Sequencing Treatment in Relapsed/Refractory Multiple Myeloma: The Right Treatment at the Right Time for the Right Patient

Welcome to *Managing Myeloma*, my name is Dr. Paul Richardson, and today it's my pleasure to review with you the potential sequencing of various treatments in the management of relapsed/refractory disease and share with you some thoughts around what may be the right treatment, at the right time, for the right patient. In this presentation, I'll compare and contrast some of the new and emerging drug classes for the treatment of relapsed/refractory myeloma. I'll seek to identify the efficacy and safety of some of these new emerging therapies in the context of treatment in the relapsed/refractory setting, and discuss how one might consider a risk-adapted approach to this in patients with relapsed/refractory disease.

Speaker Disclosure

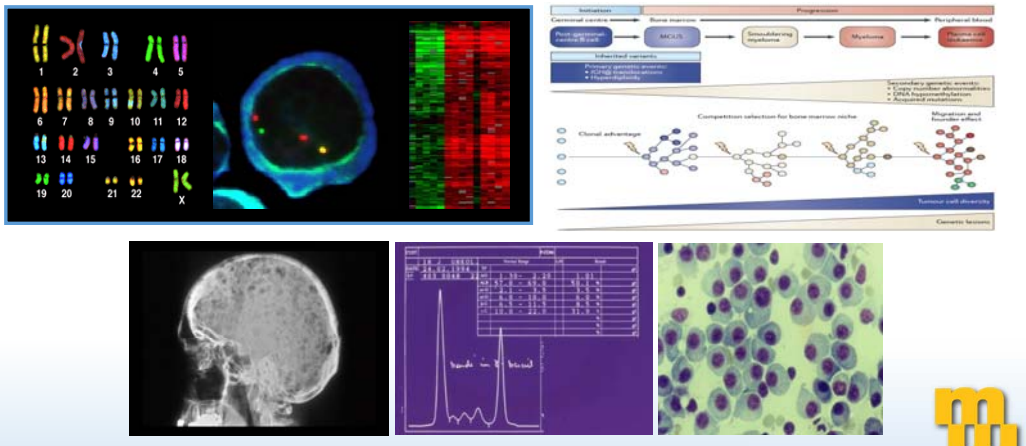
- Formal advisory activities:
  - Amgen Inc.
  - Celgene Corporation
  - Janssen Pharmaceuticals, Inc.
  - Karyopharm Therapeutics
  - Oncopeptides, AB
  - Takeda Oncology
- Research activities:
  - Bristol-Myers Squibb Company
  - Celgene
  - Takeda Oncology

Here are my disclosures - and now let's move on to the presentation.

Multiple Myeloma …Not Just One Disease!

- Risk stratification, recognition of clonal heterogeneity
- Individualization of treatment, advent of novel therapies

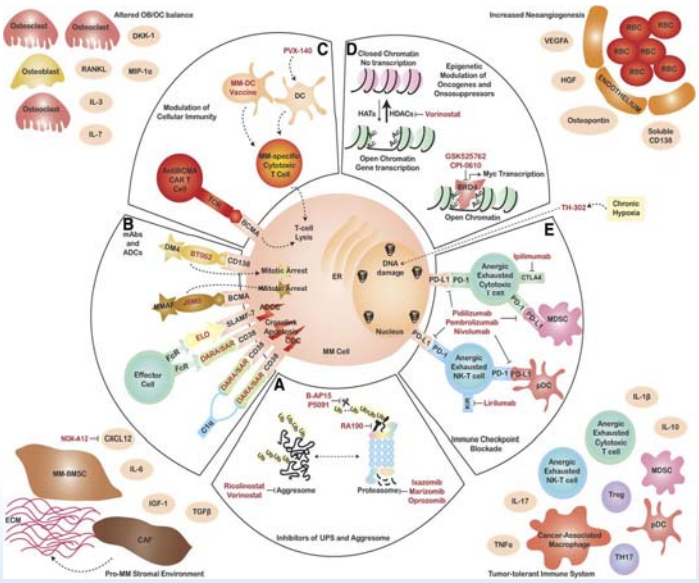
3 decades



Drach J. ASH 2012.; Morgan GI, et al. *Nat Rev Cancer.* 2012;12:335-348.

I want to start by sharing with you that multiple myeloma is truly not just one disease. It's very important to understand that it's a highly heterogeneous illness, not only between patients, but very importantly during the course of a patient's illness the disease may change – the so-called clonal tiding and clonal evolution is now well-recognized. In this context, this allows us to individualize treatment, and with the advent of novel therapies, we've not only been successful in risk stratifying but also in having answers to those respective risk groups accordingly. What I mean is that our novel treatments have in general been able to overdrive and overcome some of the classical resistance patterns that we've seen of old, and improve outcome even for our higher-risk patients. However, it's important to recognize that in that context, outcomes for higher-risk patients remain very challenging.

Multimodality Targeting of MM in the Context of the BM Microenvironment



Bianchi G, et al. *Blood.* 2015;126:300-310.

Now how do we set about doing this? Well, the multimodality targeting of myeloma is very, very important to appreciate. I show this next slide in the context of the new therapies. This is actually from a paper led by my colleague, Dr. Giada Bianchi some years ago, and Giada showed in this particular schematic the variety of drug approaches that we have. Box A incorporates proteasome inhibition, Box B targets monoclonal antibodies and their great promise. As you move further around the circumference of the diagram you can see that there are a variety of strategies: through the mobilization of cellular immunity or its modification, through to histone deacetylase inhibition, and then across to checkpoint effects as well as other novel approaches to targeting the immune system. Then around this schematic, we focus on supportive care strategies as well as immune effector cells in the context of the immune milieu. The message here is that there is a multimodal approach to targeting multiple myeloma in the context of its microenvironment and this provides us with therapeutic opportunity

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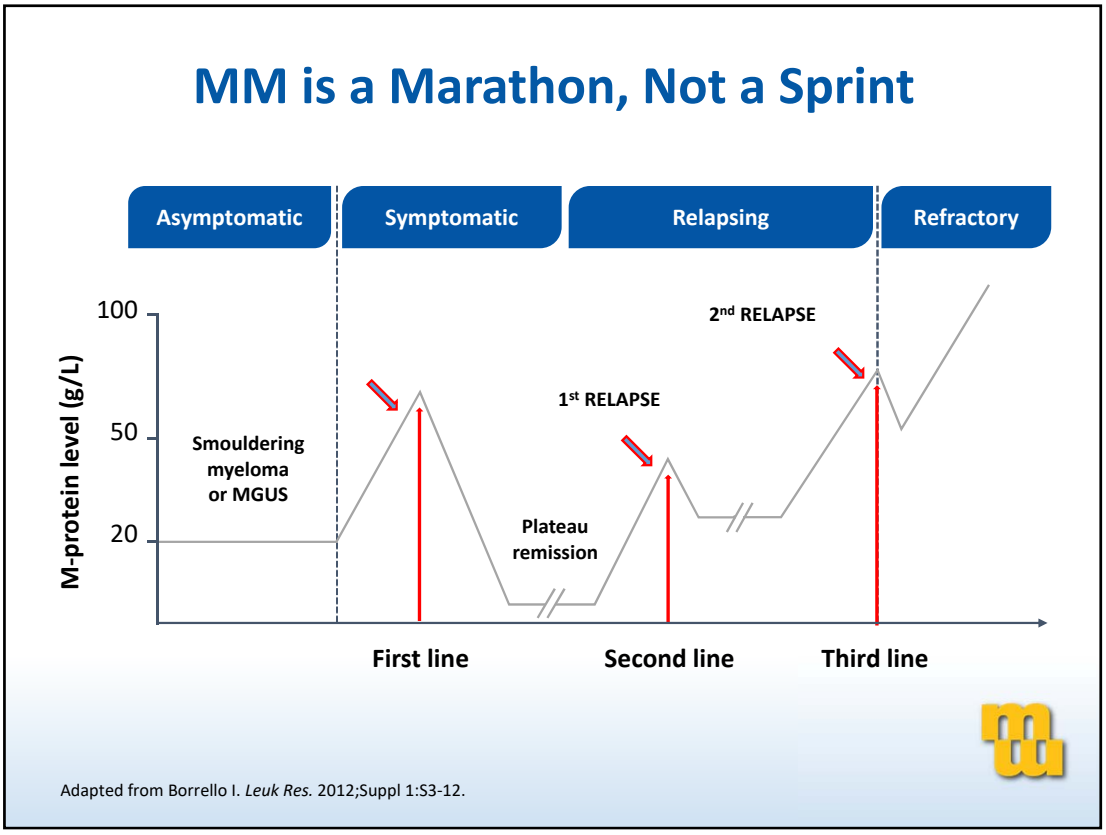
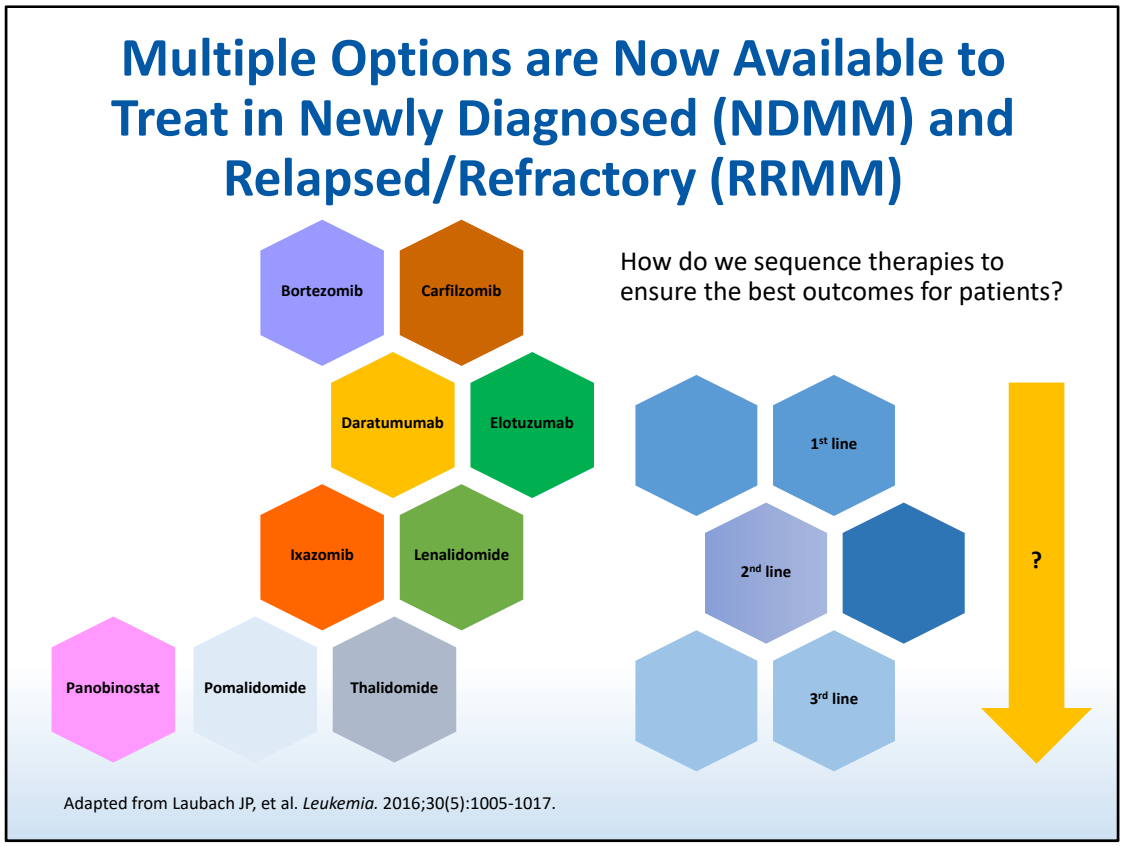
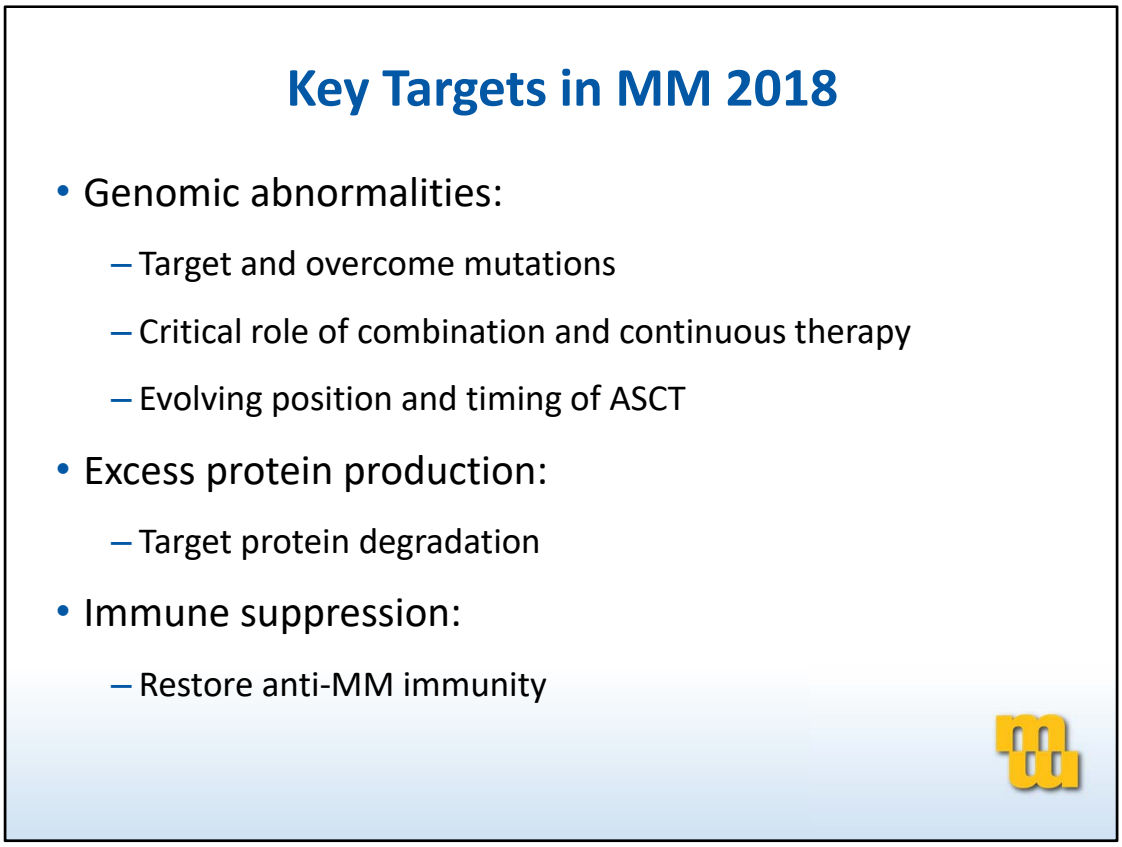


When we think of this in the context of treatment, it's important to share that the treatment of multiple myeloma is a marathon and not a sprint. From initial disease treatment, to maintenance, to relapse, and then the more relapsed/refractory patients who can be exquisitely challenging, the long-term view is very important both for efficacy and toxicity.

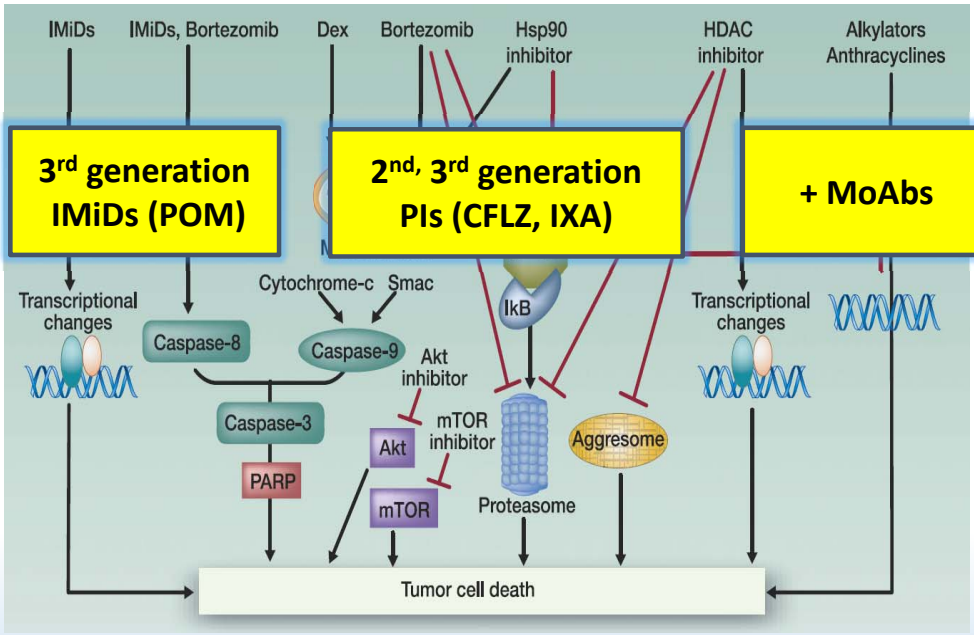


In that same spirit it's important to recognize that there are multiple options now available to treat relapsed/refractory disease. This lovely paper from my colleague Dr. Jacob Laubach seeks to summarize what those are. One critical question is how do we sequence therapies to ensure best outcome?



Going forward with this is the construct that in that same setting there are key targets to think about. These are genomic abnormalities: the targeting and overcoming of mutations, the critical role of combination and continuous therapy in doing this, and we have the dynamic of the evolving position and timing of transplant. Then as we think about novel targets in the myeloma itself, excess protein production remains a fundamental target in this disease. When we think of immune suppression and the restoration of antimyeloma immunity, I think there is a very wide range of strategies that we can pursue, and I'll come to those in a minute.

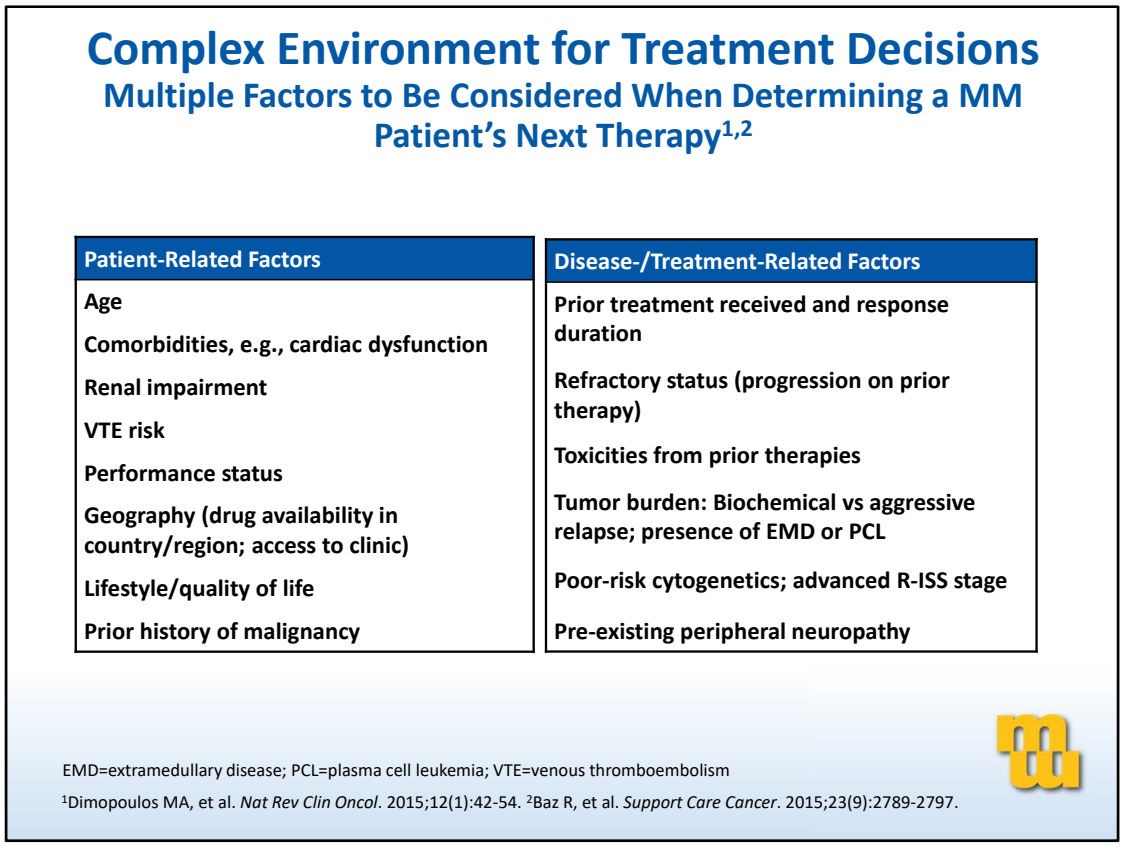
Rational Combination Strategies in RRMM



Adapted from Lonial S, et al. *Clin Cancer Res.* 2011;17:1264-1277.

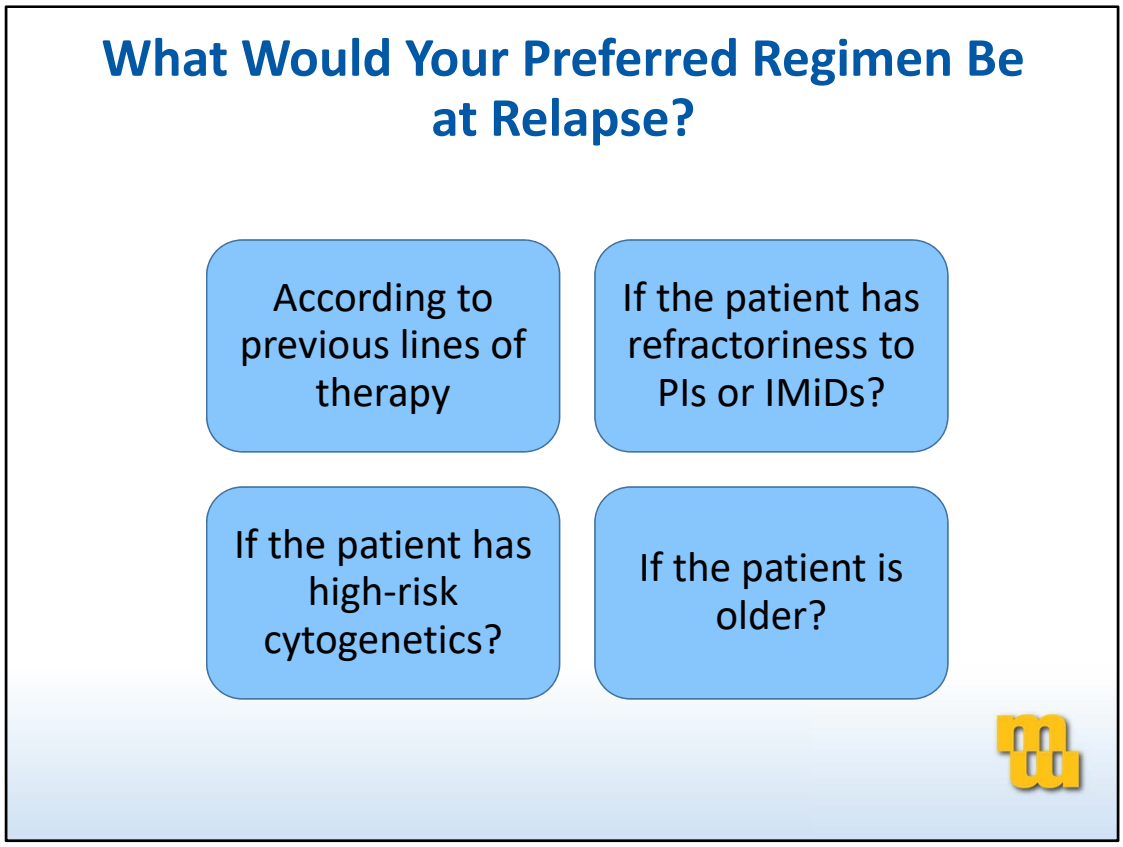
In terms of rational combination strategies in myeloma, it's important to recognize the fundamental paradigm of combining a proteasome inhibitor with immunomodulatory treatment as a key therapeutic backbone. There are then a variety of other small molecules and indeed conventional cytotoxics that can be integrated into that treatment paradigm.

Of course, now we have third-generation immunomodulatory drugs such as pomalidomide. We also have second- and third-generation proteasome inhibitors, including carfilzomib and ixazomib, and then we have the true paradigm-changing effects of monoclonal antibody therapy.



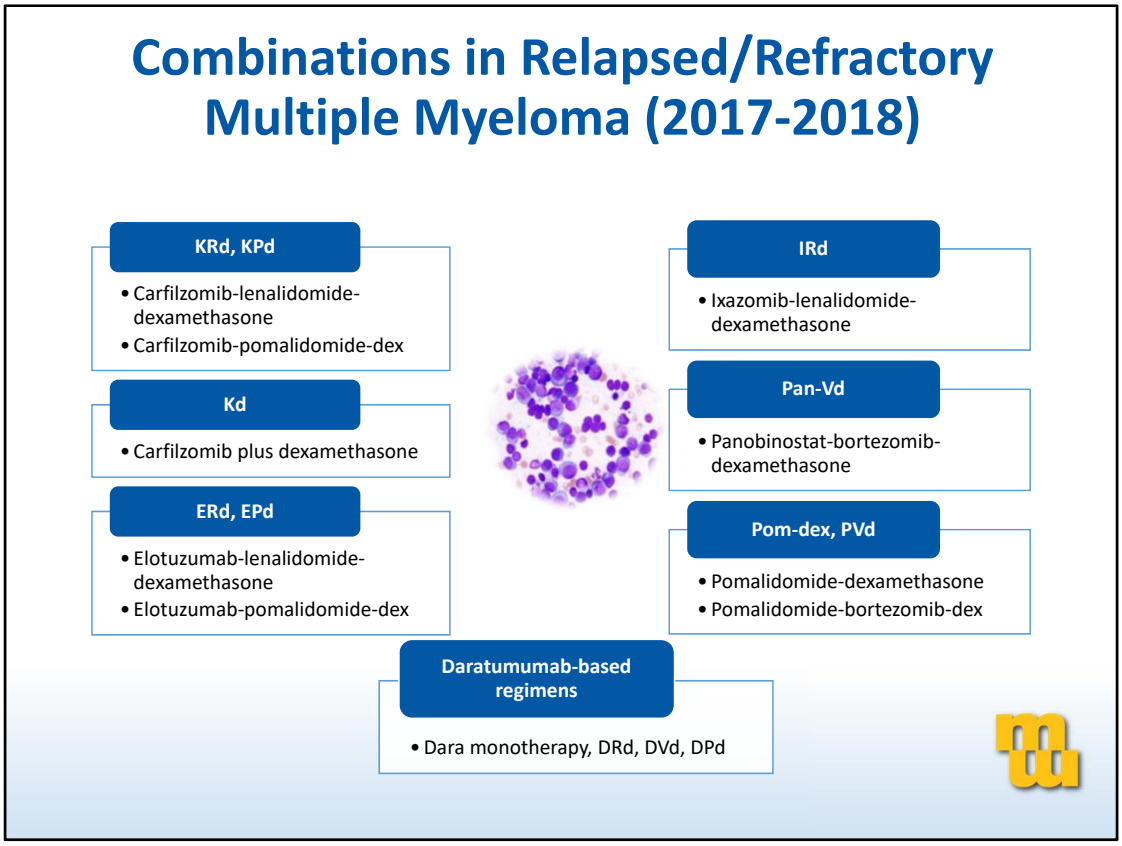
Now, when we think about this, there is therefore a complex environment for treatment decisions and I would argue there are multiple factors to be considered when determining a patient's next therapy. In this slide, I've sought to help summarize these for you. There are patient-related factors on the left. These obviously include comorbidities, renal dysfunction, and other important factors, not least of which is lifestyle and geography. On the right we've gone through disease- and treatment-related factors to help you understand how these matter. For example: what is the prior treatment that's been given; how long did the response last; is the patient refractory on treatment or within, say, three to four months of a prior treatment; is the patient refractory to maintenance versus combinations; and so forth. Then what's very important is what are the toxicities from prior therapies: what's the tumor burden like; is it minimal, is this a biochemical progression or is it much more aggressive and, say, characterized by extramedullary disease or even plasma cell leukemia?

Now in that same context, to help us understand how disease may behave, we have the benefit of cytogenetics of FISH as well as the utilization of the revised ISS stage to help us understand what may be a higher-risk group. In terms of toxicities, pre-existing neuropathy is a relevant consideration as are other considerations such as cardiovascular risk.



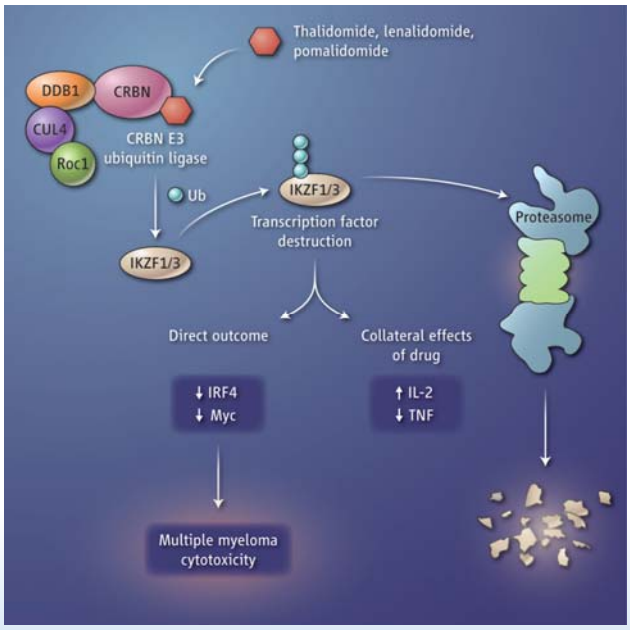
[What would be your preferred regimen at relapse?

According to previous lines of therapy this would be very important: has the patient had one, two, or three lines of therapy? This would be critical in defining what you do. Second, if the patient has refractoriness to either a PI, an IMiD, or both, what would one then choose? Is the patient characterized by high-risk cytogenetics? These are of course disease-related characteristics. Then in terms of the patient themselves, is the patient older or frailer and how should this be considered in terms of treatment choices?



With this in mind, there are a number of choices available. I think it's critical in the relapsed/refractory setting to be aware of combination strategies. We have the combination of carfilzomib plus lenalidomide and dexamethasone; we have carfilzomib plus pomalidomide and dexamethasone; we have ixazomib plus lenalidomide and dexamethasone, and studies ongoing combining ixazomib with pomalidomide would now make this a very attractive option. We have the doublet of carfilzomib and dexamethasone. We have, in the same context, bortezomib, dexamethasone and panobinostat which is FDA approved, and can be particularly valuable in high-risk disease including deletion 17 disease. Then as we move forward in the same context of high-risk disease, it's important to note the value of pomalidomide-based approaches including pomalidomide, dexamethasone, and bortezomib. As we think about antibodies, these have truly been paradigm-changing as I alluded to. Daratumumab monotherapy; daratumumab combined with lenalidomide and dexamethasone; daratumumab, bortezomib, and dexamethasone; daratumumab, pomalidomide and dexamethasone; and of course combinations of daratumumab now with carfilzomib and other approaches are showing great promise. Finally I want to touch on the role of elotuzumab. Elotuzumab, lenalidomide, and dexamethasone is FDA approved and has shown clinical benefit in the relapsed and relapsed/refractory setting. A particularly exciting recent combination has been that of elotuzumab, pomalidomide, and dexamethasone, where an important progression-free survival benefit has been shown for the three-drug combination of elotuzumab, pomalidomide, and dexamethasone when compared to pomalidomide and dexamethasone alone. This constitutes an important choice that may be particularly valuable when other strategies have failed.

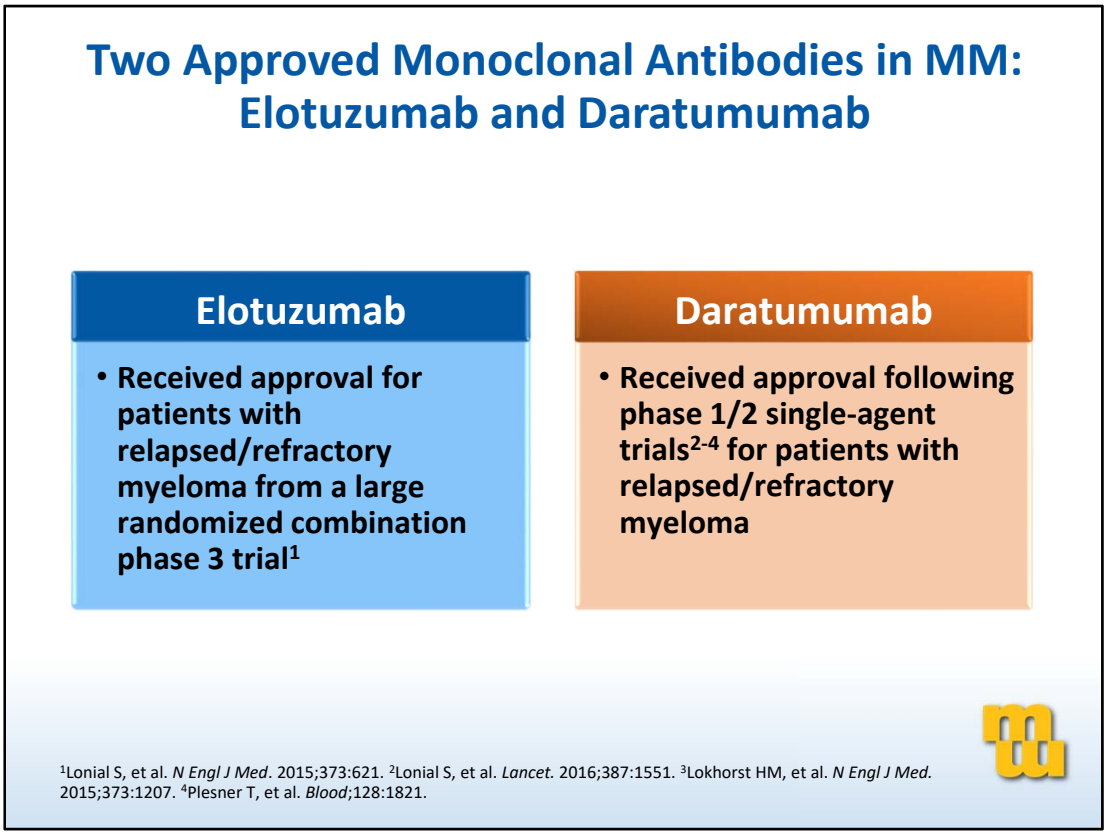
Mechanism of Action of Immunomodulatory Drugs (IMiDs)



Thalidomide,
Lenalidomide,
Pomalidomide
CC 92220,
CC 92480

Krönke K, et al. *Science.* 2014;343(6168):301-305.; Lu G, et al. *Science.* 2014;343(6168):305-309.

I do also want to mention that there is more to come in the space of immunomodulatory treatment and very importantly there are advances now being made with next-generation IMiDs or so-called CELMoDs. In particular there are two molecules under study, 220 and 480 that are highlighted in red that are showing considerable promise in current clinical trials. While we await data with great interest, I can't actually report much on these specifically simply because presentation is pending, but suffice to say the preclinical data has been particularly encouraging and certainly early clinical experience has been favorable.



Let's focus back on the monoclonal antibodies. Obviously elotuzumab is a true immunoadjuvant by helping with the activation of natural killer cells and also targeting myeloma through the SLAMF7 pathway. Daratumumab is much more pleiotropic in its effects. It has multiple effects both apoptotically and in the context of T-cell effects, as well as ADCC and so forth that certainly generate a broad spectrum of activity, which explains in part its extraordinary activity as a single agent. However, when combined it's even more powerful.

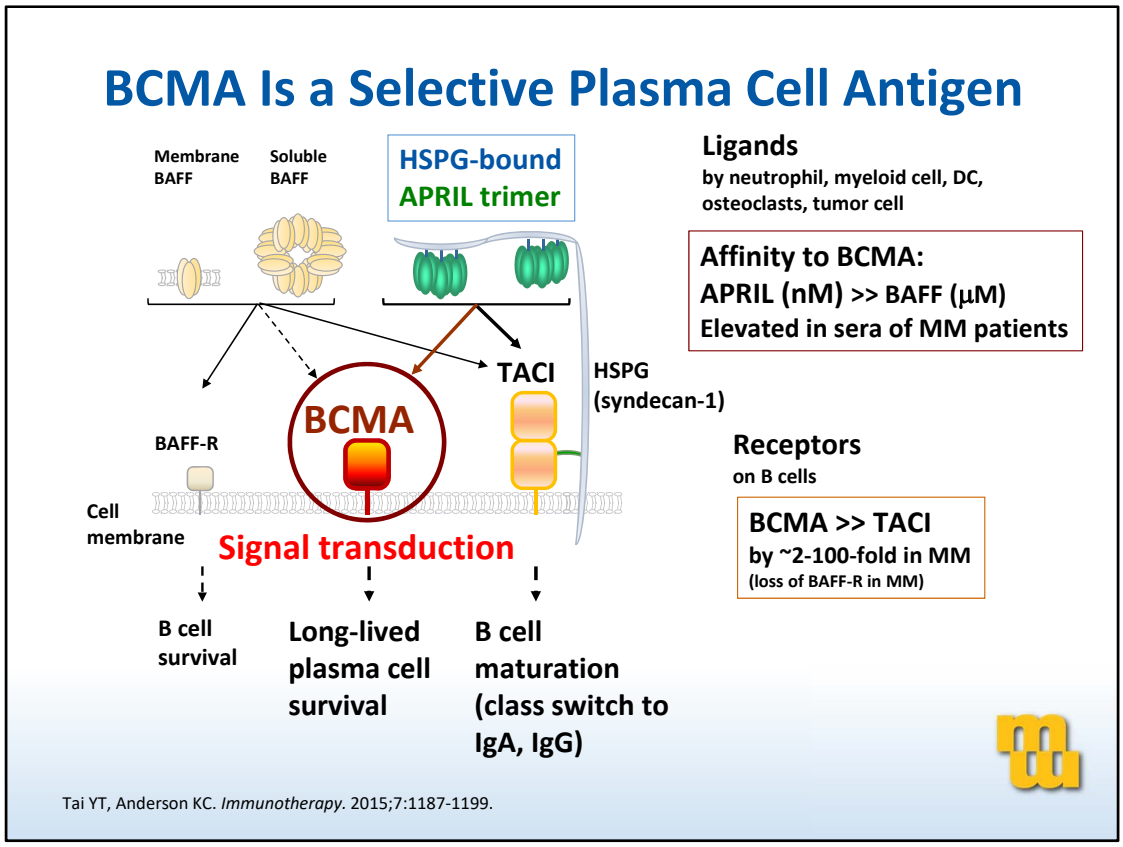
Isatuximab (Anti-CD38 mAb) in Relapsed/Refractory Myeloma (RRMM)

Phase	Population	N	Treatment	Median Prior Tx (Range)	≥PR/ORR (%)
1	≥2 prior anti-MM regimens[1]	57	ISA given in 2 schedules: • 3, 5, or 10 mg/kg Q2W • 10 or 20 mg/kg QW for 4 weeks and then Q2W thereafter Len 25 mg Dex 40 mg	5.0 (1–12)	56
1b	≥2 prior MM therapies, including lenalidomide and a proteasome inhibitor[2]	26	ISA 5, 10 or 20 mg/kg Pom 4 mg Dex 40 mg	4.0 (2–11)	65
1	Relapsed/refractory MM[3]	10	ISA 10 mg/kg Q2W, 10 mg/kg QW ×4 then Q2W and 20 mg/kg QW ×4 then Q2W Cfz 20/27 mg/m^2	4.5 (2-8)	80
2	≥3 lines of anti-MM therapy or refractory to immunomodulatory drugs and proteasome inhibitors[4]	97	ISA 3 mg/kg Q2W, 10 mg/kg Q2W ×2 cycles then Q4W, 10 mg/kg Q2W, or 20 mg/kg QW/Q2W	5.0 (2–14)	21 (24 at ≥10 mg/kg dose)

A phase 3 study of Pom Dex +/- Isa in RRMM is ongoing and enrollment has just been completed[5]

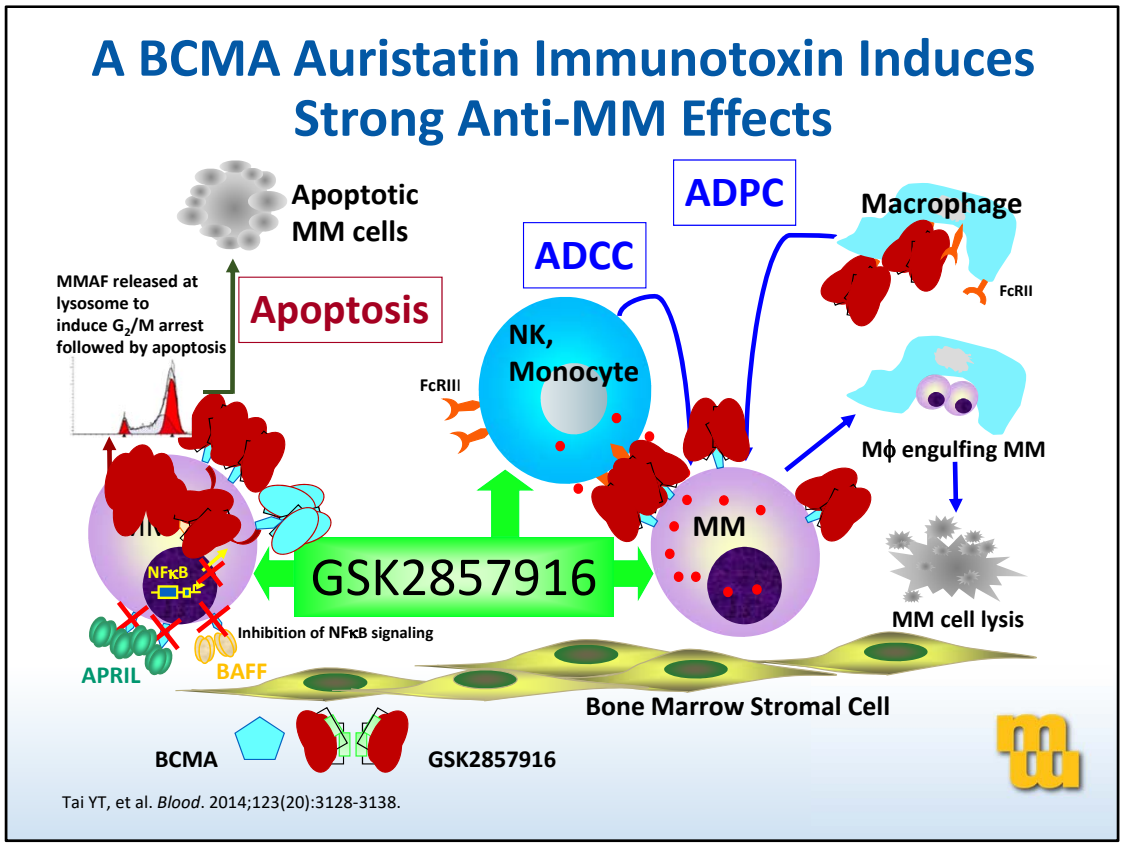
[1]Martin T, et al. *Blood*. 2017;129:3294. [2]Mikhael J, et al. *J Clin Oncol*. 2017;35:Abstract 8007. (Updated results at ASH 2017). [3]Martin TG, et al. *Blood*. 2016;128:Abstract 2111. [4]Richter JR, et al. *J Clin Oncol.* 2016;34:Abstract 8005. [5]Richardson PG, et al. *J Clin Oncol*. 2017;35:Abstract 8057.

In that same spirit, there is a next-generation CD38-targeting antibody that, as opposed to daratumumab which is fully humanized, is chimeric. This is isatuximab, an anti-CD38 monoclonal antibody that has shown great clinical activity in clinical trials and in combination is coming forward. It's not yet FDA approved but certainly phase 2 data to date has been very encouraging.



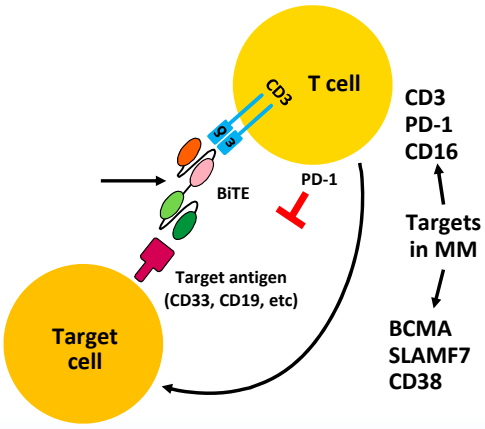
What about other future directions in the relapsed/refractory space? I think it's very important to share these with you because they constitute clinical trial opportunities that could be very important for patients, and I would encourage patients who are candidates of the studies to be referred to appropriate centers because these really offer great promise going forward.

One of the most important targets in myeloma now is so-called BCMA. BCMA is a B-cell maturation antigen by full description and has high affinity for a number of key growth and survival pathways in myeloma biology. We sought to summarize them from this excellent review from my mentor, Dr. Ken Anderson, and my laboratory partner Dr. Yu-Tzu Tai who published this a few years ago. It's a very nice schematic showing exactly how critical and central BCMA is in the context of myeloma biology.



Targeting this with a variety of strategies, including antibody drug conjugates such as 916, has not only shown great promise pre-clinically, but has also translated it to very exciting results clinically and further studies are currently ongoing.

Bispecific Antibodies (BiTEs)



Clinical trials:

- Phase 1 study of blinatumomab in combination with salvage ASCT in RR MM[1]
- Phase 1 dose escalation of IV BI 836909 monotherapy in last line RR MM patients[2]

BiTE=bispecific T-cell engager

Adapted from Richardson PG, Multiple Myeloma Research Foundation. ASH 2017.

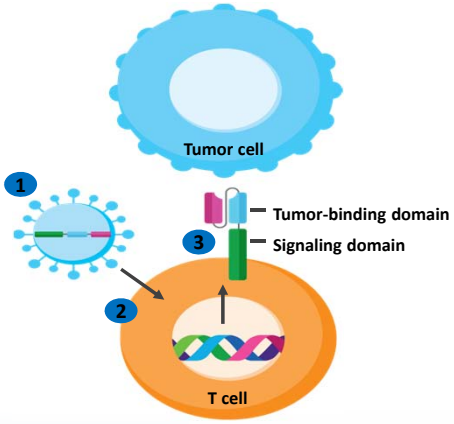
[1]ClinicalTrials.gov Identifier: NCT031734301. [2]ClinicalTrials.gov Identifier: NCT02514239.

In that same spirit, there are a number of bispecific antibodies currently in development which are also T-cell engaged (so-called BiTES) and a number of these are showing great and early promise in clinical trials.

CAR T Cell Therapy in MM

Process

- Peripheral blood mononuclear cells are collected via leukapheresis
- Autologous T cells transduced with an engineered vector (lentiviral) encoding a novel CAR
- Re-introduce new T cells
- +/- Cytoreductive chemotherapy



Berdeja JG et al. *J Clin Oncol*. 2017;35:Abstract 3010.

In that same spirit, CAR T therapy has really been a true paradigm-changer in relapsed/refractory disease. In patients who may be candidates for such approaches, and are typically younger and fitter, this may be a particularly valuable approach, and early data have been particularly exciting. The process is summarized on this slide were essentially autologous T cells are transfused with an engineered vector to encode for the myeloma target. In this regard, these T cells are then reintroduced after cytoreductive therapy with effects thereafter.

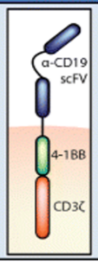
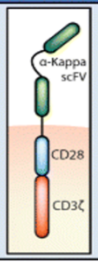
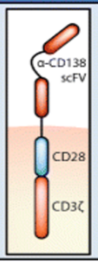
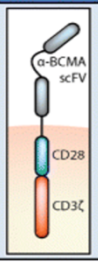
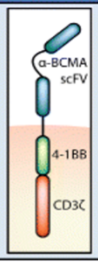
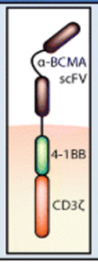
Myeloma CAR T Therapy Considerations

- Which target?
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1 (SLAMF7), BCMA
- Many questions remain about CAR design
  - Optimal costimulatory domains
  - Optimal vector
  - Optimal dose and schedule
  - Need for chemotherapy
  - Perhaps "cocktails" of multiple CARs or CARs + chemotherapy will be required for best outcomes

Richardson PG, Multiple Myeloma Research Foundation. ASH 2017.

As I mentioned, BCMA is probably the most important target and remarkable results are being seen, but there remain a number of questions about how CAR T therapy may evolve.

CAR T Cells in Development for Myeloma 2018

	α-CD19-BBz	α-Kappa-28z	α-CD138-28z	α-BCMA-28z	α-BCMA-BBz	α-BCMA-BBz
						
Institution	Penn	Baylor	Chinese PLA General Hospital	NCI	Penn	bluebird bio
scFV Clone	FMC63	CRL-1758	NK-92	11D5-3	ND	bb2121
scFV Origin	Murine	Murine	Murine	Murine	Human	Humanized
Gene Transfer System	Lentivirus	Retrovirus	Lentivirus	Retrovirus	Lentivirus	Lentivirus
Intracellular Domain	4-1BB ICD-CD3zeta	CD28 ICD-CD3zeta	CD28 ICD-CD3zeta	CD28 ICD-CD3zeta	4-1BB ICD-CD3zeta	4-1BB ICD-CD3zeta
Patients Treated	11	8	5	12	6	9
Dose(s)	1-5e7 CARTs/pt	0.2-2e8 CARTs/m2	0.44-1.51e7 CARTs/kg	0.3-9e6 CARTs/kg	1e7-5e8 CARTs/pt	5-80e7 CARTs/pt
Best Response (number of patients)	CR (1), VGRP (6), PR (2), PD (2)	SD (5), NR (3)	SD (4), PD (1)	Stringent CR (1), VGPR (2), PR (1), SD (8)	Stringent CR (1), VGPR (1), SD (1), MR (2), PD (1)	Stringent CR (2), VGPR (1), PR (4), SD (1), PD (1)
Reference(s)	25··	27··	26	28	29	ASH 2016 Abstract

Adapted from Ormhøj M, et al. *Curr Hematol Malig Rep.* 2017;12(2):119-125.

There are a number that are on study and I've shown this in this slide. Studies of these variety of different modalities are ongoing. Again, very exciting results have been reported to date, and I think we will see this approach continue to evolve with potential for great benefit for our patients in the future.

The Impact of Novel Therapies in MM ~ 2018

Patient DG, age 62 years

- 2009 – Higher risk IgG kappa MM; DSS 3, ISS 2; elevated LDH; 17 del positive; 13 del positive (by FISH), PMH – HTN, requiring triple therapy; RD + zoledronic acid => RVD (VGPR), well tolerated, minimal PN (G1)
- 2010 – ASCT (CY – HDM) (CR); R/Z maintenance
- 2011 – PD – RVD (PR)
- 2012 – PD – Pom + VD (VGPR)
- 2013 – PD (aggressive relapse with extra-medullary disease) DARA [501] 16 mg/kg (CR) to present (> 5 years) "Best I have ever felt since prior to diagnosis"

To conclude, the impact of novel therapies in relapsed/refractory myeloma has been profound. I want to share with you a case that is well-known in our world and certainly at my center, because the patient concerned, who was very happy for me to share her photograph, has been a paradigm for us of the success of monoclonal modern antibody therapy in myeloma. She was originally diagnosed in 2009 with classical high-risk disease, and she carried the most challenging finding which was 17 deletion positivity at that time. She was otherwise very well, but had comorbidity including hypertension requiring triple therapy but was essentially, apart from a high-risk myeloma, a very fit and well person.

After initial induction remission treatment which successfully achieved with very good partial response, she went on to autologous stem cell transplant. She received lenalidomide maintenance back at that time and was not keen to received parenteral therapy, so bortezomib was deferred even though she had high-risk features. Unfortunately, her disease returned within a year and in that context, she was successfully salvaged with the reintroduction of proteasome inhibition. Then with the further introduction of a next-generation IMiD, she did somewhat better the following year. Unfortunately, consistent with 17p deletion, her disease then relapsed aggressively with extramedullary disease. At the time we considered carfilzomib-based therapy, but because of her hypertension which was particularly challenging, we deferred on that option and instead she participated in the phase 1 clinical trial at the time of daratumumab monotherapy. Remarkably, she had a fabulous response to the antibody, entered complete response, and has been for the last five years in CR on continuous daratumumab monotherapy, and has been enjoying an excellent quality of life as illustrated by her photograph.

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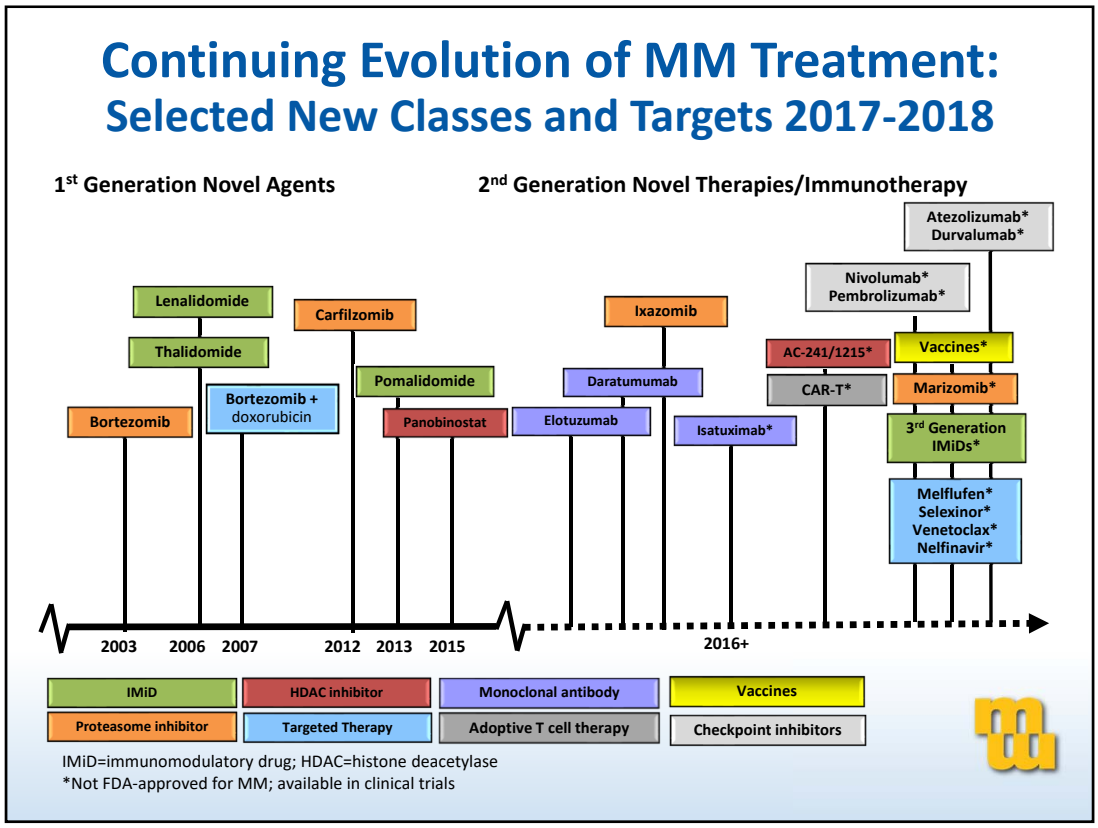


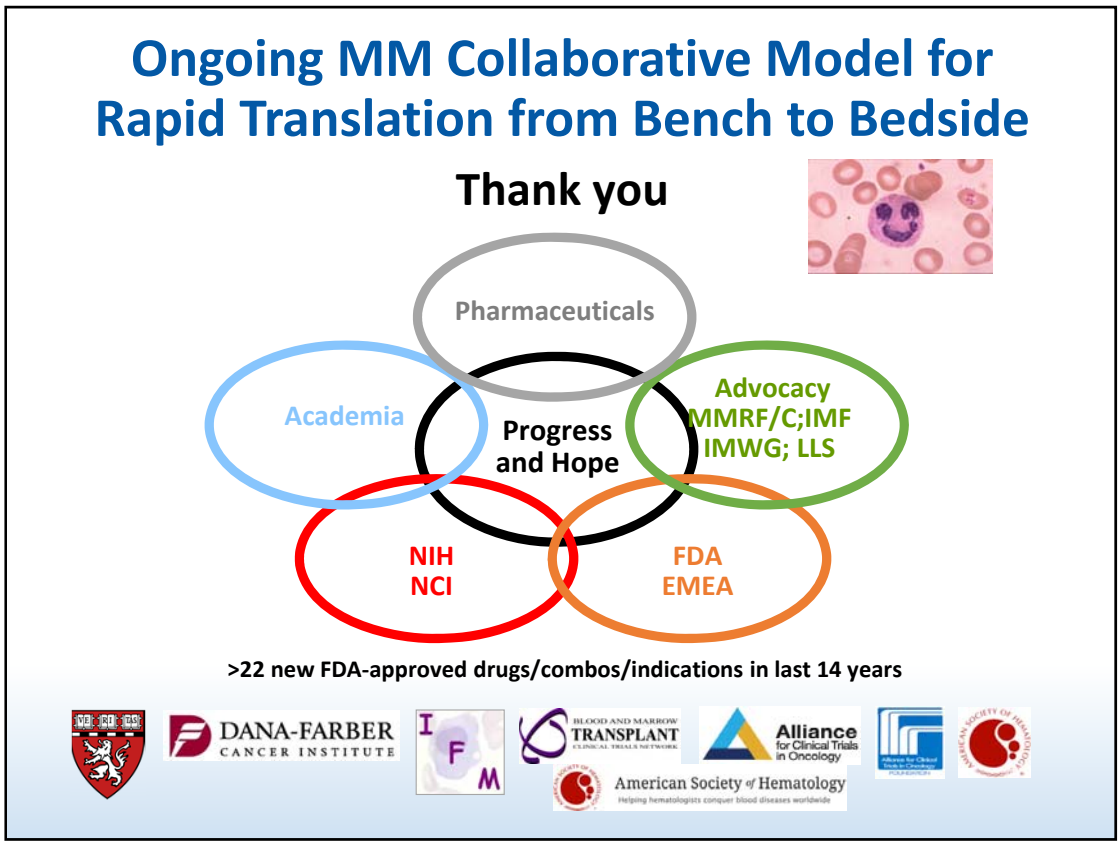
To conclude, in multiple myeloma treatment we have multiple options in relapsed/refractory disease. We have a number of choices that can be deployed, and I seek to summarize not only the approved agents on this slide but also new and upcoming exciting new directions including next-generation proteasome inhibitors, next-generation immunomodulators, and then novel targeting drugs such as venetoclax, selinexor, and melflufen as just three examples.

I think all of these have great promise for the future. Most importantly in this same context we have other new drugs being developed that refine on existing advances: one example being HDACs which include the approved panobinostat to the left, with exciting new drugs such as 241 under development to the right. Melflufen, as one example, is a modified alkylator with a highly targeted approach to cytotoxicity, which may make it also an exciting new option. Selinexor, which is a selective inhibitor of nuclear export protein, is a remarkably active drug in combination and is moving forward in clinical trial. Venetoclax targets BCL-2 over-expression and translocation (11;14) patients in particular appear to benefit from this approach. These are just examples of what can be on offer to relapsed/refractory patients.

Key Points

- Compare and contrast new and emerging drug classes for the treatment of relapsed/refractory multiple myeloma
  - Multiple options with combinations of three drugs or more the new standard
  - PI/IMiD "backbone" key
  - MoAbs: paradigm changing
- Identify the efficacy and safety of new and emerging therapies for the treatment of multiple myeloma in the relapsed/refractory setting
  - Immune therapy
  - Targeting protein degradation
  - Small molecule inhibitors
- Incorporate risk-adapted treatment decisions for the management of patients with relapsed/refractory multiple myeloma

I will leave you with these key takeaway points. In terms of relapsed/refractory multiple myeloma we have multiple options with combinations of drugs, at least three or more, becoming a new standard. The emphasis on the proteasome inhibitor being a backbone is key, and recognizing that monoclonal antibodies are truly paradigm-changing. In terms of the new and emerging treatments for the treatment of multiple myeloma in the relapsed/refractory setting, immune therapy is a key new target. Of course also, the further targeting of protein degradation as I touched on momentarily before, as well as the emerging role of small molecular inhibitors. Finally, one can incorporate these approaches in a risk-adapted way for our patients that can guide therapeutic choices, recognizing that in the relapsed/refractory setting patients typically are considered high-risk by virtue of the very nature of their position and timeline in the course of the natural history of their disease, as well as key features such as cytogenetic abnormalities, extramedullary disease, peripheralizing plasma cells, renal dysfunction, and so forth. Nonetheless, despite all these challenges, the outlook for these patients continues to be remarkably improving, as I illustrated in the previous few slides.



Finally, I want to thank you very much for your kind attention and gratefully acknowledge the remarkable partnership summarized in this slide that has led to all these advances. Again, thank you for your kind attention.