treatment since 2001. Over the years with LLS, I've shared my story as an honoree, advocated in Washington, DC, for public policy changes, and recruited volunteers for many LLS fundraising programs. But what I enjoy the most is actually talking with many patients and letting them know of LLS resources and the importance of staying educated about their disease, because there have been so many treatment advances, especially in myeloma during the last 15 years.

When I was diagnosed, there were only two treatment paths, oral melphalan-prednisone or transplants. The good news today is that there are so many more treatment options. But that also means it can be difficult to decide which option is best for you, and it really behooves you to know the treatments available that you, together with your oncologist, and perhaps with a second opinion from a myeloma expert like Dr. Krishnan, can all make an informed decision. Knowledge is so critical. So, like you, I'm looking forward to hearing Dr. Amrita Krishnan present, provide this update of treatment options for myeloma patients, and with that I'll stop talking.

Lizette Figueroa-Rivera, MA

Thank you so much, Jack. And following this presentation, we'll take questions from the audience.

I also really wanted to take the time to thank all of you who are participating today, especially in these challenging times. LLS is closely monitoring the coronavirus or COVID-19 pandemic, and we're really here for you during this time of uncertainty.

PRESENTATION

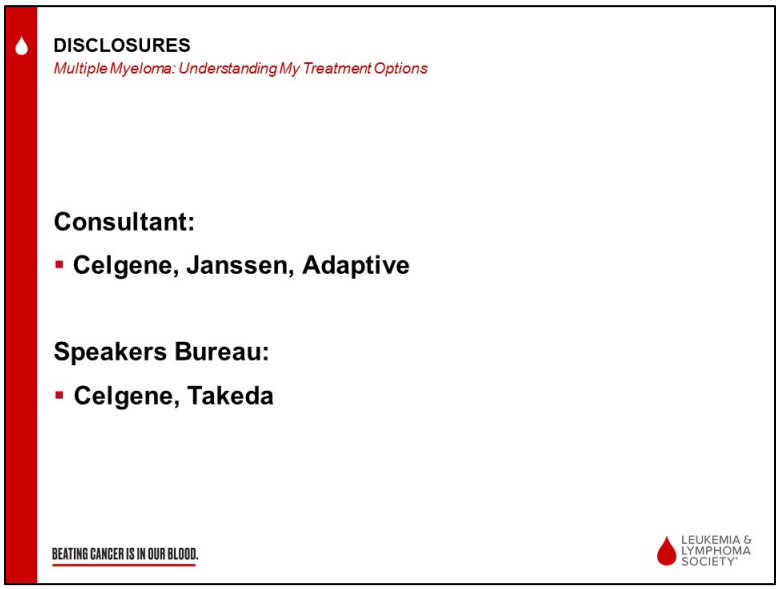
Lizette Figueroa-Rivera, MA

I'm now pleased to introduce Dr. Amrita Krishnan, Professor for the Department of Hematology & Hematopoietic Stem Cell Transplantation and Director of the Judy and Bernard Briskin Center for Multiple Myeloma Research at City of Hope's Medical Center in Duarte, California.

On behalf of The Leukemia & Lymphoma Society, thank you so much for volunteering your time today, Dr. Krishnan, especially in these challenging times. I'm going to turn over the program to you now. Thank you.

Amrita Y. Krishnan, MD

Thank you so much everyone and thank you everyone for joining. Yes, as you mentioned, I just wanted to echo from our standpoint that all the myeloma centers around the country, I was just on a conference call, in fact, at 7 AM this morning, just addressing some of the national trials and how we are reacting and trying to do everything we can with patient safety first and foremost in our minds, so, be assured we're all working together to try and do the best thing for all our patients with myeloma.



So, let me just now turn to our talk and with the recognition that everyone may be at different stages of their knowledge in myeloma as well as their disease course.

History of Myeloma

- 3300 BC - Pre-Columbian America
- 3200-500 BC - Egyptian mummies – Thebe
- 200-1300 AD - American Indian Skeletons
- 11th-15th Century AD - Iceland

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So, I thought it would be nice to put it in the context, I've always found this interesting, and these are from Dr. [Robert] Kyle, who as everyone knows, is sort of the grandfather of myeloma. He gave a great talk that I enjoyed, just really saying myeloma is not new. In fact, we've done some CAT (computerized tomography) scans of Egyptian mummies and found those lytic lesions or holes in their skulls that were very consistent and suspicious that they had myeloma and similarly in other skeletons that have been found over the years.

First descriptions…

Sarah Newbury, 39 F

- 1840: Severe back pain while stooping
- April 1842: Fractured femurs
- April 15, 1844: St. Thomas Hospital
- Rx: Orange peel infusion, rhubarb pills, arrow-root, mutton chop, wine, a pint of Porter and opiates
- April 20, 1844: Death

Solly S, Med Chir Trans Lond 27:435, 1844

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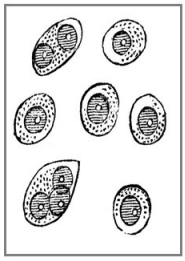
The first actual report in the medical literature was in the 1840s. A young woman presented with back pain, fractured femurs who was admitted to the hospital in London; and you can see here at the bottom, she got for her treatment orange peel, pint of porter, which may have been the best thing in that regimen. Unfortunately, you know, she succumbed to it four days later.

Sarah Newbury: Autopsy

- Multiple fractures
- Thorax reduced in size with compression of lungs
- Bone marrow: Modena red with round or oval cells with 1 or 2 nuclei

The disease began with a "morbid action of the blood vessels in which the earthy matter of the bone marrow is absorbed and thrown out by the kidneys in the urine"

Samuel Solly, 1844



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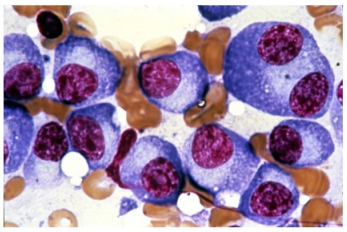
Now certainly since then, things have gotten more sophisticated, but they were actually quite knowledgeable, even back in the 1800s. They did an autopsy and found these abnormal cells that they recognized were the malignant cells.

Myeloma

- MM is characterized by
  - Excessive numbers of abnormal plasma cells in the bone marrow
  - Overproduction of intact monoclonal immunoglobulins (IgG, IgA, IgD, or IgE) or Bence-Jones protein (free antibody light chains) and concomitant drop in other immunoglobulins



Kufe. *Cancer Medicine*. 6th ed. 2003:2219

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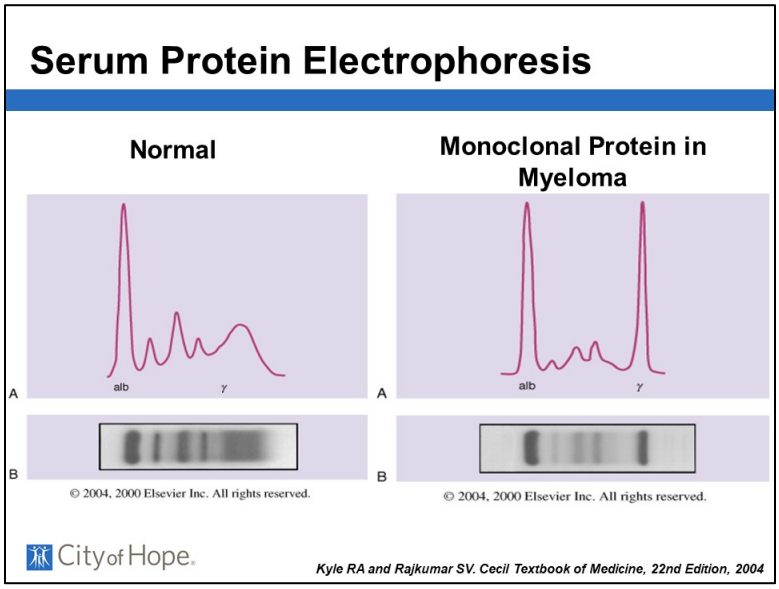
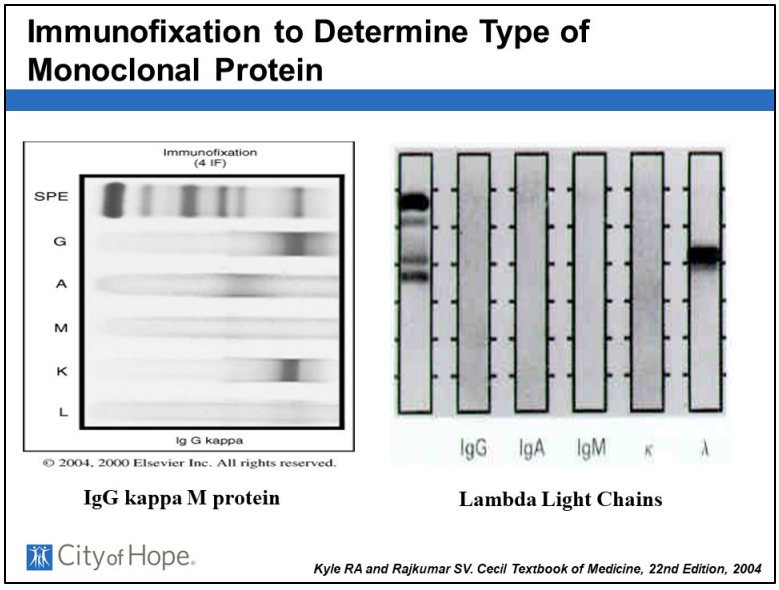
Reproduced with permission from the Multiple Myeloma Research Foundation Web site. Available at: http://www.multiplemyeloma.org/about_myeloma/index.html

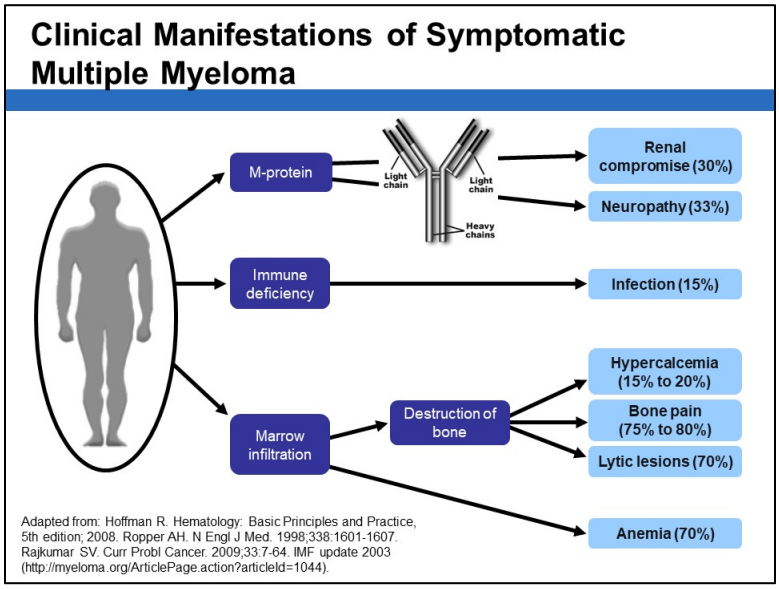
Since then, obviously, things have advanced; and many of you can recognize these are the plasma cells. The blue cytoplasm is the immunoglobulin made by these plasma cells. It's one of the first cells that medical students learn to recognize. We call it the fried egg cell.



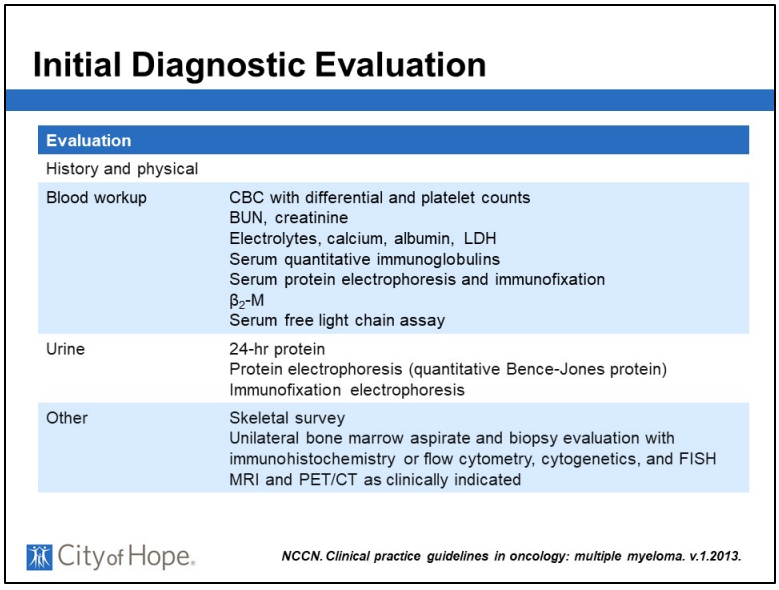
As testing evolved, we learned how to do an electrophoresis, which is basically by electric current; and the gels migrate based on their weight. The proteins migrate. So, you can see here that this is a normal pattern of proteins in the blood versus this is one in a patient with myeloma where there's this thing that everywhere now is known as the M spike, an abnormal focus of protein.



We do further testing to exactly figure out what is that protein that's the so-called immunofixation. And you can see here this patient has an IgG kappa, so the most common kind of myeloma. So those are the tests that at initial diagnosis and at follow-up.



Now turning to symptoms, as many of you know, symptoms can really be a gamut. Some people have no symptoms, and they just found anemia on routine bloodwork. Other people show up with a fracture or bone pain. Bone pain, back pain are common. Less common things, that sometimes recurrent infections can be a clue or neuropathy is another symptom.



Now I'm going to just go through, not really spend time on these. These are just to give you a sense that there's a lot of tests, blood tests, urine, and imaging tests that are done as part of the initial workup and focus more on therapy.

Induction Therapy

- Combination therapy with 3 drugs is standard for fit patients, true also for patients with renal failure
- Ongoing trials are investigating 4-drug combinations
- Which three drugs?
- Goal of therapy; MRD?

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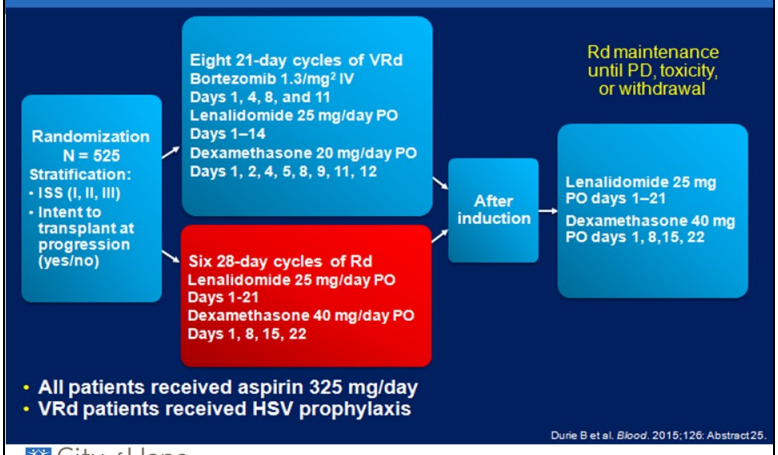
So right now, in 2020 using three drugs, if patients are fit or able to tolerate it, is really our standard of care. But as the field moves forward, I'm going to share with you some data looking at four drugs and really looking at what are our goals of therapy. Are we trying to get deeper and deeper responses, the so-called MRD (minimal residual disease)?

SWOG S0777: Study Design



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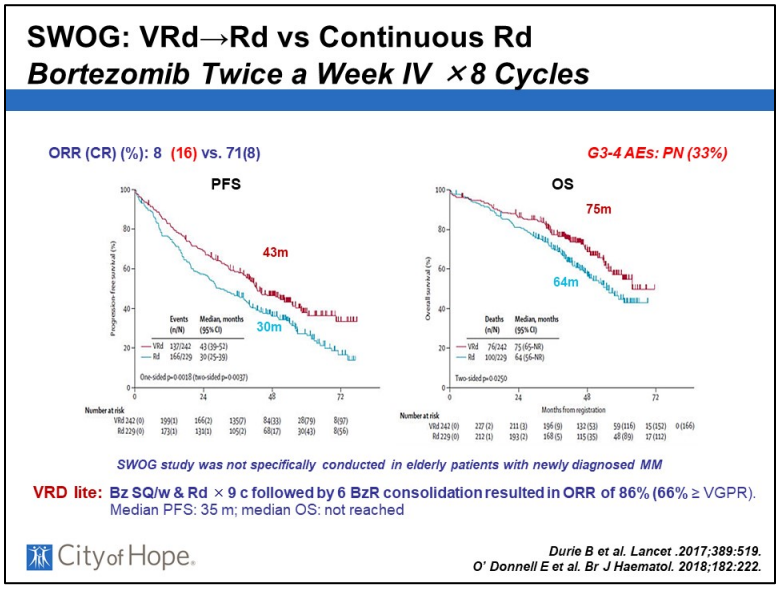
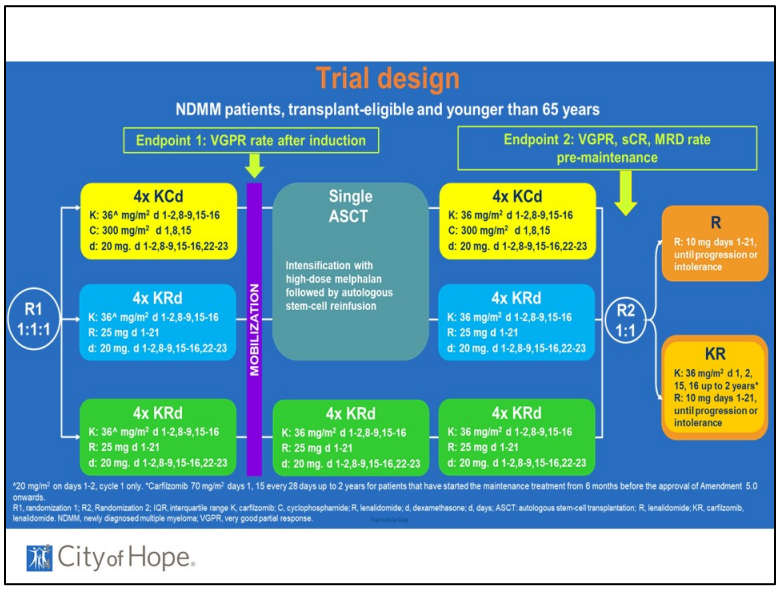
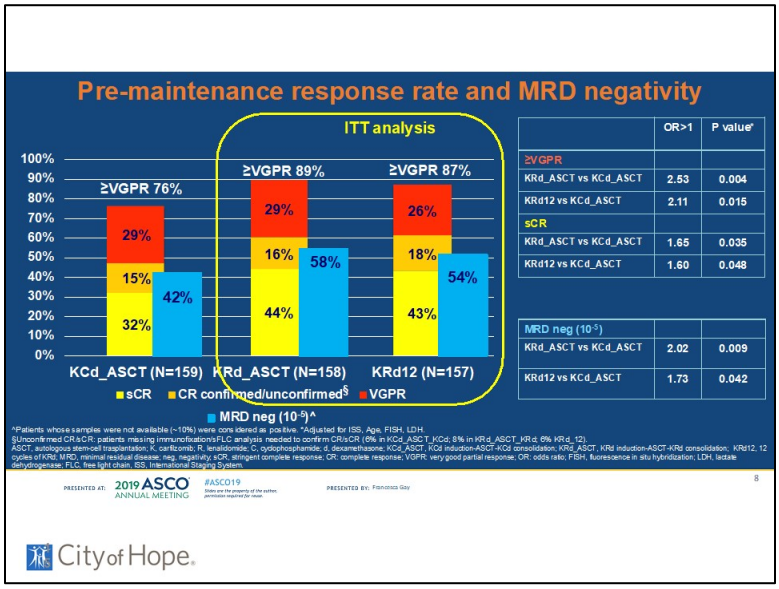
So why three drugs? Well, this is based on the SWOG trial; and Jack Aiello, I'm sure, was involved in this. This is the SWOG 777 trial, and I won't spend a lot of time, but just to say that this trial cemented for us that using your best drugs upfront really is the optimal route in terms of improving survival. Because when this trial first came out, bortezomib was relatively newer on the scene; and the question was should we save our drugs for relapse, not use all our best drugs upfront?



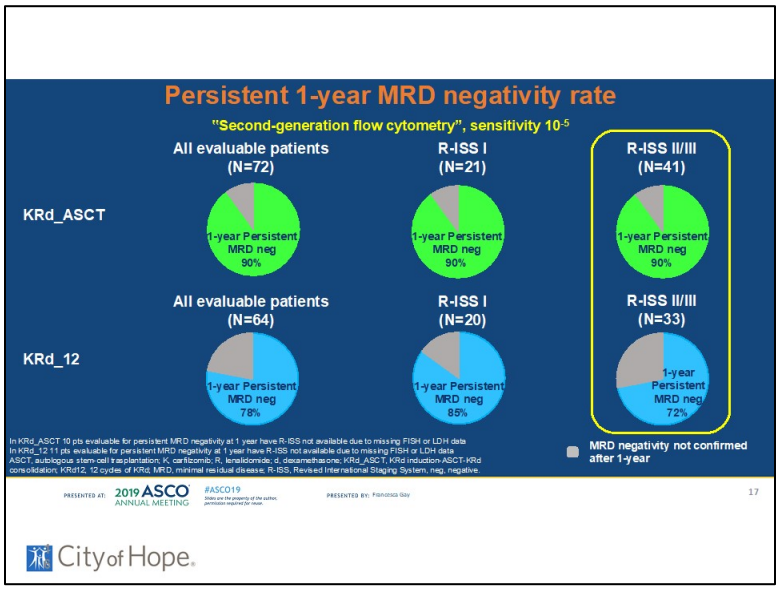
And, in fact, we learned that if you use three drugs upfront, you actually can improve survival. So, using your best drugs at the beginning really does seem to be the best route for therapy, and that really cemented for us this question of a three-drug induction.



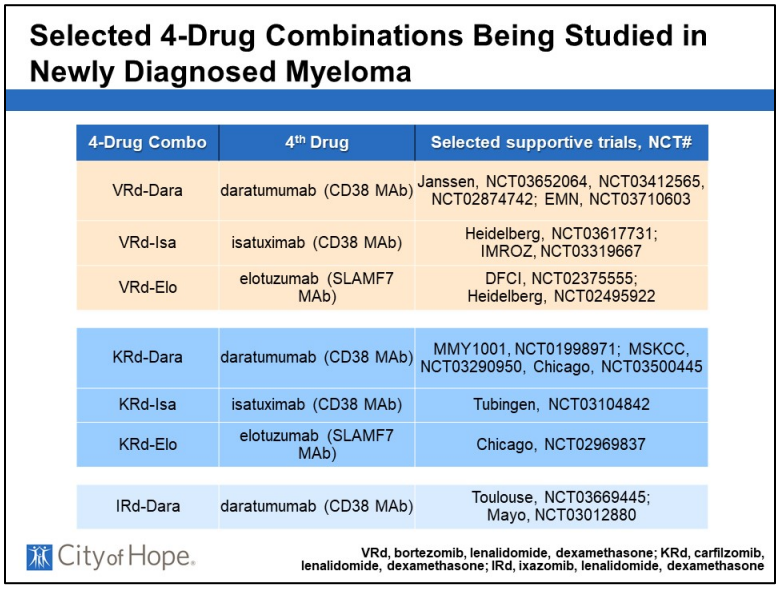
What's changed though is which three drugs should we use, and that remains sort of a moving target. The SWOG trial was based on bortezomib, a PI, a proteasome inhibitor, lenalidomide (len), and immunomodulatory agent and steroids. But since then there have been two other proteasome inhibitors approved, and so this trial, the FORTE trial looked at carfilzomib or Kyprolis®, a different proteasome inhibitor. Now it's not approved for newly diagnosed myeloma, but this trial did use it in that context; and it looked at two things – using carfilzomib-len-dex[amethasone] without a transplant and using it with a transplant.



And it showed that we had very high response rates, over 89% of patients getting very good partial response or a 90% drop in their myeloma protein, so suggesting this was a very, very active regimen and also a lot of patients becoming MRD-negative.



And as a transplanter what also made us very interested in this regimen was that in patients who had higher-risk myeloma, R-ISS (Revised International Staging System) stage II and III, the use of transplant in conjunction with this carfilzomib-based initial therapy seemed to be given the best shot of staying MRD-negative. So, again, this you may have seen. Some of you may even be on this regimen, a paradigm shift among myeloma doctors to using this more and more as the initial therapy for patients, especially those with what we deem to be higher-risk myeloma.



Selected 4-Drug Combinations Being Studied in Newly Diagnosed Myeloma

4-Drug Combo	4th Drug	Selected supportive trials, NCT#
VRd-Dara	daratumumab (CD38 MAb)	Janssen, NCT03652064, NCT03412565, NCT02874742; EMN, NCT03710603
VRd-Isa	isatuximab (CD38 MAb)	Heidelberg, NCT03617731; IMROZ, NCT03319667
VRd-Elo	elotuzumab (SLAMF7 MAb)	DFCI, NCT02375555; Heidelberg, NCT02495922
KRd-Dara	daratumumab (CD38 MAb)	MMY1001, NCT01998971; MSKCC, NCT03290950, Chicago, NCT03500445
KRd-Isa	isatuximab (CD38 MAb)	Tubingen, NCT03104842
KRd-Elo	elotuzumab (SLAMF7 MAb)	Chicago, NCT02969837
IRd-Dara	daratumumab (CD38 MAb)	Toulouse, NCT03669445; Mayo, NCT03012880

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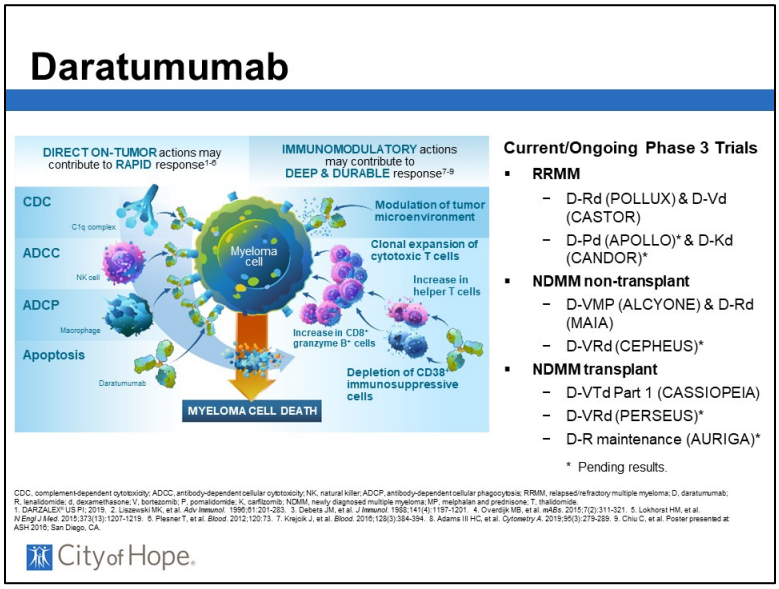
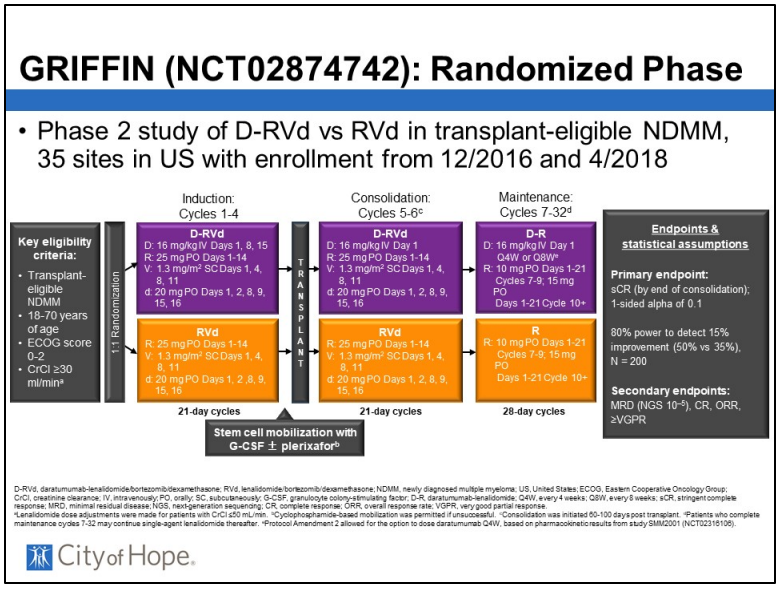
VRd, bortezomib, lenalidomide, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; IRd, ixazomib, lenalidomide, dexamethasone

Now the future though, as I mentioned, may be, in fact, four drugs; and I'm not going to go through these but just to give you this idea that there are many, many trials around the world, in fact, looking at the addition of antibody to our standard backbone, whether that backbone be bortezomib, lenalidomide-dex, or carfilzomib-lenalidomide-dex. And you can see we have exactly the same mirroring across those trials.

So, we wait for those trials to get longer follow-up and readout, but I'll share with you some of the data that we have from these initial trials. And just to remind you, daratumumab (dara) is an anti-CD38 antibody, isatuximab, also an anti-CD38 antibody recently approved for relapsed disease, and elotuzumab (elo), a SLAMF7 antibody also approved for relapse.



So dara, we're going to get into the details later, but just to focus here on the trials in the setting of stem cell transplant, the CASSIOPEIA trial led to the approval of daratumumab plus bortezomib-thalidomide and dex for transplant-eligible patients. But having said that, in the US, we rarely use thalidomide, especially not for newly diagnosed patients. And so, we use lenalidomide.



So, this is the US trial, daratumumab plus lenalidomide and dexamethasone in comparison to lenalidomide-bortezomib-dexamethasone. It was presented at our American Society of Hematology [Annual Meeting] earlier this year (December 2019), and you can see it includes transplant, it includes a consolidation phase, the treatment after the transplant, followed by a maintenance of either the daratumumab plus lenalidomide or lenalidomide alone as the standard arm.

Most Common TEAEs[a]

	D-RVd (n = 99)		RVd (n = 102)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hematologic, n (%)				
Neutropenia	48 (49)	32 (32)	32 (31)	15 (15)
Thrombocytopenia	43 (43)	16 (16)	31 (30)	8 (8)
Leukopenia	34 (34)	15 (15)	27 (27)	7 (7)
Anemia	32 (32)	8 (8)	32 (31)	6 (6)
Lymphopenia	30 (30)	23 (23)	29 (28)	23 (23)
Non-hematologic, n (%)				
Fatigue	61 (62)	5 (5)	56 (55)	4 (4)
Peripheral neuropathy[b]	58 (59)	7 (7)	74 (73)	7 (7)
Diarrhea	53 (54)	6 (6)	43 (42)	4 (4)
Constipation	46 (47)	2 (2)	41 (40)	1 (1)
Nausea	46 (47)	1 (1)	47 (46)	1 (1)
Upper respiratory tract infection	46 (47)	1 (1)	37 (36)	1 (1)
Pyrexia	39 (39)	2 (2)	25 (25)	3 (3)
Insomnia	39 (39)	2 (2)	30 (29)	1 (1)
Cough	38 (38)	0	25 (25)	0
Edema peripheral	32 (32)	2 (2)	35 (34)	3 (3)
Back pain	32 (32)	1 (1)	28 (28)	4 (4)
Infusion-related reactions	41 (41)	5 (5)	–	–

- Any-grade infections occurred in 81 (82%) patients in the D-RVd arm and 56 (55%) patients in the RVd arm; grade 3/4 infections were similar between groups (17 [17%] patients each)
  - Pneumonia occurred in 10 (10%) patients in the D-RVd arm and 9 (9%) patients in the RVd arm

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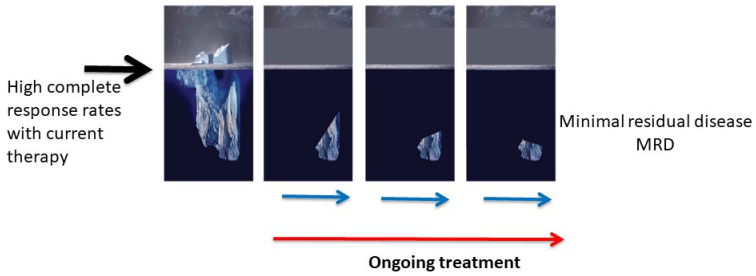
TEAE, treatment-emergent adverse event
[a]Any-grade TEAEs are listed that occurred in ≥30% of patients in either group. The safety analysis population included all randomized patients who received ≥1 dose of study treatment; analysis was according to treatment received. [b]Includes patients with neuropathy peripheral and peripheral sensory neuropathy.

And just to focus on this key point, especially in this era, the issue is that certainly adding more drugs improves depth of response but does come at a price and the price being somewhat more toxicity. Hematologic toxicity, so more patients had neutropenia, low white counts, lymphopenia. And what I think is a special note is this question of infection. So, 82% in the daratumumab arm had infections versus 55% in the non-dara arm. Though the severe infections were similar between both groups, I think this does sound a note of caution when we consider the addition of these antibodies to these regimens.

The impact of myeloma treatment



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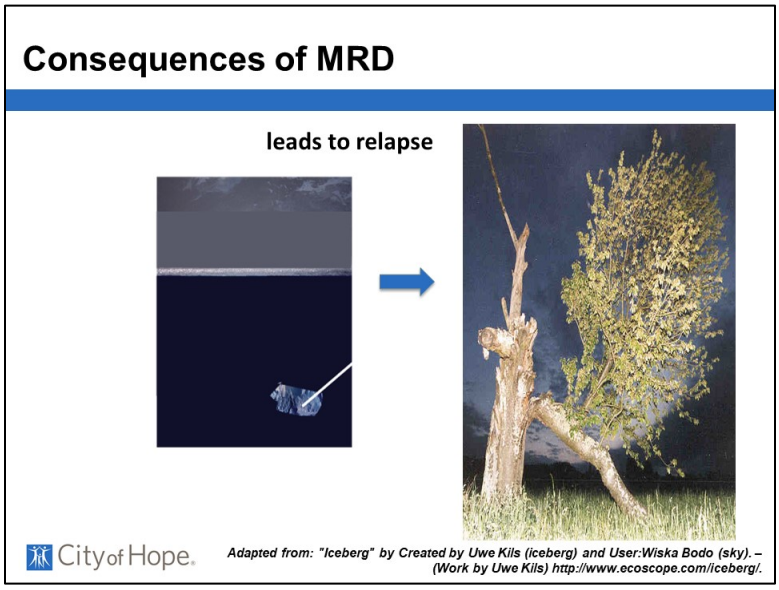
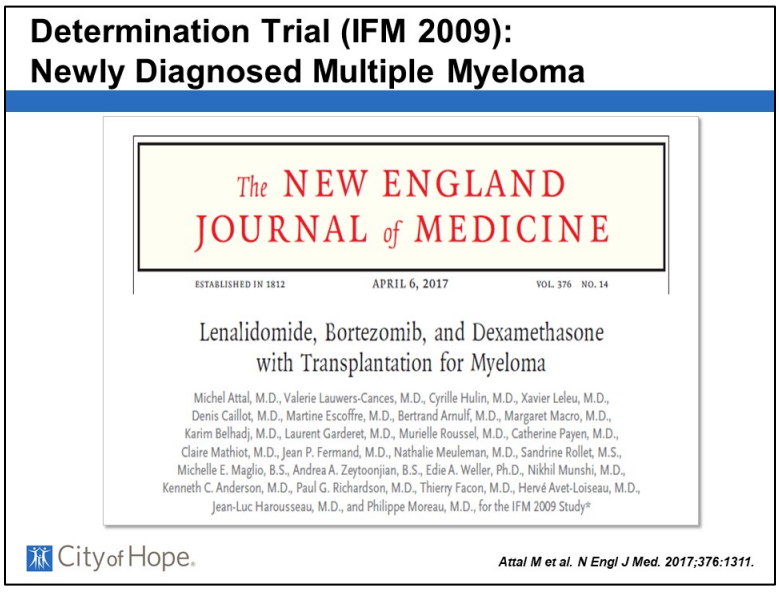
Adapted from: "Iceberg" by Created by Uwe Kils (iceberg) and User:Wiska Bodo (sky). – (Work by Uwe Kils) http://www.ecoscope.com/iceberg/.

Now let's talk a little bit about sort of downstream. So, everyone's familiar with the iceberg now. This is a favorite myeloma analogy that when you start out you have a lot of myeloma that you can see.

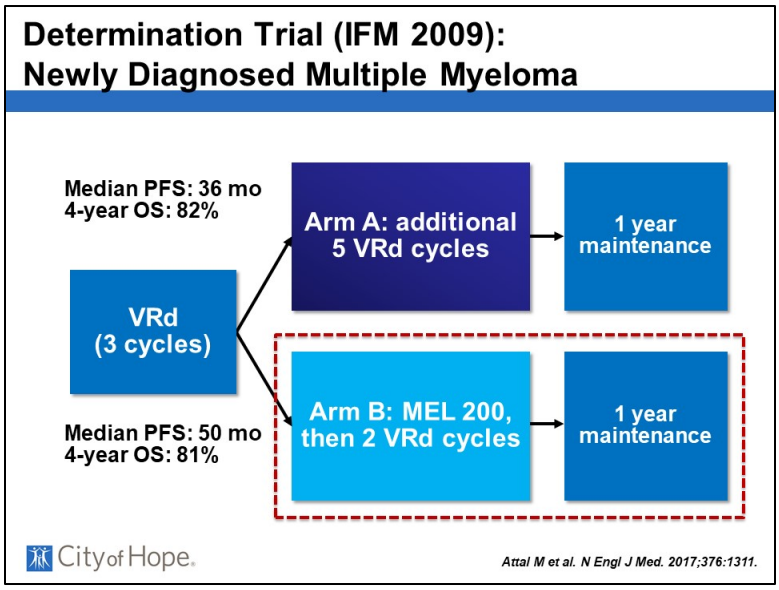
We have very good regimens that get it down to lower levels. We think of stem cell transplant as one way of chipping away further below the surface till we get to this tiny little bit left.



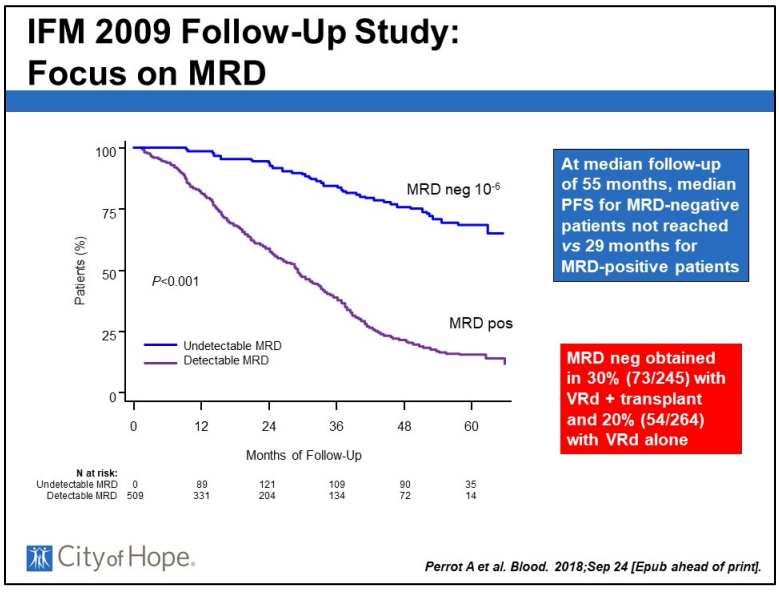
But it's this minimal residual disease (MRD) that we think is really where the relapses come from in myeloma. So, if we can get lower and lower and ultimately eradicate this minimal residual disease, we hopefully will prevent relapse.



And we have some data from the famous trial, the IFM (Intergroupe Francophone du Myélome) trial that was published in *The New England Journal of Medicine* using, again, our standard induction lenalidomide-bortezomib-dex (VRd), 50% of the patients randomized to transplant, 50% just continuing on this same regimen, VRd or VRd plus a transplant.



The French portion–very important to remember this–used only one year of len maintenance. The US trial is ongoing and is continuing lenalidomide maintenance.



So, we have only early data from the French. What we have, it cements our idea that being MRD-negative leads to a better progression-free survival and meaning longer remissions for patients. Having said that too, the sensitivity of your MRD test is important when you look at these trials, and this one is a very sensitive test, 10^{-6}, which is really the most sensitive MRD assay we have at the moment.

And as a transplanter, I would say this is the other important point that about 10% more patients were able to become MRD-negative in the transplant arm compared to the VRd arm. So, our biased view somewhat as a transplanter is that transplant incorporation with these induction regimens gives you the best chance of becoming MRD-negative.

What is the definition and objectives of maintenance?

- Therapy administered for a prolonged period to maintain the response previously achieved
- Maintenance therapy must
  - Be convenient
  - Be safe and well tolerated long term
  - Not prevent the use, or reduce the efficacy, of other future treatments
- **Objective:** To eliminate MRD or maintain the absence of MRD, reduce the risk of relapse, and finally prolong PFS and OS

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Now the other point is that it's not just enough to become MRD-negative, but it also is to try and maintain that response, and how do we do that? Well, maintenance therapy is the way that we've been trying to do that; and so, we have multiple different options for maintenance therapy.

Maintenance for Everyone

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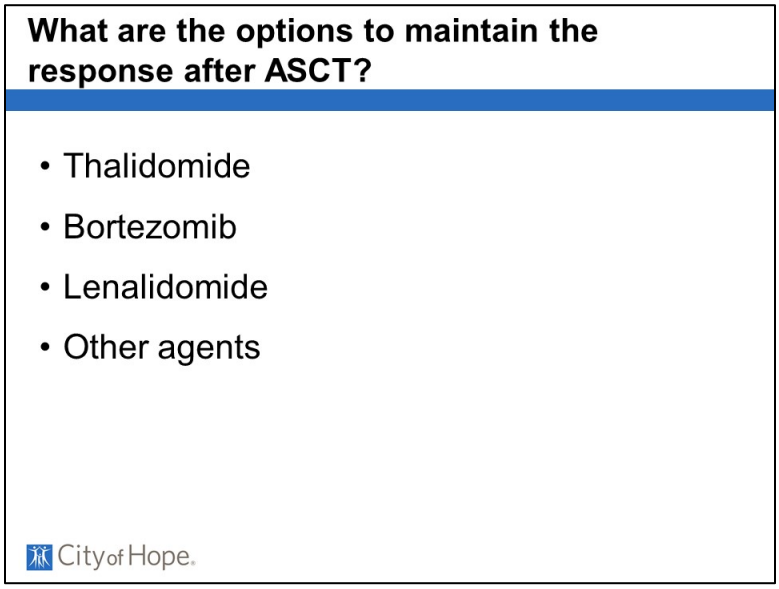
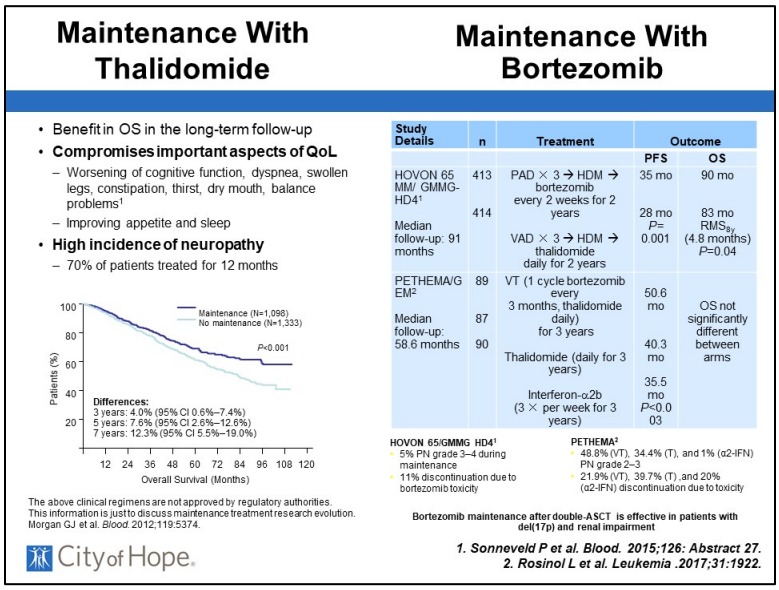
So, one approach right now, this is our general approach is we give maintenance to everybody.



The question is what drugs do we use? So, and Jack alluded to thalidomide. This was really our first initial attempt at maintenance which we now, as you many of you know, it's a very hard drug to take for maintenance because of the side effects. We certainly still use bortezomib. We'll talk about that, but really the only FDA-approved drug is lenalidomide right now.

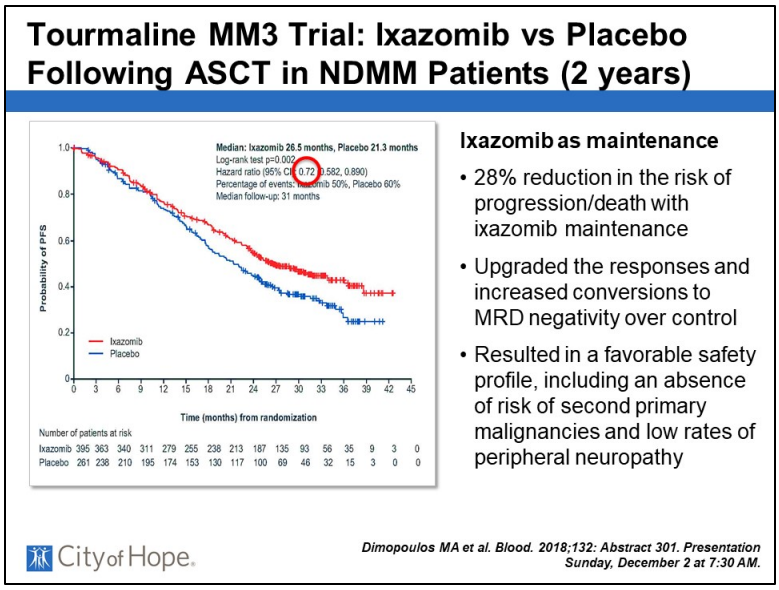
But nonetheless, the trials I'll show you with lenalidomide are old now. They're published in 2012, so the field has moved beyond that; and so, we'll talk a little bit about some of the other agents under study for maintenance.



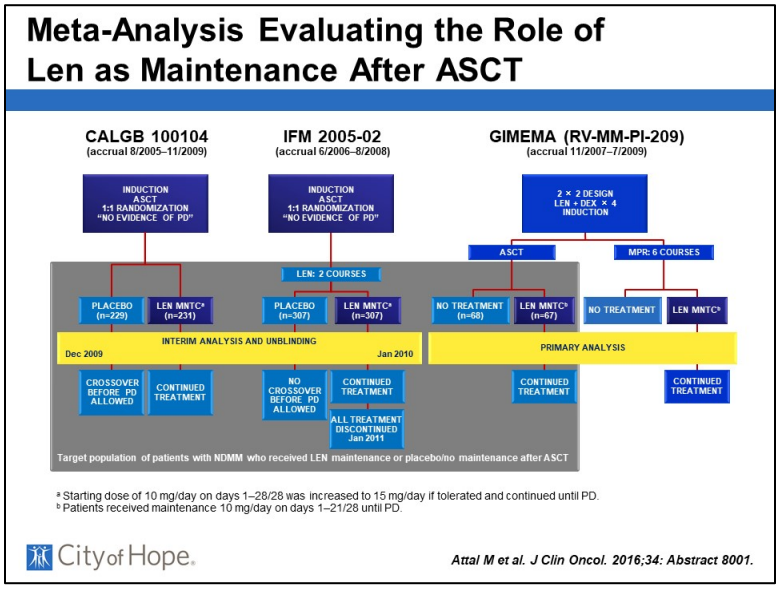
So, again, I'm not going to dwell on the thalidomide story except just to say, obviously, 70% of patients got neuropathy, really couldn't stay on it.

TRANSCRIPT

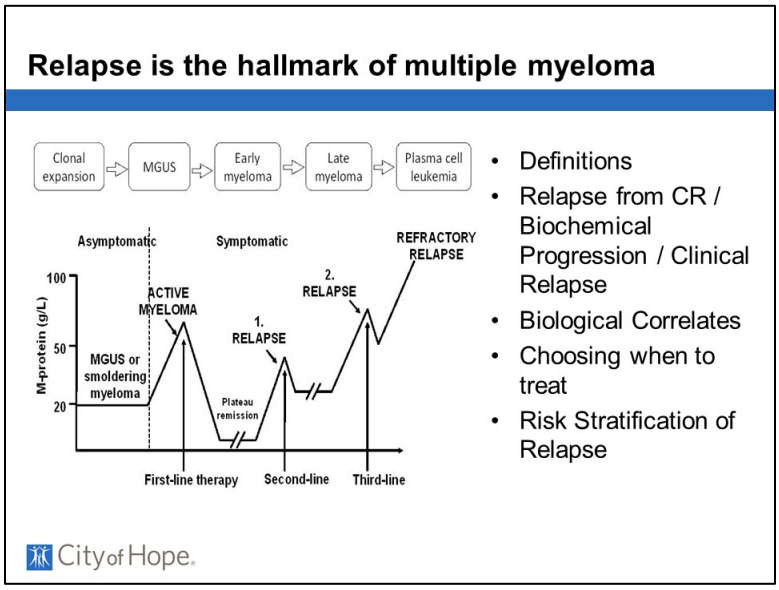
Bortezomib is a drug that we still tend to use. We don't have as many great trials. Just without getting into the weeds, the trials weren't specifically designed to answer the question of is bortezomib better maintenance because it was used both as the initial therapy as well as during maintenance. But nonetheless, they give a signal that bortezomib maintenance is also an active regimen for patients.



And then you may be familiar with the TOURMALINE trial, ixazomib (Ninlaro®), also that showed improvement in progression-free survival or reduction in risk of progression or death with ixazomib compared to a placebo.



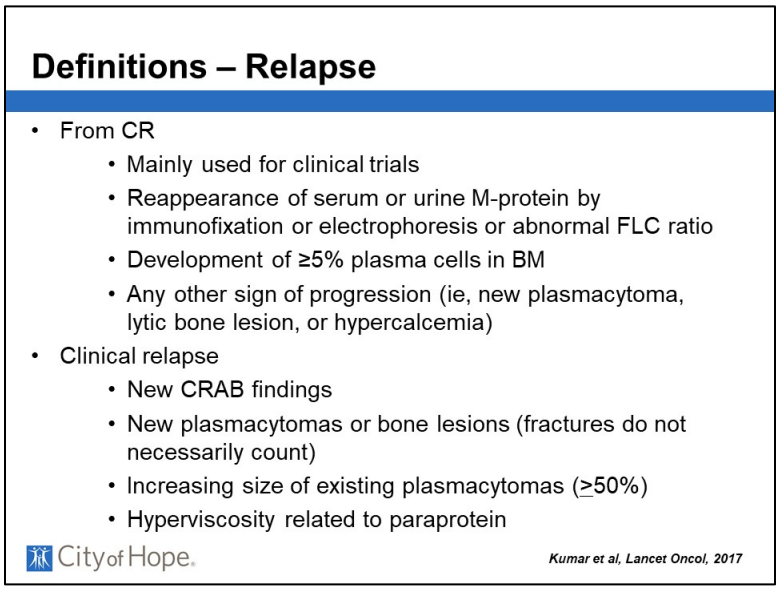
But I think the thing that we hang our hat on the most is this meta-analysis, so 1,200 patients from three trials across the world, so the US, France, and GIMEMA, being Italy, slightly different trial designs, but the ultimate endpoint of this was that using lenalidomide maintenance improved overall survival by 2.5 years. So, I think that's a good number to hang your hat on when we think about the use of maintenance.



Now, ultimately, what we see though is these are the challenges we have with myeloma. So we think that everyone has this long period that we may not always catch that initial time zero, but of MGUS (monoclonal gammopathy of undetermined significance), smoldering, active myeloma, as I've told you now, we're pretty good at getting patients into remission, fortunately. Over 90% of patients respond to our regimens, and as you see now, the data from the FORTE trial KRd, 90% of patients

can get a very good partial response or better. And those remissions can last a long time. They average four, five, six years. Even in first relapses, I'll show you some data, we're getting better here too. We have a lot of very active drugs, and we can get people, the majority of patients into remission and keep those remissions going for several years.

Our challenge is in this space here. By the time you get to the fourth relapse, third relapse, it becomes harder to get long responses and long remissions; and that's where I'm going to focus some of the talk on just some of the newer agents that we're very excited about for this group of patients.



First, just to kind of remember, relapse is not the same in everybody. So, for example, we have what we call biochemical relapses. This is basically just this reappearance of your M protein. You have been at an M spike of 0, and it goes to 0.1, 0.2. Now that's a little different than a clinical relapse where you really have new plasmacytomas, new bone disease, significant anemia, or kidney dysfunction. And the reason I say it's different is because biochemical relapse doesn't necessarily need to be treated immediately versus a clinical relapse which does indicate for immediate therapy.

Definitions – *Progression*

- Increase of 25% from lowest confirmed response value in one or more of:
  - Serum M-protein (absolute increase must be ≥0.5 g/dL)
  - Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL
  - Urine M-protein (absolute increase must be ≥200 mg/24 h)
  - Light chain disease: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)
- Non-secretory: 25% increase in bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%)
- Appearance of a new lesion(s), ≥50% increase from nadir
- ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

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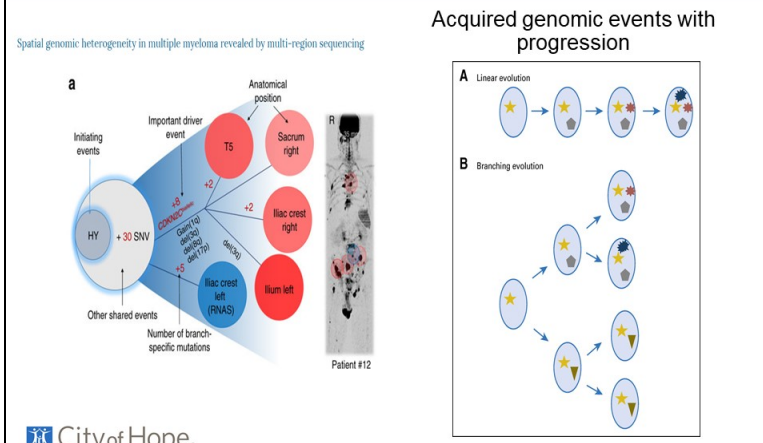
Kumar et al, Lancet Oncol, 2017

And then these are just the things for patients on trials. We have certain set criteria that mean progression and based on M protein values and/or light chain values, depending on what's being followed, so when you hear that term used.

Multiclonal disease with spatial and temporal heterogeneity



Acquired genomic events with progression

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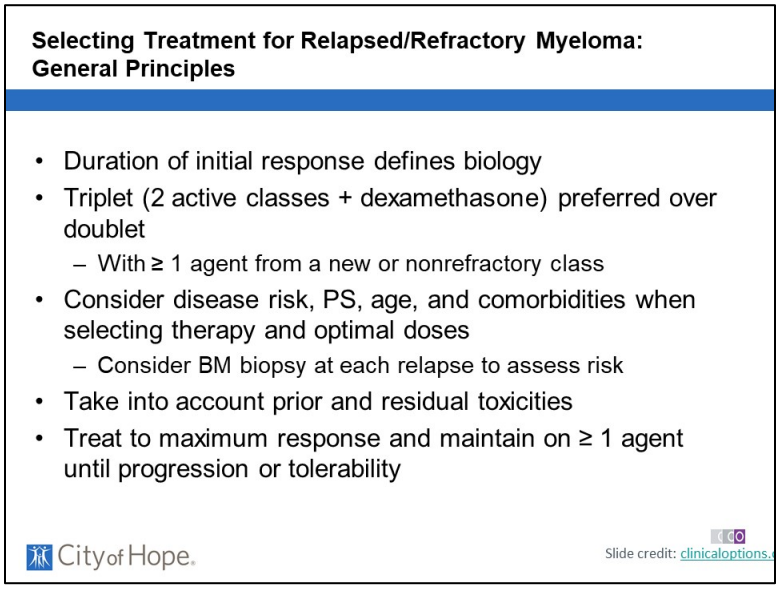
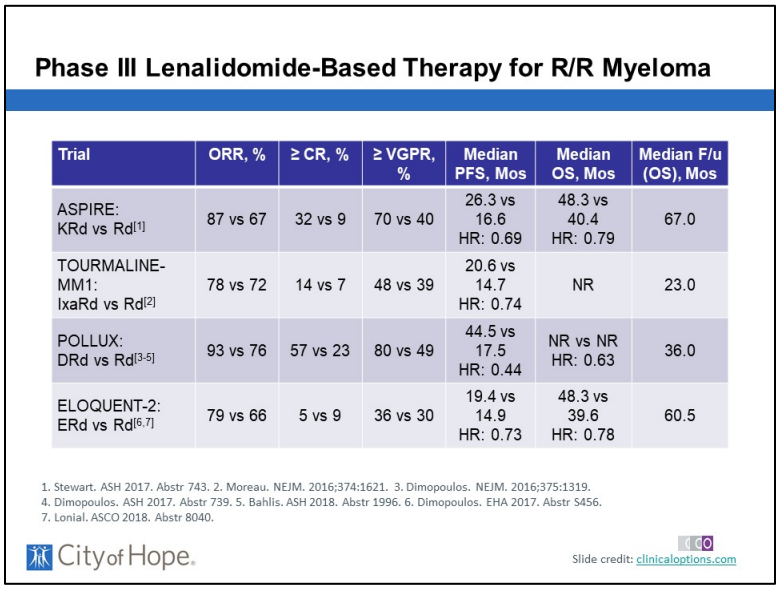
Rasche L et al Nature Communications 8, Article number: 268(2017)

Now this slide shows you just the concepts of progression or relapse and the understanding that it's a clonal disease, and even within one patient, multiple clones may exist. And that when relapse occurs, it can be either mutation of a clone or an emergence of a different, one of the subclones. So, again, that, in part, is why I think it's very important that when people relapse, consider doing another bone marrow biopsy because sometimes cytogenetics or FISH (fluorescence in situ hybridization) studies can change, depending on emergence of different clones.

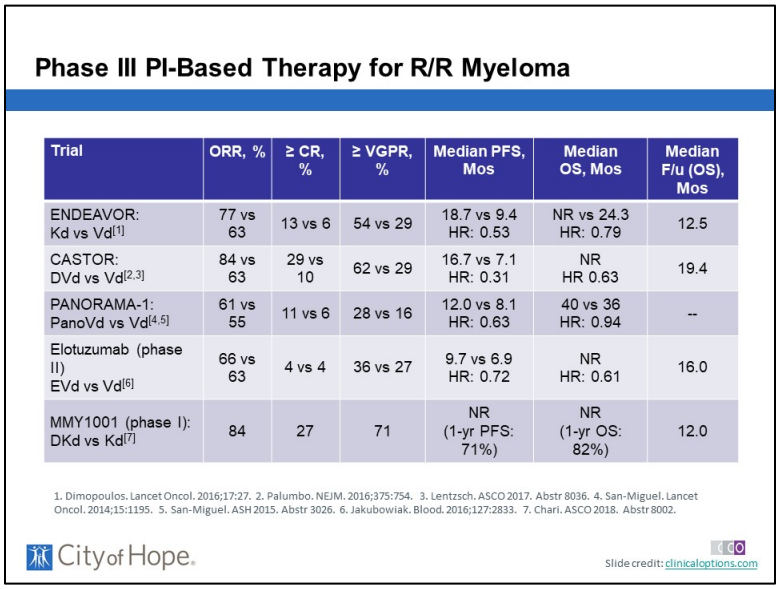


Our general principles for treatment really are again the same thing that we used triplet therapy or three drugs if we can, depending on how healthy patients are or how good their blood counts are. We, obviously, look at their previous treatments as well to help guide us in choosing current treatments. The other thing is even in the relapsed setting, we tend to continue on therapy and not, in fact, even more so, until disease progression.



Now I'll show you just the general framework of the trials, and they kind of fall into two different categories. So phase III means comparing it to a standard arm and a new drug; and all these phase III trials used lenalidomide as their control arm, and they added a new drug, in this case carfilzomib, in this case ixazomib, in this case daratumumab, in this case elo. So, you get the sense, and all of

them kind of show the same thing. You add a new drug, you get longer remissions of varying amounts and better response rates. So not a surprise.



Phase III PI-Based Therapy for R/R Myeloma

Trial	ORR, %	≥ CR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos	Median F/u (OS), Mos
ENDEAVOR: Kd vs Vd[1]	77 vs 63	13 vs 6	54 vs 29	18.7 vs 9.4 HR: 0.53	NR vs 24.3 HR: 0.79	12.5
CASTOR: DVd vs Vd[2,3]	84 vs 63	29 vs 10	62 vs 29	16.7 vs 7.1 HR: 0.31	NR HR 0.63	19.4
PANORAMA-1: PanoVd vs Vd[4,5]	61 vs 55	11 vs 6	28 vs 16	12.0 vs 8.1 HR: 0.63	40 vs 36 HR: 0.94	--
Elotuzumab (phase II) EVd vs Vd[6]	66 vs 63	4 vs 4	36 vs 27	9.7 vs 6.9 HR: 0.72	NR HR: 0.61	16.0
MMY1001 (phase I): DKd vs Kd[7]	84	27	71	NR (1-yr PFS: 71%)	NR (1-yr OS: 82%)	12.0

1. Dimopoulos. Lancet Oncol. 2016;17:27. 2. Palumbo. NEJM. 2016;375:754. 3. Lentzsch. ASCO 2017. Abstr 8036. 4. San-Miguel. Lancet Oncol. 2014;15:1195. 5. San-Miguel. ASH 2015. Abstr 3026. 6. Jakubowiak. Blood. 2016;127:2833. 7. Chari. ASCO 2018. Abstr 8002.

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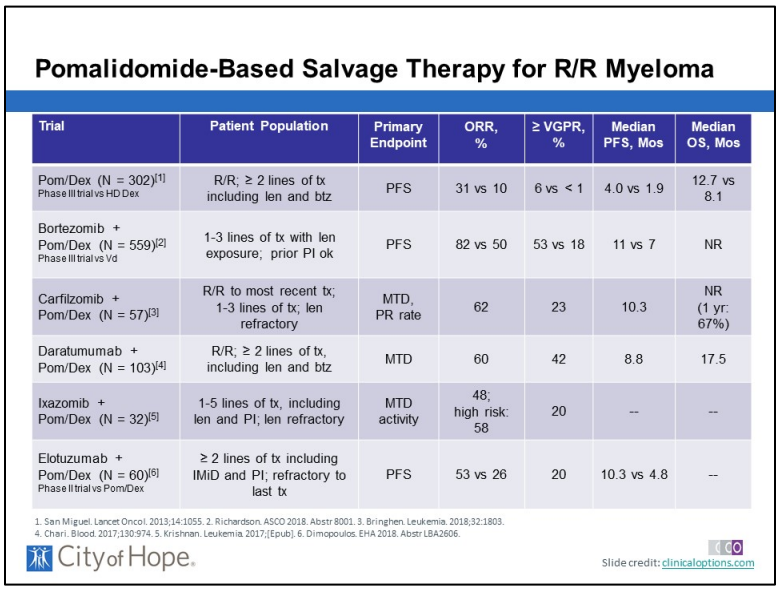
Slide credit: clinicaloptions.com

The other flavor of phase III trials uses bortezomib, and same kind of idea here. You can see using the CASTOR trial is daratumumab plus bortezomib. The PANORAMA trial, panobinostat. Elotuzumab and dara, the CANDOR trial, which is one of the newest ones, daratumumab plus carfilzomib.



Pomalidomide-Based Salvage Therapy for R/R Myeloma

Trial	Patient Population	Primary Endpoint	ORR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos
Pom/Dex (N = 302)[1] Phase III trial vs HD Dex	R/R; ≥ 2 lines of tx including len and btz	PFS	31 vs 10	6 vs < 1	4.0 vs 1.9	12.7 vs 8.1
Bortezomib + Pom/Dex (N = 559)[2] Phase III trial vs Vd	1-3 lines of tx with len exposure; prior PI ok	PFS	82 vs 50	53 vs 18	11 vs 7	NR
Carfilzomib + Pom/Dex (N = 57)[3]	R/R to most recent tx; 1-3 lines of tx; len refractory	MTD, PR rate	62	23	10.3	NR (1 yr: 67%)
Daratumumab + Pom/Dex (N = 103)[4]	R/R; ≥ 2 lines of tx, including len and btz	MTD	60	42	8.8	17.5
Ixazomib + Pom/Dex (N = 32)[5]	1-5 lines of tx, including len and PI; len refractory	MTD activity	48; high risk: 58	20	--	--
Elotuzumab + Pom/Dex (N = 60)[6] Phase II trial vs Pom/Dex	≥ 2 lines of tx including IMiD and PI; refractory to last tx	PFS	53 vs 26	20	10.3 vs 4.8	--

1. San Miguel. Lancet Oncol. 2013;14:1055. 2. Richardson. ASCO 2018. Abstr 8001. 3. Bringhen. Leukemia. 2018;32:1803. 4. Chari. Blood. 2017;130:974. 5. Krishnan. Leukemia. 2017;[Epub]. 6. Dimopoulos. EHA 2018. Abstr LBA2606.

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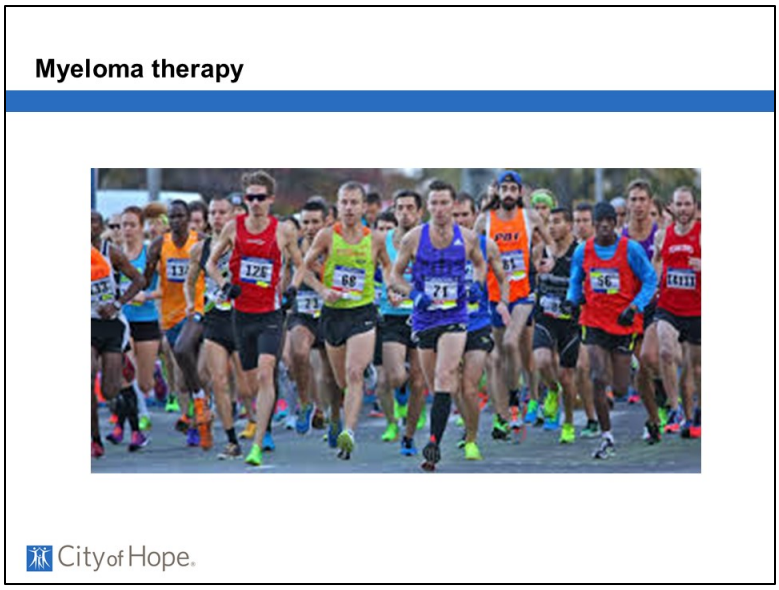
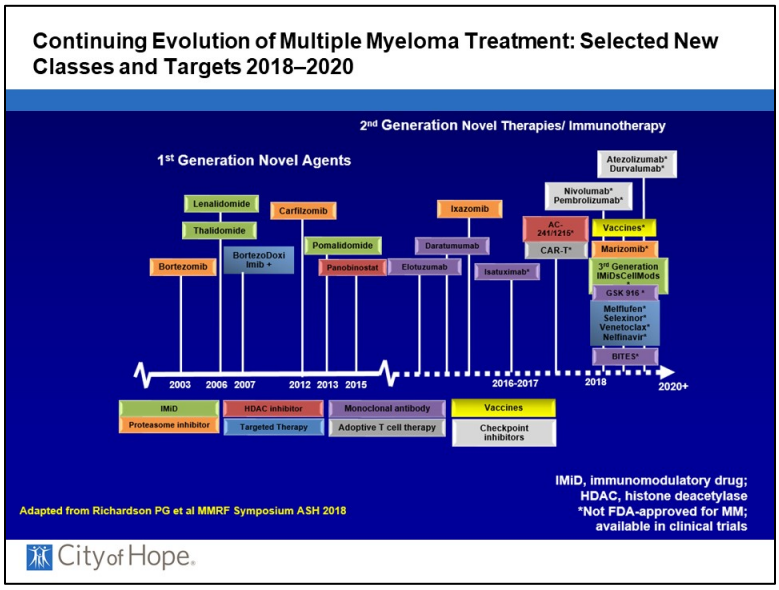
Slide credit: clinicaloptions.com

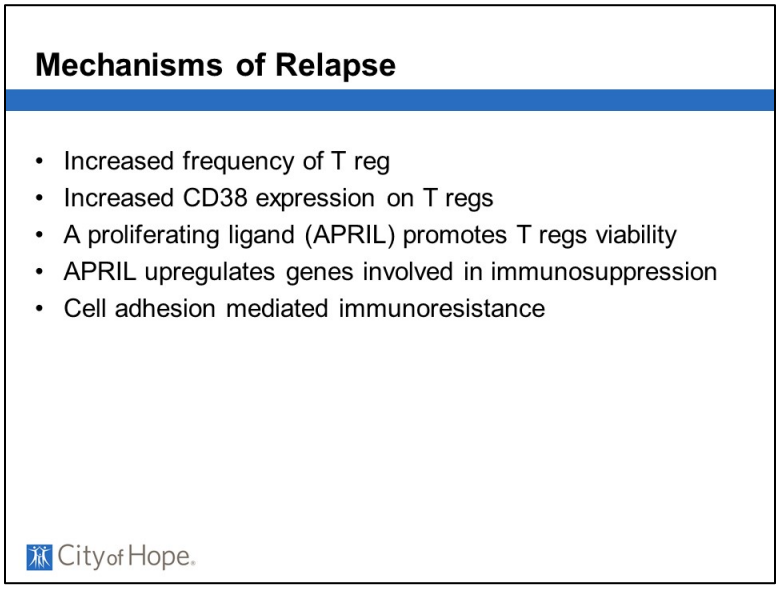
For more advanced patients, so these are patients, as you can see here, over two lines of therapy. So usually, again, a couple of relapses generally; and all of them had to have generally prior lenalidomide or be lenalidomide-refractory, the use of pomalidomide and adding new drugs to a pomalidomide backbone.



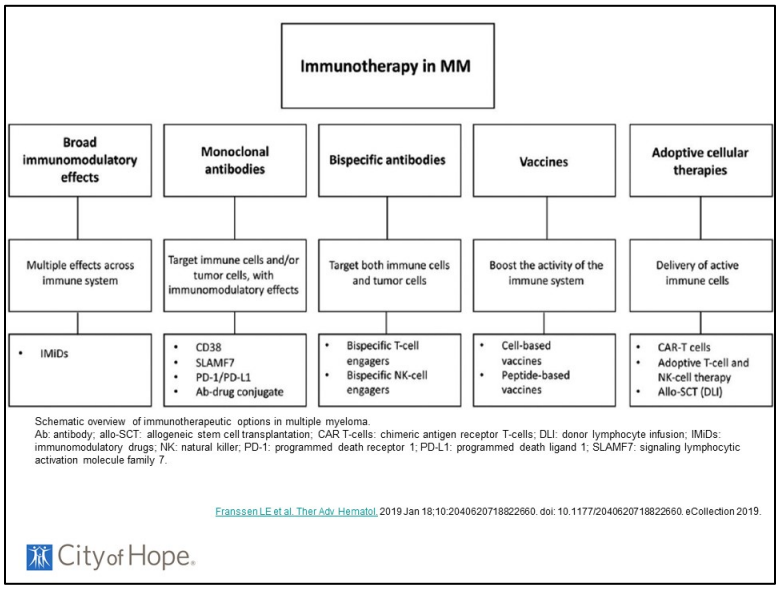
Now the thing is that you may have heard this from some of your doctors. We think of myeloma therapy now as a marathon and not a sprint; so, obviously, we're looking at things that can give long remissions, minimize toxicity, and ideally be also somewhat convenient for patients. I think that's somewhat of a challenge for us still in some of the therapies that we use.



Now the good news is we have a lot of players in the race right now, and I'm going to focus really on this side of the curve here, immunotherapy space now because that's really where the biggest focus has been in the last two years. And I think that's where some of the most exciting work and data that we're seeing now.

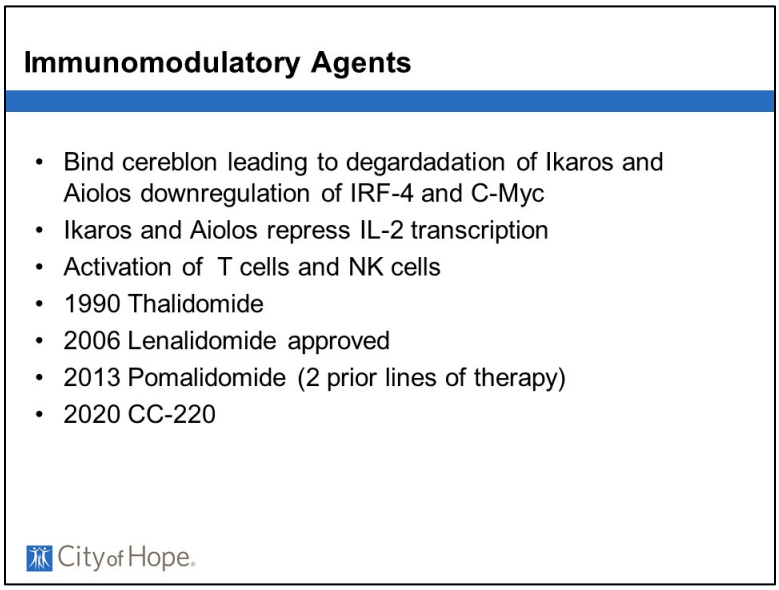


So, this sounds sort of fancy, but really just to drill it down, it means that we're getting smarter about understanding that relapse is not just to do with the myeloma cell itself but has a lot to do with the immune system. And that if we can manipulate the immune system, we can do better in terms of treating relapse or preventing relapse, and there are multiple different ways to harness the immune system.

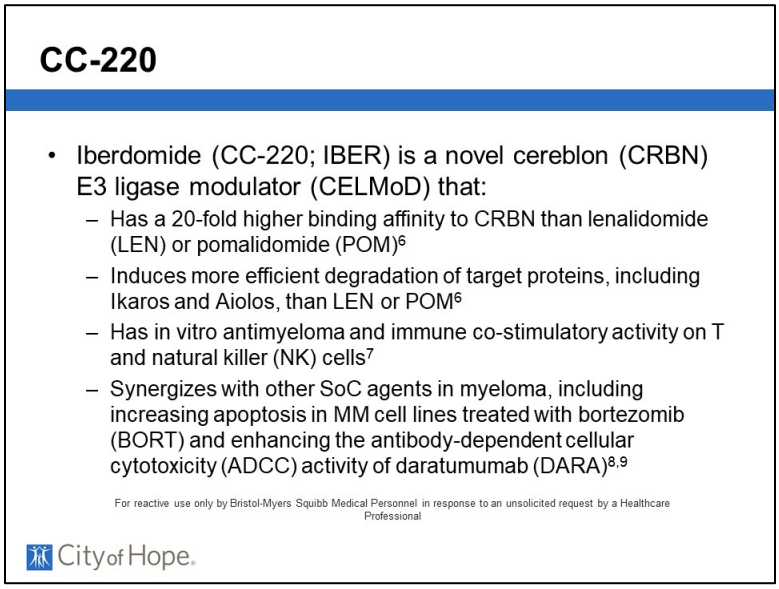


And this gives you a sense here of those different options, and the ones I'm going to focus on today are really this one, the one that we've certainly been looking at, at City of Hope, CAR (chimeric antigen receptor) T cells. Allo stem cell, obviously, is something we've done and done many trials on in the past. And then focus, I'm not going to spend a lot of time here, but vaccine therapy certainly is a big area of interest. And the area that we're really focused on right now, we have three trials,

ongoing first in-human trials of the bi-specific T-cell engagers and also spend a little time talking about antibody drug conjugates because we anticipate that we'll have the first antibody drug conjugate approved for myeloma very soon.

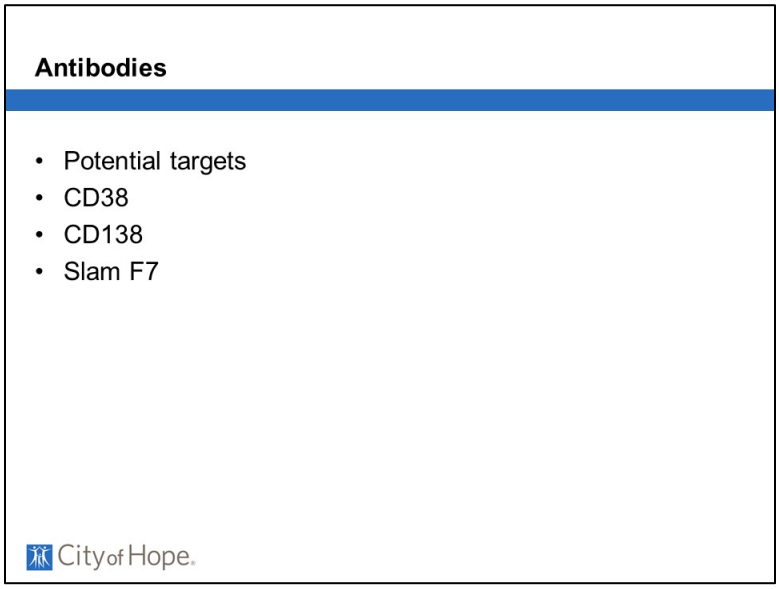


But let's not forget our immunomodulatory agents. They've really been a backbone of our therapy for years and years, look, in 1990 now when thalidomide was approved. But since then, we've taken it for granted lenalidomide and pomalidomide; and in one sense, to be honest, we've sort of lost excitement about those because they've been around for so long. But now we have a new one, CC-220 that Sagar Lonial had presented at ASH (American Society of Hematology Annual Meeting). It's called Iberdomide. I find it easier to say CC-220.

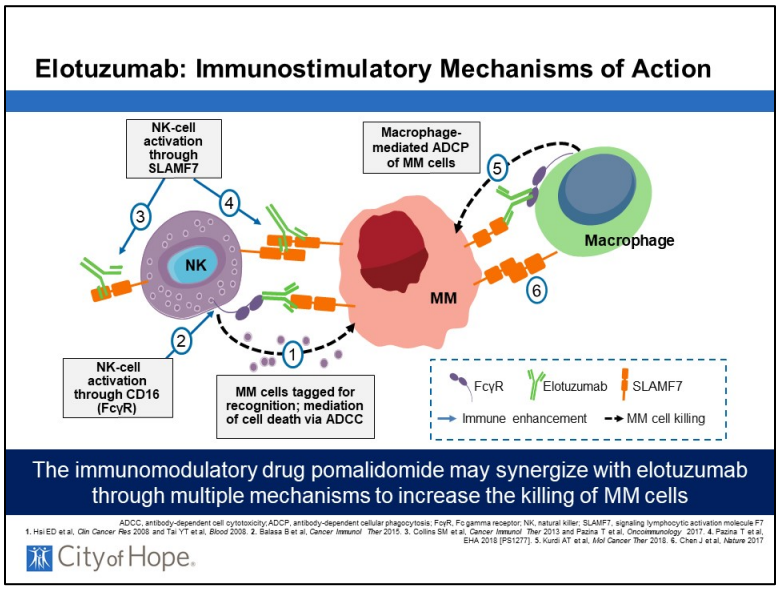


And the important things to know about it is that it may be more potent than the previous ones. It has a 20-fold higher binding affinity to cereblon, which the target that we think leads to the downstream activity of lenalidomide and pomalidomide. And, therefore, it leads to more degradation of these target proteins that drive myeloma cell proliferation. We also see synergy with daratumumab and with bortezomib.

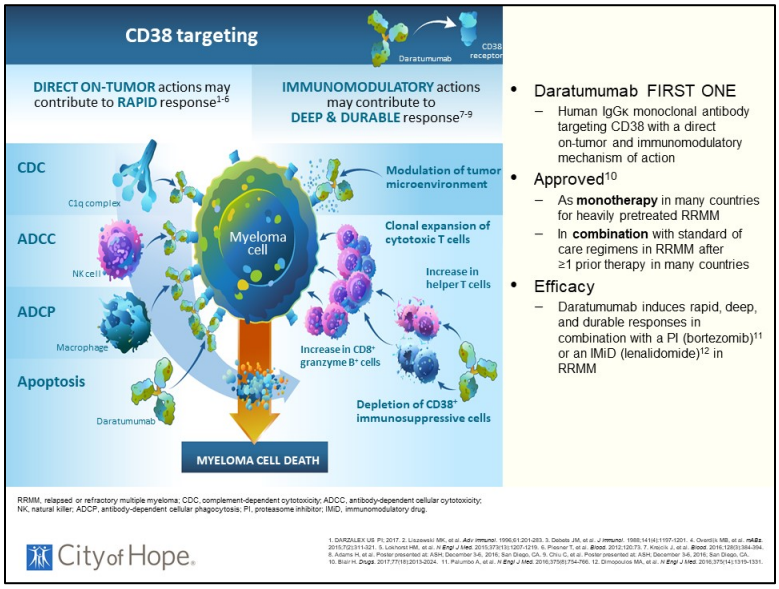
So now let's talk about, so that's on phase I, phase II; and we have it in trial, and certainly it's been active. It has some degree of cytopenia, so that is something to be sort of aware of when you're on those studies. But certainly, it's a very promising agent.



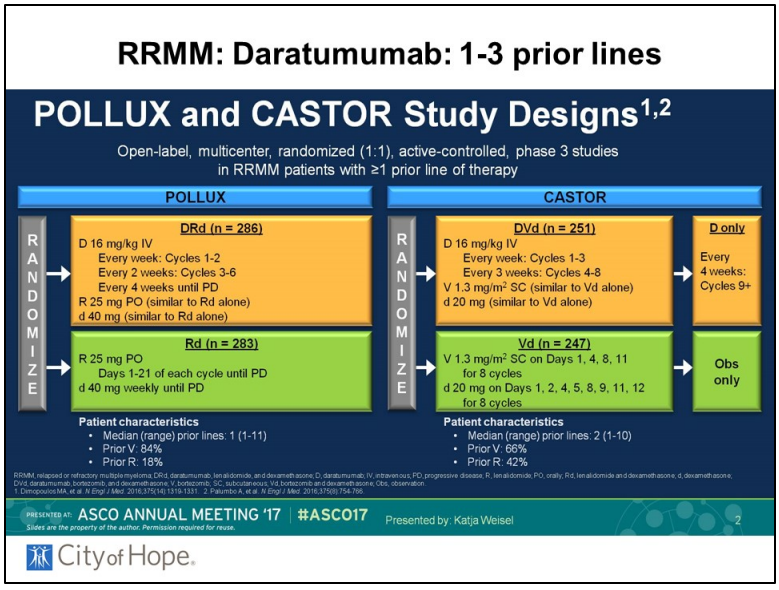
Now what about antibodies? So, again, there's three different targets. We have now two CD38 antibodies approved. CD138 has been in trial, but there is no approved antibody. And then SLAMF7 or CS1 has elotuzumab approved for it.



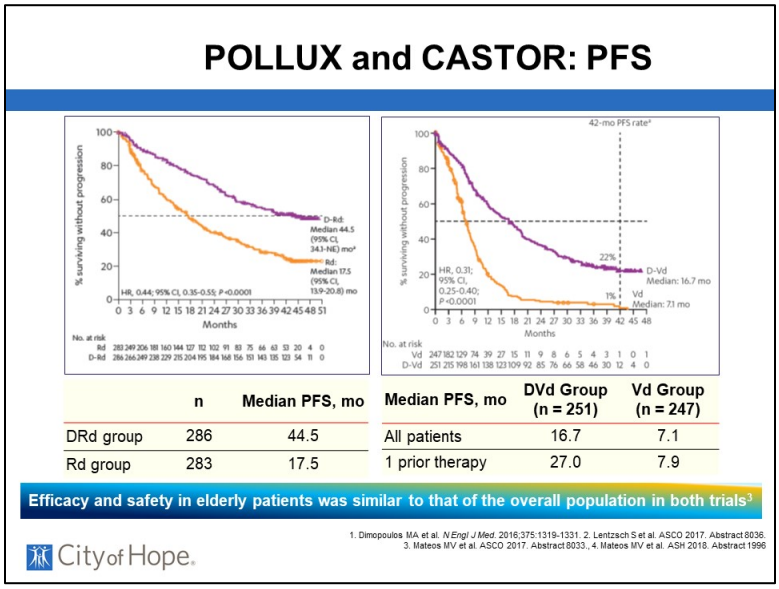
So, let's talk about elo first. It's been around a long time now. It requires immune system activation because you need NK (natural killer) cells to make elo really active, which is why we give elotuzumab with an immunomodulatory agent, the most recent one being pomalidomide, though it was originally approved with lenalidomide.



And then daratumumab, the anti-CD38 antibody. I think this is the one, at least at our center, we've had the most experience with since we were part of the original SIRIUS trial with it for relapsed disease. And as you can see on this slide, you can understand that dara has multiple mechanisms leading to cell death.

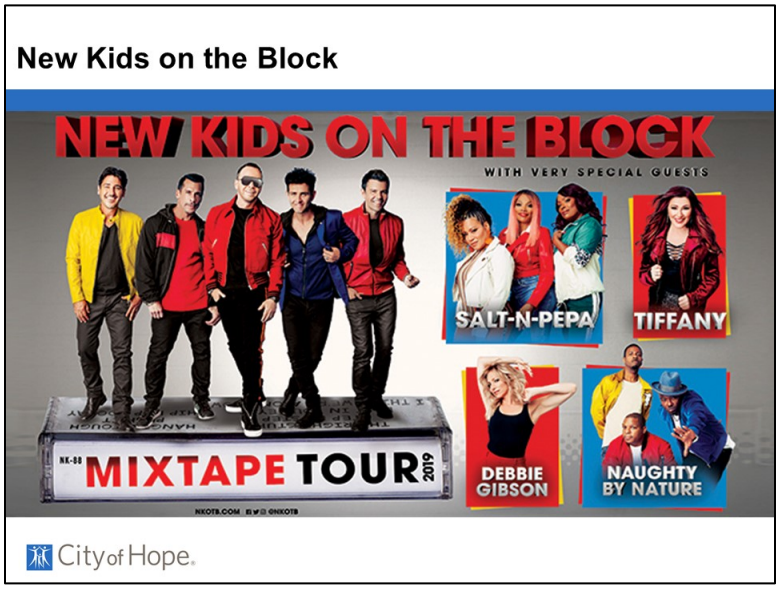


And these are the two trials that really laid the groundwork for the widespread use of dara, the POLLUX trial using daratumumab plus lenalidomide and dexamethasone compared to lenalidomide-dexamethasone alone and daratumumab plus bortezomib and dex compared to bortezomib-dex alone.

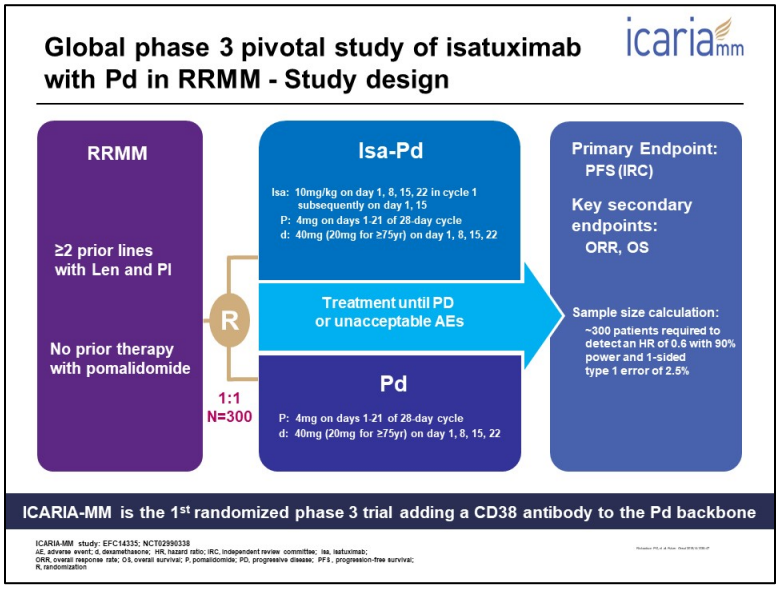


And you can see here this nice upper curve being the dara curve, both with dara plus bortezomib, and dara plus lenalidomide having significant improvement in what we call progression-free survival or sort of a subgroup way of saying it is of how long patients should stay in remission in both arms.

I wouldn't compare across the trials, meaning you can see here 44 versus 16, because these are slightly different groups of patients. The patients in the CASTOR trial were more heavily pretreated, for example. So just more to say, that they're active agents.

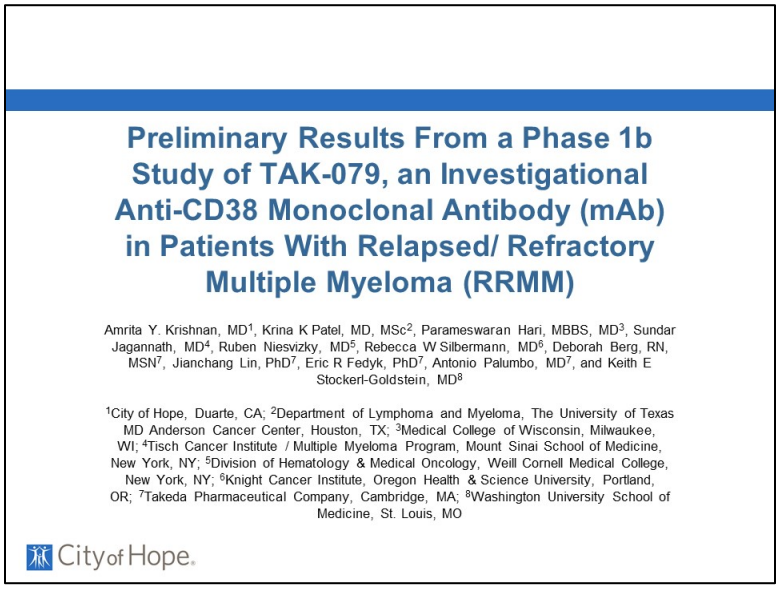


Now what about some of the new kids on the block that were probably most interested?

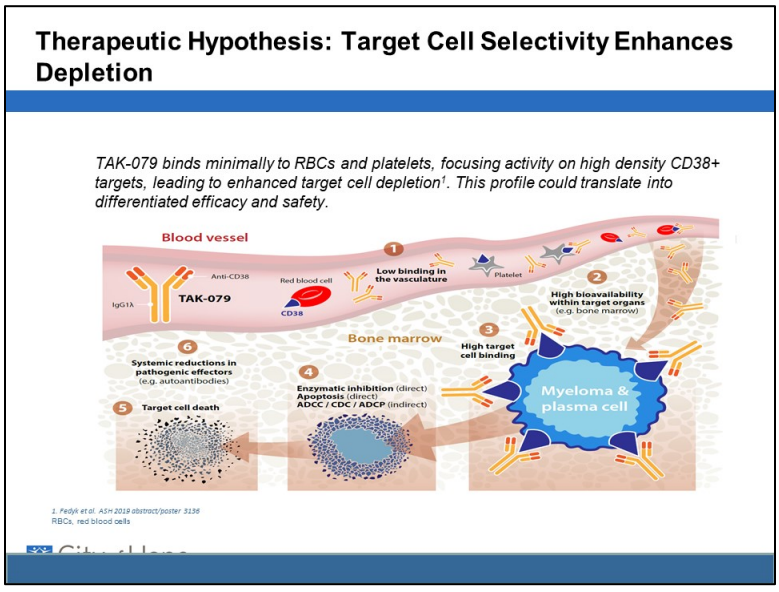


So, I mentioned to you there's another anti-CD38 antibody, isatuximab (isa), which recently within the past month was approved for relapsed myeloma based on this phase III ICARIA trial, which is isa plus pomalidomide (pom) and dexamethasone compared to pomalidomide and dexamethasone again. And, again, I didn't put in the data. You can certainly look that up. It's been quite widely publicized but suggesting again a marked improvement in progression-free survival for the isa-pom-dex compared to pom-dex alone. And this was the first phase III trial showing that CD38 added to a pom-dex backbone improves progression-free survival.

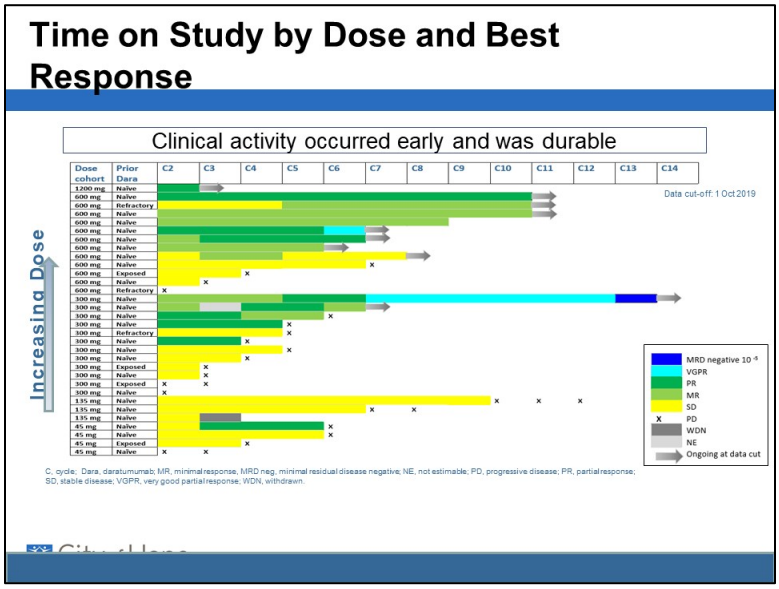
So, we have isatuximab on trial at City of Hope as well, and we've used it. I'm happy now if there's some questions at the end of this about it because as it's now approved, we'll obviously have some discussions about how to best use it.



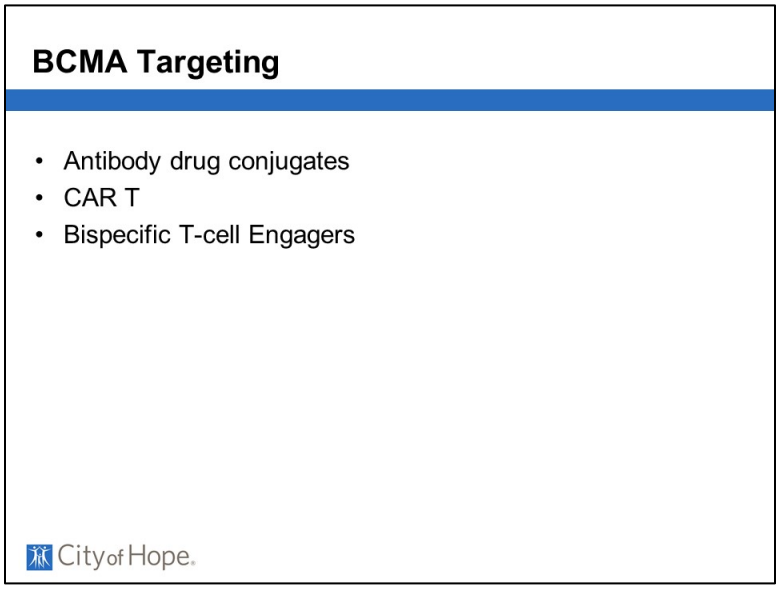
And then TAK-079. This is a trial we also have at City of Hope, and we presented this at ASH. This is a subcutaneous injection which has been very nice, and it's also somewhat more selective for myeloma cells, and so less binding on bystander cells, especially red blood cells.



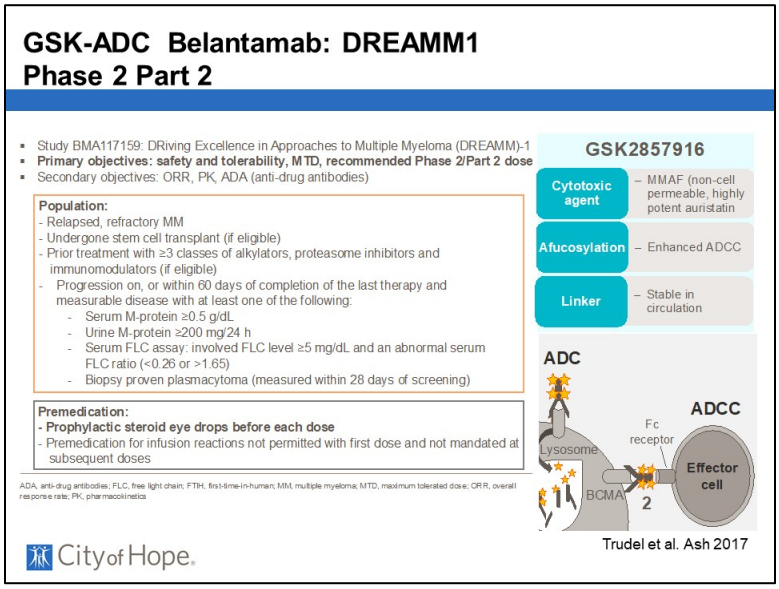
So, you know, we've treated about 90 patients across the country with this; and I have to say it's been extremely well-tolerated. We've had no infusion toxicities, no significant site reactions, meaning at the injection site either. So, these trials are ongoing. We have a trial with TAK-079 as a single agent. We also have a trial of TAK-079 plus pomalidomide, so we hope to share some of that data at ASCO (American Society of Clinical Oncology Annual Meeting), which may or may not occur or at future meetings when they do.



But just to show you here the sense that this drug has activity once you get to the higher dose levels and this activity seems to be durable with patients staying on treatment over a year now.



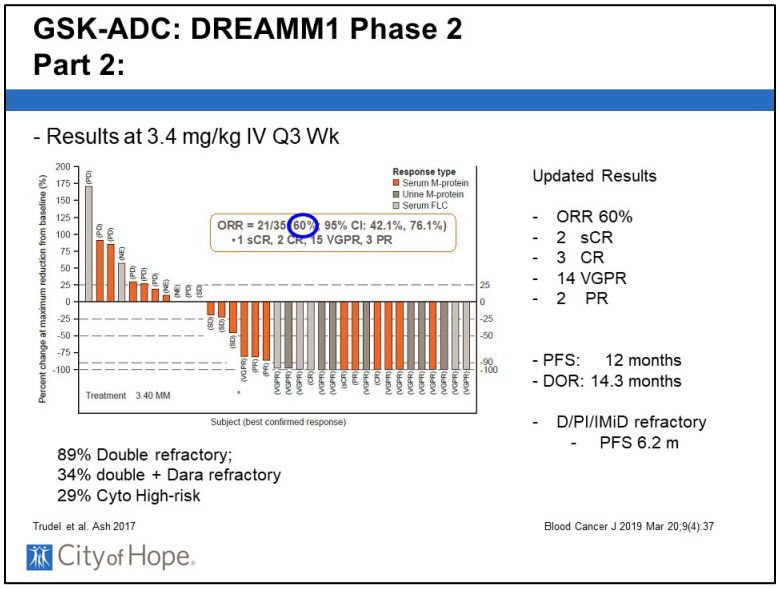
And then BCMA (B-cell mutation antigen), another target that we're very excited about. We target BCMA in a couple different ways: antibody drug conjugates, CAR T cells, and bi-specific T-cell engagers.



The first antibody drug conjugate belantamab, the nickname everyone calls it is bela, is probably going to get approved very shortly. This is a new class of drugs where you have a target, so the BCMA, you have an antibody, but it has what we call a warhead or chemotherapy attached to it. Now that chemotherapy, if you just gave it as an IV infusion would be very, very toxic, usually to the liver. So, the way you get around that is by linking it to this antibody, so it delivers it right to the myeloma cell. It gets internalized into the myeloma cell, so it only gets released in the myeloma cell, so you spare toxicity to other organs.

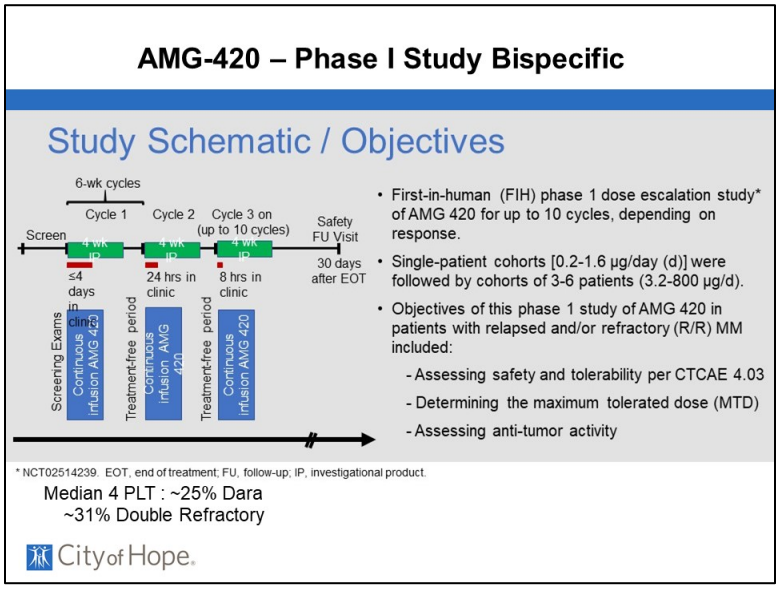
Now the problem is, as I mentioned though, that you have a couple challenges just engineering wise. First of all, whatever you use to link that antibody to the warhead has to be fairly stable, so it doesn't fall off and float around in your blood. But on the other hand, it also has to be able to get it into the cell and release it.

Now the other thing is this class of warheads, MMAF (monomethyl auristatin F) and auristatin has a particular toxicity that's well known because we use it in other diseases as well, and that toxicity tends to be ocular toxicity. And so, this trial, belantamab, this is the original phase II trial, there is a phase III trial that was published: and the DREAMM-2 study in *The Lancet* recently.

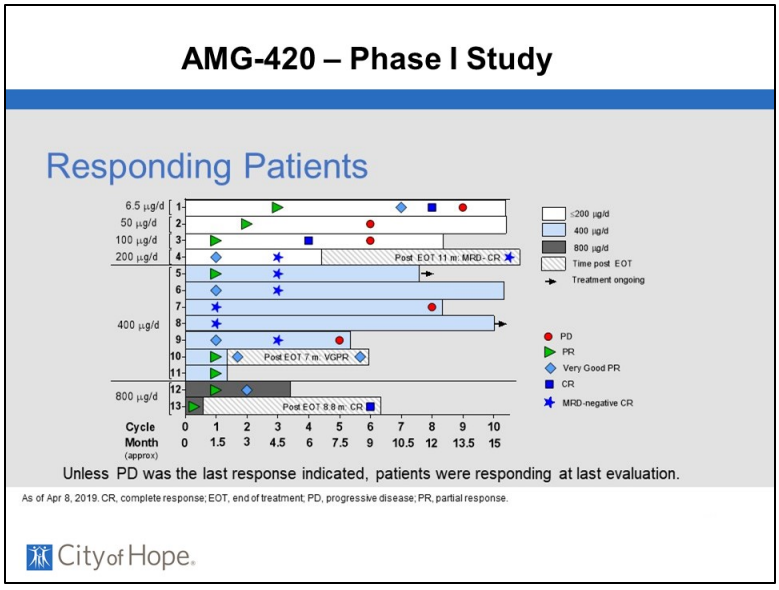


So, the phase II was very exciting and, again, it showed that it has response rate of 60% in patients with advanced relapsed disease, though the minority of these patients had prior daratumumab. Now the DREAMM-2, the response rates in more heavily pretreated population are more reflective of the true world population. The response rate's about 34%, so I would really hang my hat on the 30% number and not the 60% number.

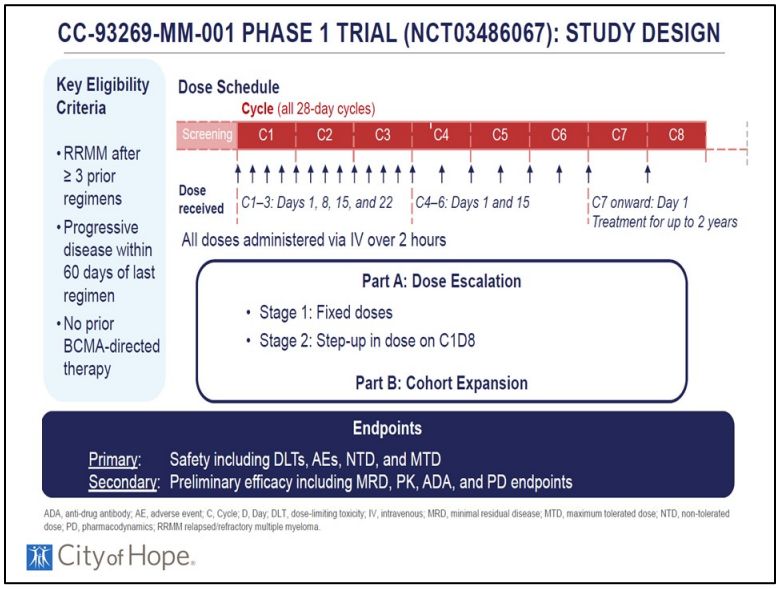
The other issue being about over 40% of patients do get some degree of ocular toxicity. Now with most patients, that's keratopathy, a fancy way of saying dry eyes; but it can be blurry vision. There're specific precautions advised. You need to have an eye exam within a week to 14 days of starting the drug. Patients are advised not to wear contact lenses and limitations on driving also, so in those things that we have to learn as we move ahead once this drug gets approved in terms of managing these toxicities.



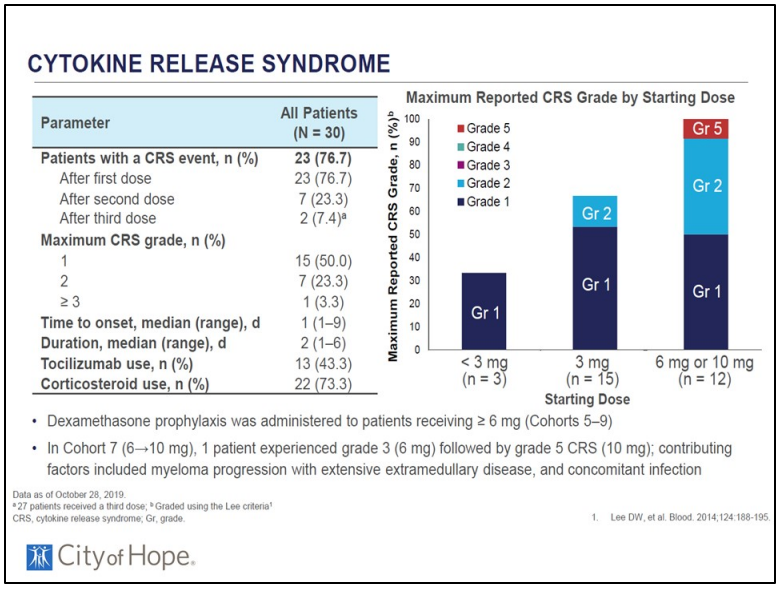
So other drugs that are much earlier in the pipeline, but also show a lot of excitement, are AMG-420 bi-specific antibodies; was presented by Dr. Ludwig from ASCO. So, this was in Europe it targets BCMA one arm, other arm against CD3 on the T-cells. So, brings the T cells closer to the myeloma cell, and this just gives the schema of the trial.



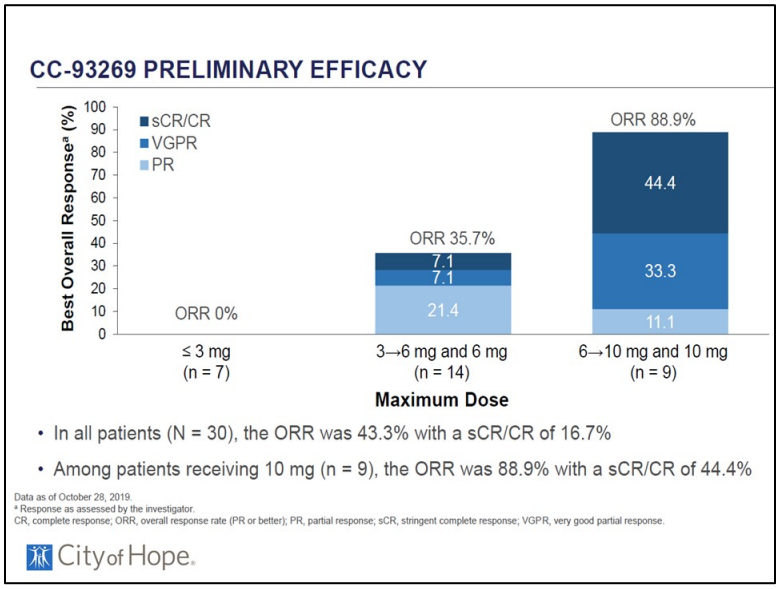
Now the challenge with this drug is it's a continuous infusion, but you can see here that we saw promising responses.



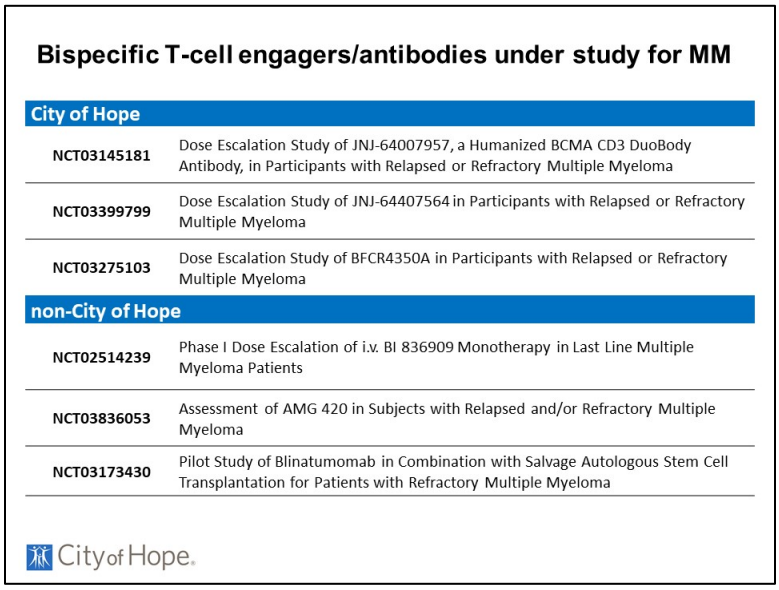
Now this trial is the BCMA trial from Celgene. This was the one that was presented by Dr. Costa at ASH, so this is the most recent one that we have. And just to go back, this generated a lot of excitement. Again, this is not a continuous infusion. It's IV over two hours. You can see here the schedule weekly and then bi-weekly. Relapsed/refractory over three prior regimens,



and we saw promising responses, but we also saw cytokine release. Anytime you activate T-cells, you have this risk of something called cytokine release syndrome (CRS) – fevers, low oxygen, low blood pressure. And you could see that this did occur especially when you get to higher doses of the drugs. Seventy-five percent of patients got CRS at some degree of severity. Most of it was mild, but in a fraction of patients, it was what we call Grade 3 or more severe.

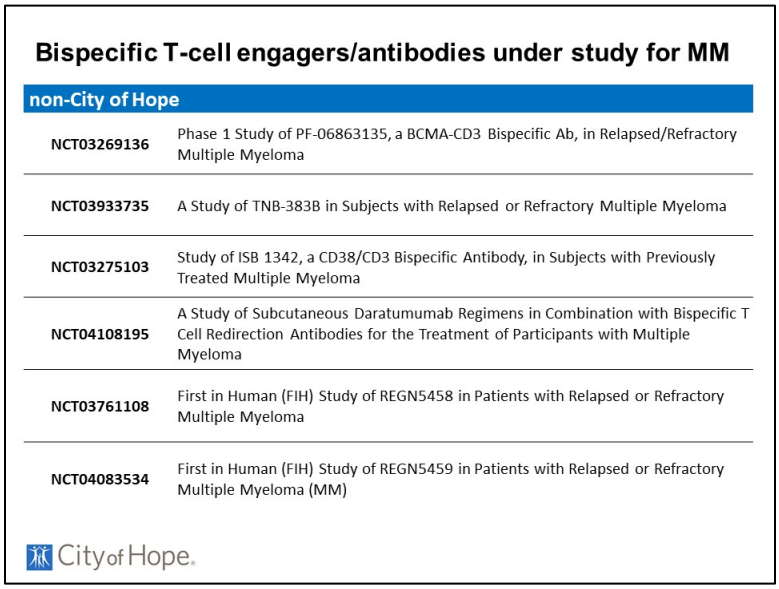


But the reason this drug generated such excitement was in the overall response rate of about 90% at what we think is the target dose of a minimal of 6 milligrams, so, again, we wait to see, and even about 40% of patients getting complete responses. And talking to some people who've been part of this trial, they have been very impressed with the efficacy of this drug but certainly also have been cautioned about the cytokine release.

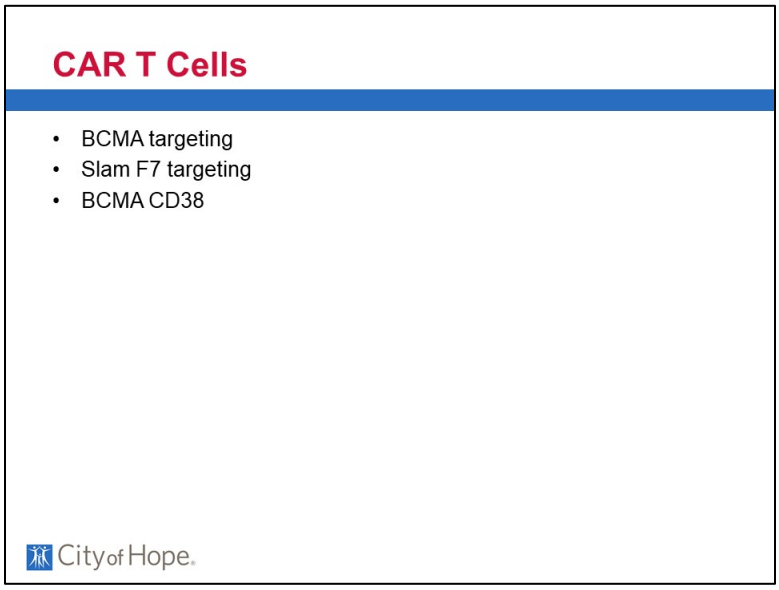


And then just to share as I mentioned, we have multiple T-cell engagers on trial at City of Hope. We have a BCMA one. We have new targets, FCFR5, GPRC5 as well, and first-in-human phase I, and these are international trials that we're very excited about. And now have enrolled fairly significant numbers of patients, so hopefully these results will be starting to be presented soon so you can get some sense of their activity.

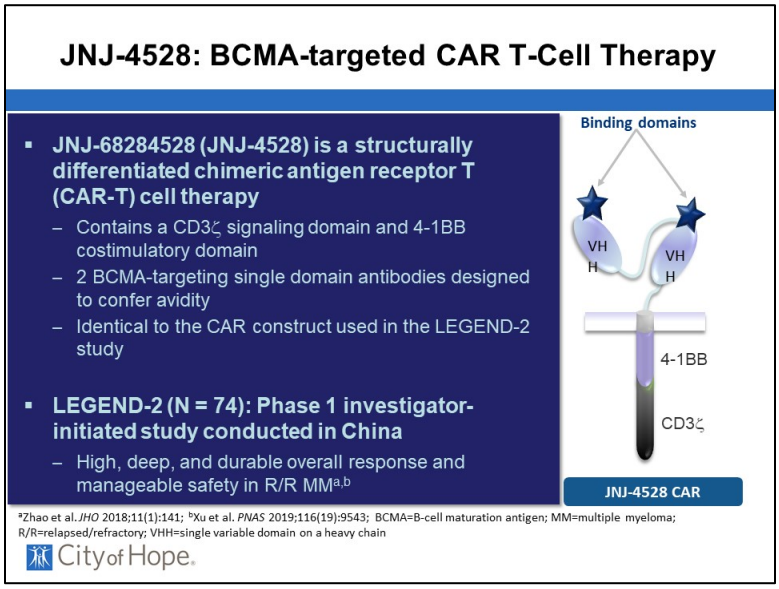
And then non-City of Hope, also many, many other phase I bispecifics are ongoing, sort of, again across the world.



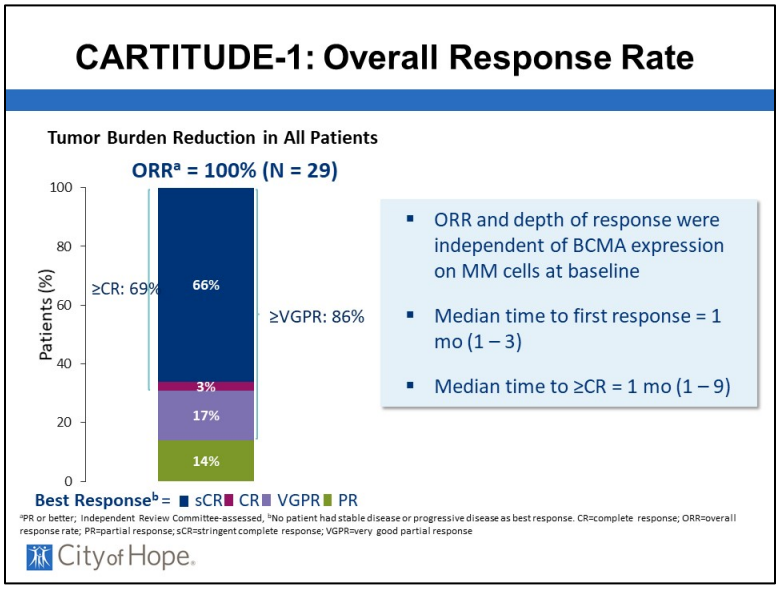
So, I think this class of drugs is going to be a very, very big part of our armamentarium in the near future.



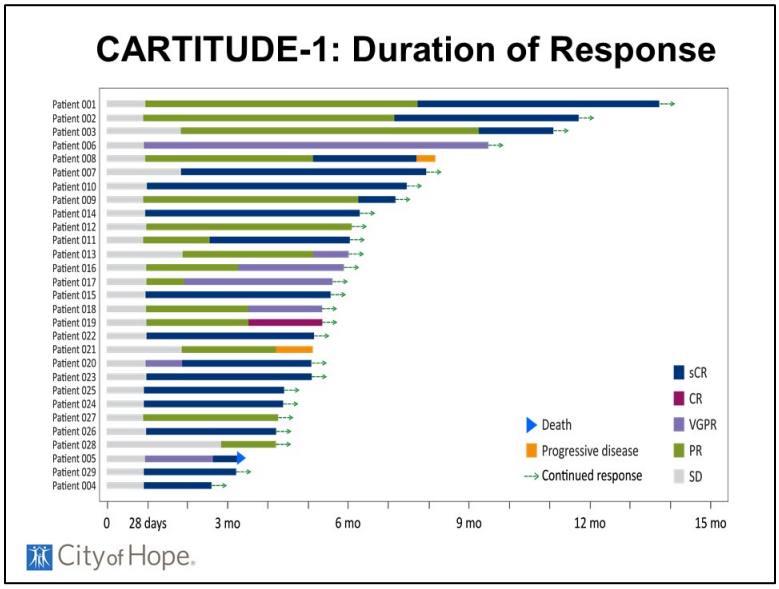
And then CAR T cells. No myeloma talk would be complete without CAR T cells; and, again, CAR Ts have different targets. We have CAR T just against BCMA. We have CAR T against SLAMF7, and we have biotargeting, which is very, very early on; and I'm not going to talk too much about that. There was a presentation from China about a BCMA CD38 targeting CAR T.



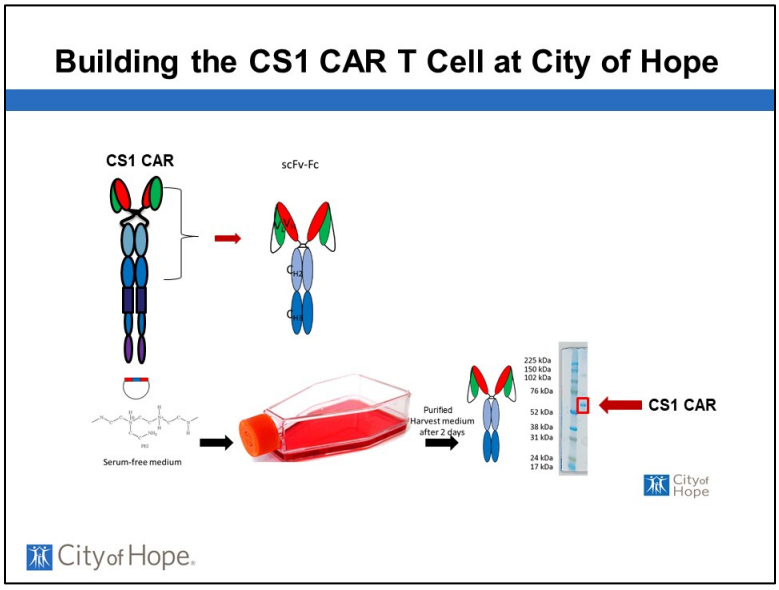
The JCARH one was the one that got the hugest publicity at ASH in the sense that it was, when we get to the response rates, you'll see; but, again, BCMA targeting.



And the reason it got such a big notoriety was the response rate of 100%. Again, remember, small numbers of patients, 29 patients. But, nonetheless, something to bear in mind. Again, toxicity is something also to bear in mind.

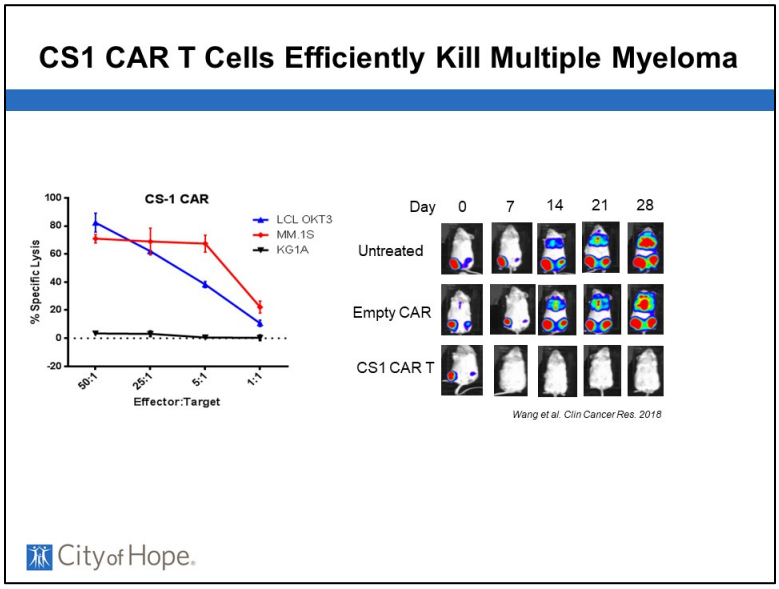


As we move forward, for example, with neurotoxicity being a concern, but we certainly see durable responses with these patients which also excites us, but follow-up is very short as well in these trials.

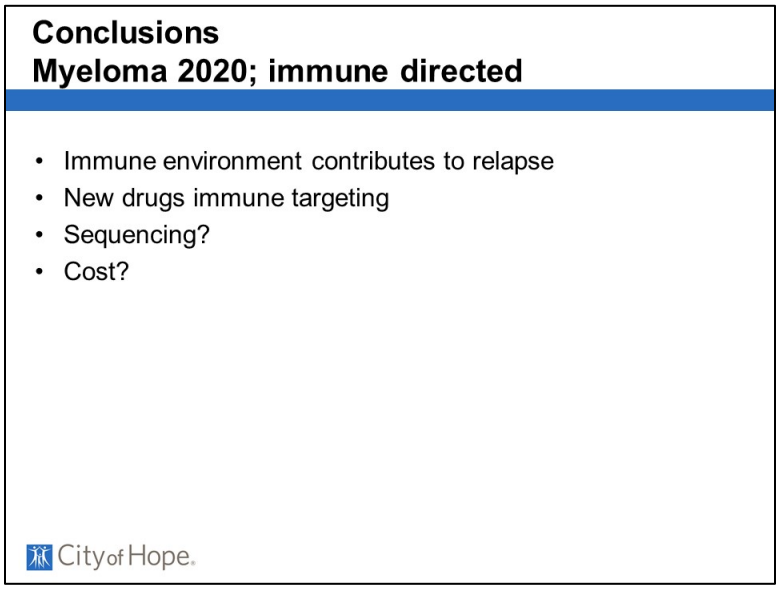


So, you need to bear a note of caution and also bear a note about as we treat more and more patients and get longer follow-up, other toxicity signals need to be monitored.

And then as CS1, so the target that elotuzumab uses, City of Hope has designed our own CS1 targeting CAR.



This just shows you in mice. We've seen that it's very, very active; and we've started a first-in-human phase I trial. We were actually about to treat our second patient with it, but we, as we may get into a little bit later, have placed all our CAR T trials on hold during this pandemic in the interest of patient safety. Again, very difficult decisions with the understanding that patients who need CAR T have fairly, very advanced disease.



So, in conclusion, right now in 2020, I would say that our focus and understanding of myeloma really is now about the immune environment. We have many grants, and we're about to publish a paper on CD38 mechanisms of resistance and understanding this not just the myeloma cell expressing CD38, for example, it's also the immune cells. So, a lot of our research is trying to understand how the

immune environment contributes to relapse and also a lot of our therapies are now directed in augmenting that immune environment.

Some of our challenges become as we get more and more drugs, how do we then incorporate them and sequence them. For example, I mentioned bela (belantamab). Bela is going to get approved, a BCMA-targeting agent. Hopefully, we're going to get BCMA-targeting CAR T cells approved. Which one do you use first? These are all things that will hopefully become clear as time evolves. And, of course, certainly being cognizant of the cost and access to these therapies as well.

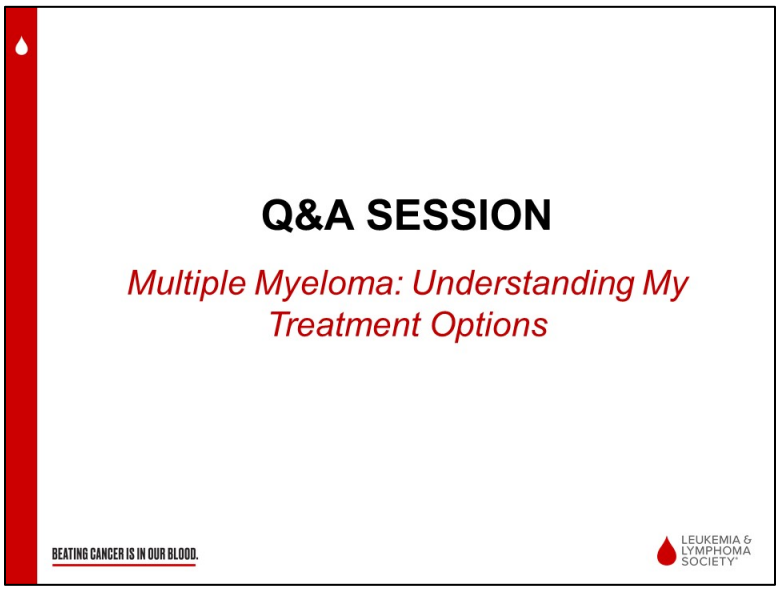
So, I think I managed to get this through, and now I think we're into the question portion. Thank you.

Lizette Figueroa-Rivera, MA

Thank you so much, Dr. Krishnan for volunteering your time with us today and to update us on the treatment options for myeloma, how it affects patients' quality of life, and what questions really to ask your healthcare team. I know that you mentioned a lot of newer treatments coming out of ASH, and Sandra thank you for reminding me.

ASH is the American Society of Hematology. It is a meeting that takes place annually, and most of the newer treatments, the doctors will present their findings at this meeting.

QUESTION-AND-ANSWER SESSION



Lizette Figueroa-Rivera, MA

It is time for our Question-and-Answer portion for this program. And we'll take the first question from our web audience. Doctor, Santo is asking, "What's the difference between relapse and refractory?"

Amrita Y. Krishnan, MD

So that's a great question. Refractory tends to mean that you don't get a response to a therapy versus relapse implies that you've had a response. And relapse really implies that you've been in remission and that you relapsed from a remission.

Lizette Figueroa-Rivera, MA

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

Operator

Our first call is from California. Please state your question, your line is now live.

Patient from California

I've been diagnosed with multiple myeloma two years ago, and I'm also on dialysis. What is the correct treatment for that? I haven't been on chemo for I would say almost a year, but I feel I have symptoms again.

Amrita Y. Krishnan, MD

So, to kind of take a general question, I think the question really is what chemotherapy options are available to patients who are on dialysis? And, generally, most of these drugs are available and they've had specific trials done, including in patients on dialysis. Some of the timing of the drugs often need to be adjusted because of dialysis. So, without going into specifics per drug, I would just say that some of the drugs require dose reductions for patients on dialysis, some of them don't. Some of them just require to be administered on days when patients aren't on dialysis. And that's kind of a discussion with your physician. But there are certainly many drug options. The only caveats being that CAR T cells have not been studied in this setting, nor have any of these other very new investigational therapies yet.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Paul. Paul is asking, "Is isatuximab likely to be effective for patients refractory to daratumumab?"

Amrita Y. Krishnan, MD

So that is probably the million-dollar question that we're all grappling with. And I would say that there are many different schools of thought about that. So, if you're in the camp that believes that resistance to CD38 antibodies is because the immune system isn't working well, then isatuximab is not going to work in people who are progressing on daratumumab.

If you're in this camp that believes that, you know, is it just when you bind onto what we call the epitope or you're binding to a different part of the target and that maybe if you bind to a different part, you can still get some activity, then possibly it could work. I tend to believe, based on data from our center that we've done, that if you don't respond to daratumumab and certainly if you're actively on daratumumab and progressing, switching to isatuximab is unlikely to provide you a response.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Karen from Texas. Please state your question, your line is now live.

Karen from Texas

Thanks for letting me listen. I have myeloma plasma cell leukemia, and I've had it for two years. I've been under maintenance chemotherapy for the last, well, since I came into remission. I've had two bone marrow transplants, and everything was going great. I am now seeing protein in my urine, so they're running tests – blood tests, urine tests, culture just in case I have an infection – but I have no pain. Only symptom I'm seeing right now is the protein in my urine, and the next step for me is

CAR T. I'm kind of interested in, you said there's several different CAR T-cell therapies, and I'd be interested in the clinical trial if available.

Amrita Y. Krishnan, MD

So, I guess the question is choosing among CAR T therapies. Honest truth, I don't think we have a sense yet of one being better than the other. And I think really the challenge is just access to CAR T and just getting onto a trial, which is, I think, the biggest challenge for patients right now just there aren't enough spots. And so, an eligibility for these trials, I should add that note, is very, very stringent. And I think, unfortunately, that's another hardship for patients that these trials select patients very, very stringently. And to be honest, many of them exclude plasma cell leukemia. And so, a few may allow it as there's more and more trials opening, but that's one of the things, caveats, among that.

Now having said that, we hope that later this year, CAR T is going to get commercial approval and then that certainly widens the options for patients.

Lizette Figueroa-Rivera, MA

Thank you. And, doctor, for those on who also have plasma cell leukemia, can you just speak to that and how it's really related to myeloma?

Amrita Y. Krishnan, MD

So, plasma cell leukemia is just defined by a percentage of circulating plasma cells, and we actually revised our definition from the International Myeloma Working Group (IMWG) now to lower that percentage. It used to be 20%. I have to double check. Offhand, I believe we reduced it to five, but I need to double check, so don't hang your hat on that. But it really just tends to be more biologically aggressive. When you look at bone marrows in people with plasma cell leukemia, they tend to have much more chromosome abnormalities. And we generally use very aggressive treatment for it and then have had better and better results of getting people into remission. At least my approach for that has been to keep people on extremely intensive maintenance, so I wouldn't use lenalidomide alone, for example, for a patient with plasma cell leukemia as a maintenance. And we've had good results with keeping people on aggressive maintenance regimens to keep people in remission, so I think things are becoming more promising for that group of patients.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And the next question comes from Dory. Dory asks, "Do I have a compromised immune system?" She's four and a half years after transplant and she's been in remission four and a half years.

Amrita Y. Krishnan, MD

I think that's one of the questions we just don't know. So, one could argue that, certainly, your immune function improves if you're in remission for myeloma. There's some long-term data looking at that in patients, and the patients, for example, who tend not to relapse have better immune function. What we don't know is, you know, without very sophisticated testing, really how much has your immune function has it improved back to that of someone without myeloma? Probably not. But, certainly, as time goes on from the transplant, it's clearly improved. And just to kind of cite the example, that's, in part, why we give vaccines. We give them at a year after the transplant because we know people can mount an immune response. And we even do live vaccines at two years after the transplant for certain people. So, again, with the sense that that timepoint immune function is quite good. But then although if patients are on maintenance drugs, it also could alter immune function, so it really depends on each individual patient's clinical situation.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Juan from California. Please state your question, your line is now live.

Juan from California

Yes, hi. I'm 73 years old. Six years ago, I was diagnosed with multiple myeloma. Five years ago, I had a bone marrow transplant. I'm taking 10 milligram dosage of Revlimid® (lenalidomide) on a 21/7 dosage routine. My question is since that five and six years is quite a bit of time already, is a CAT scan my next move to see, you know, if any of my vital organs or whatever anything inside me is telling me different than my condition?

Amrita Y. Krishnan, MD

So, to kind of make it as a general framework, so the question, which is a great question, is how do I get assessed for myeloma in a restage? How do I know if I'm in remission? I think the take-home message from that is that patients always ask, "What's the best test I can get to find out if my myeloma, if I have?" And the unsatisfying answer is there's no one perfect test. And every patient's myeloma is different, but even in an individual patient, things can change. And so certainly bloodwork looking for the M protein, but, unfortunately, at some point, sometimes you still have to repeat bone marrow biopsies. And many of us at the myeloma centers tend to repeat marrows every year because sometimes patients' myeloma cells stop making a lot of protein. So, their bloodwork can look okay in terms of the M spike, but there still can be myeloma. Sometimes patients can have plasmacytomas or bone things that can sort of be hidden until they've become more symptomatic, so I think the recognition is that imaging with PET CTs, really, is the one we use or certain centers have whole body MRI is an important part of our reassessment for people with myeloma.

The challenge, I have to say, is despite the International Myeloma Working Group sending out a consensus paper and arguing for this need, we continue to struggle to get insurance authorization to do PET CTs. So, hopefully, that will change as time goes on, but that's usually one of the challenges.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Ethan. Ethan is asking what type of emphasis has there been in preventing multiple myeloma from developing in patients who are at high risk?

Amrita Y. Krishnan, MD

So, the question is prevention strategies. And, you're right, that is probably the area where we know the least, but we are starting to do many, many trials. So, there are trials, for example, looking at family member screening to first identify who's at higher risk of getting myeloma. Now true intervention in that group is a little less clear. We do know some risk factors for getting myeloma. Some of them are what we call modifiable and some of them are not. And so, I think we focus on the modifiable ones right now in terms of, for example, there's some data with obesity and IL-6 comes from adipose tissues which drives growth in myeloma cells. But, that's one of the ones that we see as modifiable. Environmental exposure, unfortunately, is not something you can modify in terms of either occupational exposure. Certain jobs are at somewhat higher risk. We've seen that in patients who were 9/11 responders, for example.

So right now, we still are trying to understand what we can modify for most patients and also just trying to identify patients earlier. At some point, there are going to be - the focus has been on interventions at earlier timepoints to prevent progression to myeloma. So that's a big focus of research right now.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Theobhilus of Kansas. Please go ahead, your line is open.

Theobhilus from Kansas

Yeah, good morning. My question is why do we wait until the patients get into relapse before we start on that treatment? Can't we have some medication like we had in diabetic patients for maintenance?

Amrita Y. Krishnan, MD

So, I guess the question is maintenance. We certainly do have maintenance both in patients who had a transplant as well as in patients who are nontransplant patients, and there are a variety of

maintenance drugs that we use. So certainly, yes, maintenance is a big part of our strategy of treatment.

Lizette Figueroa-Rivera, MA

And, doctor, as well, are there any, again, like the last caller, any preventative medications to mitigate the myeloma to get worse?

Amrita Y. Krishnan, MD

So right now, there is none that's really a proven preventative medication and certainly, I think, patients try different things. There's some data from the California Teachers Health Study that metformin use actually seemed to reduce the incidence. But on the other hand, as I mentioned, certainly we're not ready to put people on metformin without clear indications, and that was an epidemiologic study. So, I think we're still trying to learn about it.

Lizette Figueroa-Rivera, MA

Thank you. And Eileen is asking, "I know green tea interacts with Velcade (bortezomib). What about Revlimid interactions with vitamins, minerals, or any herbals?"

Amrita Y. Krishnan, MD

So, certainly, I would say that there can be interactions with herbal medications. I think people are very well aware of St. John's Wort, but the other ones that it's very important to let you physician know if you're taking any because the interactions we worry about in terms of effect on liver function, also cardiac QT interval, bleeding risk with some of these herbal medications because patients with myeloma are often on anticoagulation if they're on lenalidomide, for example. So, I think that's a discussion that each individual patient needs to have with their physician.

The other one I would caveat is, especially in California, a lot of patients are interested in CBD. And, again, interactions of that with narcotics is certainly to be taken into account.

Lizette Figueroa-Rivera, MA

Thank you. And the next question coming from Sandra is she's saying that everyone cannot get a transplant because of age or insurance or even comorbidities. What may be the best course of treatment for those patients who can't go through a transplant at this time?

Amrita Y. Krishnan, MD

So, certainly, age is not our cutoff for transplant eligibility. It tends to be more comorbidities, and that's a very individualized discussion with each treating physician in regards to what is the best treatment option. But just I would suffice it to say that we have many regimens in patients who are not transplant eligible that are also, you know, highly effective, so that's encouraging.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from our telephone audience, please.

Operator

Our next call is from Lisa from Wisconsin. Please state your question, your line is now live.

Lisa from Wisconsin

Thank you. I have a transplant and was on maintenance drugs, including Zometa® (zoledronic acid), for approximately a year and a half. I have two questions. Have there been any studies done currently on having any extractions on teeth as I have had an abscess on a tooth for a year and a half and my specialist will not remove, I'm feeling that I will not heal?

The second question is I had the myeloma on my left side of my skull and ever since that, I suffer with headaches almost daily. Any research on that, please? Thank you.

Amrita Y. Krishnan, MD

So, the question really centers around the dental procedures and the risks of extraction. And the studies, really, that have been done have been more this question of identifying people who are at risk for getting this complication, osteonecrosis of the jaw. And what we know is length of time on bisphosphonates or what we call antiresorptive therapy, and that includes Xgeva® (denosumab) is a risk for getting osteonecrosis of the jaw. We know that dental extractions are a risk. And so, it becomes an individualized discussion with the patient, their doctor, and their dentist about risk versus benefit. And we, certainly, in patients who have to have an extraction, we try and delay it; hold the antiresorptive therapy. Some dentists want three months, some dentists want six months. And that's not based on any firm data. Again, it's just clinical judgment.

But I think the issue is really that people are, and for those of you who have had osteonecrosis, you know how debilitating it is. And, certainly, you know, unfortunately, some people get it with very short exposure, so there's a lot that we still don't understand about it, and that's why, again, we try to do everything we can to mitigate the risks of getting it.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Ann. She states that she has substantial shakes and side effects from coming down from dex, so now she's on a regimen of Revlimid and daratumumab. Can she eventually go back on dex? Is a lower dose a reasonable idea?

Amrita Y. Krishnan, MD

So, the question here is dealing with steroid-related side effects and, certainly, part of the things we do are reducing the dose. And sometimes some patients end up doing better with prednisone than dex, so sometimes changing steroids as well.

Lizette Figueroa-Rivera, MA

Thank you. And I'll take the next question from our phone audience.

Operator

Our next call is from Richard from Texas. Please state your question, your line is now live.

Richard from Texas

Okay. My question is I heard Jack Aiello talk about his experience when he was diagnosed in 1995, and he had an autologous transplant and then later had an allogeneic transplant. So, my question for Dr. Krishnan is, and I think I heard you say, Dr. Krishnan, that at City of Hope you're looking into more allogeneic transplants. So, are allogeneic transplants becoming more common for myeloma patients?

Amrita Y. Krishnan, MD

So, yeah, we actually led the largest trial in the country looking at comparing doing what we call tandem, so two autologous transplants to an autologous followed by an allogenic transplant. And we showed, certainly, that the allogeneic transplant reduced the risk of relapse but had more complications. And so that's what we're trying to balance. So we've had trials even still ongoing of allogenic transplant, but I have to say that the focus, and the focus from the national sort of cooperative transplant groups, the BMT CTN, has been trying to answer this question of allotransplant really as an immune therapy. So, you're just using the donor immune system as a way to fight myeloma, so our focus really has been other ways to use immune therapy, one of them being that the CTN has a vaccine trial. The other one that is going to open and, again, now with these time lines are all shifted, but, in fact, using CAR T cells after an autologous transplant so patients who have high-risk myeloma, for example, with plasma cell leukemia being a type of patient we want to target. So, it's the idea of certainly immune therapy but of different ways.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And Barry is asking, “Are there medications that will ameliorate peripheral neuropathy caused by chemotherapy?”

Amrita Y. Krishnan, MD

So, I think that’s an area where we’re very lagging. We use medications, Neurontin certainly, or gabapentin is the other name for it, Lyrica® (pregabalin), over-the-counter stuff. For example, alpha lipoic acid in diabetic neuropathy seem to be of benefit so we use that. Topical therapies, menthol or cocoa butter, which we think just activates some other receptors on this to help ameliorate it, and B-complex vitamins. So, it’s sort of a gamut of different things that we try.

Lizette Figueroa-Rivera, MA

Thank you. I know that that’s a major concern for most of our patients. And we’ll take the next question from our telephone audience.

Operator

Our next call is from Jimmy from Georgia. Please state your question, your line is now live.

Jimmy from Georgia

Yes, ma’am. I appreciate your expertise and you’re sharing it with us today. You’ve used a lot of $10 words that I’m not familiar with, but I’ve had a stem cell transplant. I’ve been through Revlimid. I’ve had Pomalyst (pomalidomide) and now my next stage is immunotherapy, but it’s on hold because of the corona situation. But after that, what does your expertise say about a second stem cell transplant? And thank you.

Amrita Y. Krishnan, MD

Thank you. And I apologize, you know, in terms of getting into too much into the technical language. I think that many doctors, and myself included, are guilty of that. And, certainly, one on one with your doctor, please, you know, stop them if you don’t understand something.

But I guess just to frame the question, the question is, is there a role for a second transplant in someone with myeloma coming back? And I would say yes. In fact, when you look at the national data, we are doing more and more of those transplants. Across the country, it’s about 300 to 400 of those done a year. The ones where it worked best are people who’ve had a long remission from their first transplant.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Bob. Bob is asking, “Is it okay for someone in myeloma remission for nine years and no maintenance drugs to donate blood?”

Amrita Y. Krishnan, MD

Thank you for thinking about that or being willing to with our blood shortage right now, but I would say those patients would still be excluded.

Lizette Figueroa-Rivera, MA

Thank you. And I’ll take the next question from our telephone audience, please.

Operator

Our next call comes from Linda from California. Please state your question, your line is now live.

Linda from California

My question has to do with because I’m in maintenance right now and with the coronavirus, I am concerned about literally driving up to UCSF and going into the center because I was alarmed that I was the only one in the center that had on gloves and a mask. I know that they told me that people have been stealing all this stuff but that alarms me, and I don’t know. I mean I’m scheduled to go back again this week for more- I am, by the way, a 13-year survivor since transplant. I started in the EVOLUTION trial, I’m back in exactly those same drugs. But my concern has to do with, you know, exposure with the coronavirus along with that I shouldn’t be out there. That’s my question.

Amrita Y. Krishnan, MD

So, I can tell you that, you know, just from my discussions around the country with my colleagues, so that, yeah, we’re all kind of grappling in terms of- I could only speak to our center specifically. Certainly, we’ve put a lot of transplants on hold for myeloma. And for patients who are coming into the center, we’ve converted as many as we can to suggest they just either have labs drawn locally if they need to and we have a telephone consultation or we’re delaying visits. Obviously, there’s some patients who need to get chemotherapy and there is no choice, and we’re moving ahead. We’re also, obviously, having very strict screening measures at the facility. I can tell you just that been circulating, is under discussion in our center right now that they’ve just implemented in Boston that all the staff wear masks all the time when they’re in the hospital to minimize risk of transmission.

So, I think every center’s kind of reacting to this and trying to maximize safety. And so, it just really depends on each individual patient’s risk-benefits of coming into the center. And, certainly, even the patients are being screened, certainly, before they come to the waiting room.

Lizette Figueroa-Rivera, MA

Sure. Thank you. And Charmaine is asking, "How long can one take Velcade therapy? Does response decrease over time?"

Amrita Y. Krishnan, MD

So, actually, the response of Velcade therapy tends to increase over time. Originally, when we did the trials with Velcade, it was given IV and that was very limiting because of its neuropathy. Now that it's given subcutaneously, people tend to have less neuropathy, so it tends to be less of a limiting factor. So, I've had patients on Velcade actually several years and tolerate it and sometime dose and schedule the value needs to be kept in mind too.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question over the telephone, please.

Operator

Our next call is from Carlos from California. Please state your question, your line is now live.

Carlos from California

Yeah, my question is, you know, I'm a patient for multiple myeloma 2007. I met Amrita at City Hall long time ago. But my question is right now I'm on chemotherapy. They give me Kyprolis 97 milligrams for 30 minutes. So, I need to know how long they've got to give me that treatment.

Amrita Y. Krishnan, MD

So, I guess the question is then in terms of just relapsed myeloma how long do you stay on therapy? And that's certainly very individualized depending on your response, but generally, you know, if patients are responding to treatment and it's also looking at side effects of treatment, that includes blood counts as well as other side effects, we tend not to have a certain set stop therapy after this many cycles. So, I think the discussion with your doctor would be what's the response and what's the plan in terms of further therapy?

Lizette Figueroa-Rivera, MA

And like you were saying, doctor, really the treatment plans should be very individualized and patients should ask their doctors about their specific treatment needs as there's so many new treatments now that one myeloma patient's treatment is not going to be the same as another myeloma patient's treatment. Correct?

Amrita Y. Krishnan, MD

Yes. I would say that's exactly why it's hard to sort of generalize on that, except to just make the point that, you know, most myelo therapy tends to be maintaining therapy but, certainly, monitoring for side effects. So, obviously, you don't want patients to have debilitating side effects as a price of staying on therapy.

Lizette Figueroa-Rivera, MA

Sure. And I know that a lot of our patients are asking about side effects. About the bone pain, we have, of course, a lot of people with neuropathy. Are there any medications or different ways that people can handle the bone pain or any of the side effects that they get from treatment?

Amrita Y. Krishnan, MD

I think that's where, to be honest, we need to do a lot better work. And it's hard because those are hard studies to do and hard in terms of figuring out what really, really works, and also hard to get companies sort of involved in developing those things. So, we tend to just use drugs that are already available for other purposes and try and repurpose them for treatment, certainly, of neuropathy, for example.

I think some of the stuff that's been going on, and it's been out of the Boston group, is trying to figure out why do some people get really bad neuropathy even with a couple doses of Velcade and why do other people seem to tolerate it? And we know certain risk factors. For example, older patients over the age of 70 tend to have a higher risk of Velcade neuropathy. Patients with diabetes because you have underlying neuropathy from diabetes higher risk. So just trying to look at certain risk factors. We know, for example, with carfilzomib, patients that tend to have more potential for toxicity are patients over age 70, especially those who don't have well controlled blood pressure. So those kind of things we can sort of control to try and minimize toxicity.

Lizette Figueroa-Rivera, MA

Sure. Thank you. I know that the quality of life issues are really important to our patients and to us, and we do get a lot of questions in regards to quality of life issues whereas we do want patients to know that they can also ask their physicians, of course, about these issues. Correct?

Amrita Y. Krishnan, MD

Oh, absolutely. And many centers sort of work with their supportive care teams as well to help with this.

Lizette Figueroa-Rivera, MA

Great. And now John is asking, "How is the strength of a chemotherapy dose determined? Should it be a maximum dose right away or should a half dose be tried first?"

Amrita Y. Krishnan, MD

So, chemotherapy dose just depends on the drug. Some of them have flat dosing, some of them have doses adjusted for renal function, some of them have doses that are weight based, and some of them are based on somewhat tolerance. You start at a lower dose and you work your way up, so, really, it just depends on the drug and depends on the patient.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Caroline from Pennsylvania. Please state your question, your line is now live.

Caroline from Pennsylvania

My question has to do with is there an age limit as far as a bone marrow transplant where that would not be considered? I'm currently taking Treanda (bendamustine) and Velcade and I'm also a diabetic, so I understand the neuropathy. But I didn't know whether it was too late to even consider a bone marrow transplant or not.

Amrita Y. Krishnan, MD

So, we don't have a specific age cutoff. I can tell you if you look at just the national registry data, we do about 500 transplants of patients age 70 to 75 years of age. Beyond age 75, there's less and less data. So not saying it can't be done, but like everything in medicine, it's sort of a risk-benefit question. And so, it's harder to prove the benefit and so that's, I think, a very individualized discussion.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Tiffany. Tiffany is asking, "What do you see as the role of physical therapy or other rehabilitation professionals in helping individuals with myeloma to address treatment-related effects and optimize overall functioning?"

Amrita Y. Krishnan, MD

I think, certainly, we're lucky we have great physical therapists and, you know, a big part of, certainly, just helping patients in terms of just staying functional, moving, addressing even there's some new things they can do for neuropathy; and even just understanding with compression fractures, bone pain, all those things help affecting mobility. I do find that they can be extremely helpful. And just teaching patients strengthening exercises as well.

Lizette Figueroa-Rivera, MA

Mike is just asking how long the CAR T cells are in the body after the trial and how long are they seeking the cancer cells after.

Amrita Y. Krishnan, MD

So, the question is sort of persistence of CAR T cells. That's really unknown and that's part of the reason that we engineer, you hear this idea of second generation, third generation CAR Ts. Part of that is they're putting in other molecules to help them persist in the system because we do think part of the question is why do people's myeloma come back? Is it that the CAR T cells they start to die out in circulation? And that certainly happens in a portion of patients.

So right now, there are a small group where they persist, but the median what we call progression-free survival (PFS) or remission, at least from the Bluebird trials was about 12 months. And so, you could say that, therefore, you know, 50% of patients that you see persistence beyond that and 50% less.

Lizette Figueroa-Rivera, MA

Thank you. And I know that a lot of patients and caregivers alike are asking if you know or you have some semblance of when a CAR T-cell therapy would be available for myeloma patients outside of a trial?

Amrita Y. Krishnan, MD

You know, we're hoping towards third quarter this year. Again, I think that's a little unknown now given everything else that's happening if that's going to get pushed back or not.

Lizette Figueroa-Rivera, MA

Thank you. I know that's one of the million-dollar questions.

Next question comes from Jack. He's asking, "With so many various treatments available, where might the science be in terms of knowing which treatment might work best for a given myeloma patient?"

Amrita Y. Krishnan, MD

So, you're asking sort of more personalized directed therapy. There's a lot of trials sort of focusing on that now. So, certainly, with genomics and trying to understand is that a way to better target therapy, you know, I think individual centers and other sort of specialized trials. I mean we have a couple that are in the very, very early stages, for example, using 3D culture modeling of patients' myeloma cells in the lab and testing out against chemotherapy drugs to figure out are we able to predict which ones will work. And we have other sort of unique platforms that we're looking at early trials as well. So, it's

something that was a great area of interest, but we're not yet ready to sort of roll that out in terms of using it to make treatment decisions yet.

Lizette Figueroa-Rivera, MA

Thank you. I know a lot of people are interested in treatment sequencing or which treatment should I get first and which treatment is better for me. So that's really important. Thank you.

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

Operator

Our next call is from Lawrence from Ohio. Please state your question, your line is now live.

Lawrence from Ohio

Hi, I'm currently on Revlimid maintenance, 10 milligrams daily, and I did not have a stem cell transplant. I was diagnosed in 2016. Been recently diagnosed with Waldenstrom's lymphoma. Have not received treatment for it yet, just watchful waiting, and was wondering if you could comment on the prevalence or significance of Waldenstrom's or any type of lymphoma in conjunction with myeloma. Thank you.

Amrita Y. Krishnan, MD

That's a good question. I think it sort of bespeaks the idea that these all come from the same cell of origin. So Waldenstrom's there's something called the lymphoplasmacytic cell, so it tells you it's kind of, they all come from B cells and so just how do they differentiate? So that bespeaks to probably you have a couple clones and this one is the more active one right now that differentiated and then so showing more of a Waldenstrom's phenotype making an IgM protein, for example. Some of the drugs are overlapped in Waldenstrom's and myeloma, so that's helpful, but some of them tend to be more effective in Waldenstrom's and less in myeloma. So, it's not unheard of. You know, for example, CLL (chronic lymphocytic leukemia) and myeloma often we see coexist.

Lizette Figueroa-Rivera, MA

Thank you. And one more question. Kerry is asking, she enjoys weightlifting with free weights. I commend you for that, Kerry. "Since I had bone fractures associated with my diagnosis, is it okay for me to now continue with this type of exercise since I'm in remission?"

Amrita Y. Krishnan, MD

I guess two comments. One is that, certainly, bony disease from myeloma, unfortunately, takes a long time to heal and the bones really never go back to normal. The issue of weightlifting, really, that's a sort of individualized discussion with your physician depending on what your bones look like. You know, people's myeloma get it different. Some people tend to have more bone disease. Some people

tend to have more kidney, and so just depending on really how it's affected your body to have that discussion. But I, certainly, with my patients, if they don't have significant disease, certainly light weights, walking are things I encourage.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And our last question today Mary asks, "At what time should I consider a clinical trial?"

Amrita Y. Krishnan, MD

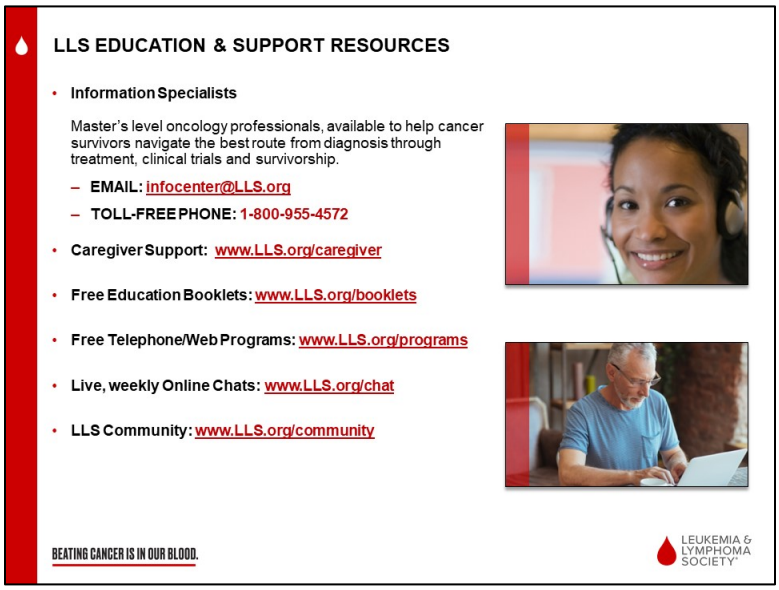
Well, you know, I guess I'm very biased in that one. I think at any timepoint. We have trials for all phases of disease, including patients who have just MGUS or monoclonal protein. So, I think that clinical trials are a tremendous help to patients because they give you access to specialists in that disease, they give you sort of the ability to be closely monitored. And the honest thing I say is, look, if I had all the answers, we wouldn't have any trials. So, we are really looking to be better than where we are right now. And the only way we can do that is through these trials.

Lizette Figueroa-Rivera, MA

Thank you so much, doctor. I know that it's really important for our patients to know that there are trials for every phase of treatment, not just after you've relapsed or after you have been refractory, so that's very important. Thank you.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA



And thank you all for all your questions, and thank you so much, Dr. Krishnan, for your continued dedication to patients and especially taking time out for us today.

And if we weren't able to get to your questions today, you can call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572, and we're available to speak with you from 9 AM to 9 PM Eastern Time, or you can reach us by email at infocenter@LLS.org and Information Specialists can assist you with answering questions about the coronavirus as well as additional resources that are available to patients during this time.

Again, we'd like to thank and acknowledge our supporters, Bristol Myers Squibb, Genentech, and Biogen and Takeda Oncology for really partnering with us and supporting us.

And thank you, Dr. Krishnan, again, for sharing your knowledge with us today. To all the patients, caregivers, and professionals participating in today's call, and on behalf of The Leukemia & Lymphoma Society, really thank you for getting on the call today. We know that it's challenging times, and we appreciate you. And let us be there for you. Okay, we are here for you.

Thank you.