How Should New Agents Be Incorporated Into Treatment?

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Dr. Kenneth Anderson: This is Dr. Ken Anderson from Dana-Farber Cancer Institute, and I am honored today to be participating with Don Harvey who is an associate professor at Emory University, the director of the Phase I Clinical Trial Section there, and Sandra Kurtin, a nurse practitioner at the University of Arizona Cancer Center, in an activity which really is entitled, "How should new agents be incorporated into myeloma patient management plans," and this is sponsored by *Managing Myeloma*, and it is extremely current given the rapid pace of progress and the evolving treatment paradigm for this disease.

The goals of this activity will be to understand how these agents actually work in terms of their mechanisms of action, to understand how the various regimens, whether they be single agents or combination treatments, to characterize their dose schedules that have been tested, the efficacy and safety data that exist so far, the ongoing clinical trials, and the strengths and weaknesses of what we know in each of these areas so far. Finally, we will importantly discuss how these new agents will impact practice of multiple myeloma medicine in the future.

So, with that as the background, I will just mention that we have had amazing progress in multiple myeloma over the last 10 or 15 years. The two major classes of agents, the proteasome inhibitors and immunomodulatory drugs, each in their own right have shown amazing activity in the advanced relapsed/refractory patients, and each of them now has moved into the earlier relapse, into the initial management of myeloma, into the management as a consolidation strategy, and finally as maintenance treatments. Trend #2 has been the use of these agents in combination predicated by preclinical studies, and trend #3 has been using these combinations earlier in the disease course. [Kyle, 2014; Lonial, 2013; Moreau, 2013; NCCN, Version 2.2015; Roschewski M, 2013; Rajkumar, 2014]

So, I will just say that in terms of active myeloma, the use of these agents in combination, whether it be for transplant-eligible patients, (Figure 1A) or not (Figure 1B) has resulted in unprecedented deep response rates and a three- to four-fold increase in survival of myeloma patients (Fig 2).[Kumar, 2008; Kumar 2014a; Kumar, 2012a; Venner, 2011; Gozzetti, 2014]

Figure 1A Combination therapies in newly diagnosed, transplant eligible patients. [Gozzetti; 2014]

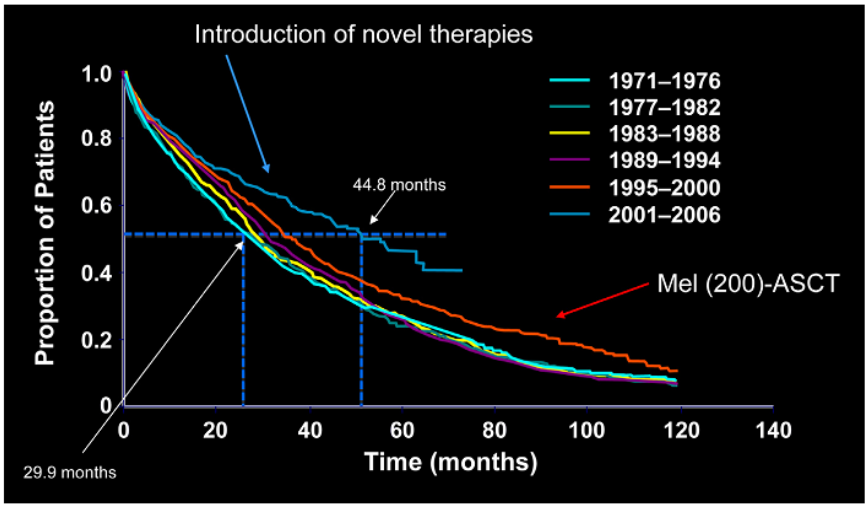
Therapy	N	Reponse post-induction		Reponse post-ASCT		PFS (months)	OS
		CR/nCR (%)	>VGPR (%)	CR/nCR (%)	>VGPR (%)		
VD	121	15	38	35	68	36	NR (3 years)
VTD	241	31	63	71	89	NR	NR (3 years)
PAD	413	15	42	49	76	35	NR (5 years)
VTD	130	35	60	46	U	56	NR (4 years)

U, unreported; NR, not reached.

Figure 1B. Combination therapies in newly diagnosed, non-transplant eligible patients. [Gozzetti, 2014]

Therapy	CR (%)	PFS (months)	OS
MPT	7–23	15–28	28–52 months
VMP	30	24	68% at 36 months
Rd	4	25	76% at 24 months
MPR-R	10	31	70% at 36 months
VMPT-VT	38	35	61% at 60 months

Figure 2 **Six-Year Interval Kaplan–Meier Curves for Multiple Myeloma (MM) Patient Overall Survival From Time of Diagnosis (1971-2006)**

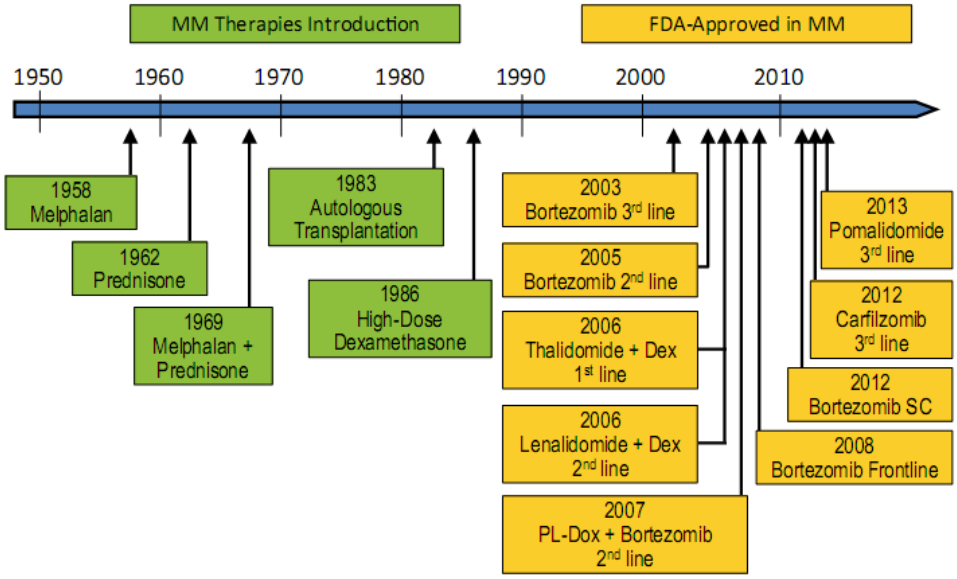


Abbreviations: ASCT = Autologous Stem Cell Transplant; MEL(200) = melphalan (200 mg/m^2).
[Adapted from Kumar, 2008; Raje, 2014]

The opportunity to use agents that are well tolerated in both of these classes, both in the proteasome inhibitors and immunomodulatory drug classes has offered clinical trials now in earlier stage, such as smoldering myeloma, that are designed to prevent or delay progression to active myeloma, [NCT01572480; NCT01169337, Mateos, 2013] but what is really important is building on this progress is the opportunity now to have novel agents in this

paradigm, second-generation agents of these two classes but also entirely new classes of agents including monoclonal antibodies and histone deacetylase inhibitors as two examples. So, I just like to start out and say in the proteasome inhibitor area, bortezomib was the paradigm changing drug that was approved first in 2003 in relapsed/refractory myeloma, and then, it was subsequently approved 2 years later in relapsed 1:3 prior therapy patients, and then as a newly diagnosed treatment option shortly thereafter (Figure 3).

Figure 3. Multiple Myeloma Therapy Timeline [Raje, 2014]



FDA=Food and Drug Administration; PL+Dox=pegylated liposomal doxorubicin; SC=subcutaneous.

Next-Generation Proteasome Inhibitors

Carfilzomib

Excitingly, we have carfilzomib now, a different class of proteasome inhibitor targeting the same chymotryptic site. It is an epoxy ketone. It in fact is given intravenously twice weekly for 3 weeks in a row of a 28-day cycle but excitingly has not much in the way of neuropathy attendant to its use. Peripheral neuropathy occurred in 14% of patients enrolled in myeloma clinical trials, but serious peripheral neuropathy events were very rare (< 1%).[Kryopolis PI, 2012] I was privileged to be involved approximately 2 years ago presenting the data for carfilzomib to our Food and Drug Administration ODAC Community, and indeed, this agent was approved with an accelerated fashion for treatment of multiple myeloma patients with relapsed/refractory disease that have received two or more prior therapies including treatment with bortezomib and an immunomodulatory drug (IMID) (Figure 3).[US FDA, 2012; Vij,2012a; Siegel, 2012] So, why don't we talk just for a minute about carfilzomib, and I might ask Don, what is your experience in utilizing this novel proteasome inhibitor?

Dr. Donald Harvey: So, thanks Dr. Anderson. At Emory, we have certainly incorporated carfilzomib into both routine patient care as well as clinical trial evaluations in combinations with some of drugs we will talk about later. We have begun to use carfilzomib more and more, and have begun to also recognize some of the unique but manageable adverse events that can be seen with the drug. [Kryopolis PI, 2012; Kortuem, 2013; Vij, 2012a; Vij, 2012b] There are certainly incidents of fever and in some patients worsening of heart function over time (Table 1 and 2).

Table 1: Warnings and Precautions for Carfilzomib and Risk Mitigation [Kyprolis PI]

Warning/Precaution	Risk Mitigation
Cardiac adverse reactions, including heart failure and ischemia	Monitor for cardiac complications. Treat promptly and withhold carfilzomib.
Pulmonary hypertension	Withhold dosing if suspected.
Pulmonary complications	Monitor for and manage dyspnea immediately; interrupt carfilzomib until symptoms have resolved or returned to baseline.
Infusion reactions	Pre-medicate with dexamethasone to prevent. Advise patients to seek immediate medical attention if symptoms develop.
Tumor lysis syndrome (TLS)	Hydrate patients to prevent. Monitor for TLS and treat promptly.
Thrombocytopenia	Monitor platelet counts; reduce or interrupt dosing as clinically indicated.
Hepatic toxicity and hepatic failure	Monitor liver enzymes and withhold dosing if suspected.
Embryo-fetal toxicity	Females of reproductive potential should avoid becoming pregnant while being treated.
Herpes zoster reactivation	Consider antiviral prophylaxis for patients who have a history of herpes zoster infection.

Table 2: Adverse Events Seen with Carfilzomib in Multiple Myeloma Trials [Kyprolis PI]

Adverse Event (≥ 30% of patients)	Grade 3/4 Adverse Event (≥ 10% of patients)	Serious Adverse Event (≥ 3% of patients)
• Fatigue • Anemia • Nausea • Thrombocytopenia • Dyspnea • Diarrhea • Pyrexia	• Anemia • Lymphopenia • Thrombocytopenia	• Pneumonia • Acute renal failure • Pyrexia • Congestive heart failure

We have elected to take a little bit of a different approach from the product information and treating patients and have extended the infusion times from the label of 2 to 10 minutes out to 30 minutes with the idea that that may abrogate some of the peak concentrations of the drugs that could be leading to potential cardiovascular complications and again a small but selected group of patients and potentially fever. [Kryopolis PI, 2012; Vij, 2012a; Vij, 2012b] Overall, we found it otherwise to be very well tolerated, and as you mentioned, the neurotoxicity that can be seen with bortezomib is absent in patients receiving carfilzomib.

Dr. Kenneth Anderson: Very nice, and Sandra, have you had experienced some treating patients with this novel agent as well?

Sandra Kurtin, NP: Yes, I would really echo a lot of what was just said. I think we have also found by extending the infusion rate people do better adding in premeds early in the phase of treatment, and then gradually we get rid of those over time and people seem to do quite well. One other very practical thing that we have done is when we initiate the therapy, it is given obviously on two consecutive days. We do not ever do that on a Thursday or a

Friday, going into the weekend, so that we are able to effectively manage any of the heaviness in the chest, the sense of dyspnea that a patient might experience. We do not want that happening over the weekend, so very practically there than able to come to us in the clinic and we are able to effectively manage that in the early phases of treatment. I think as we go on we see far less difficulty, and I agree with the reduced incidents of neuropathy with this drug, which is a good thing.

Dr. Kenneth Anderson: Yes, it indeed is, and with bortezomib we have tried to reduce the neuropathy by giving it weekly [Bringhen, 2010; Reeder, 2010] and subcutaneously [Moreau, 2011; Arnulf, 2012] and have been very successful in doing so, but it is obviously key to be able to give drugs for prolonged periods of time for patients to appreciate the benefit, and I will just mention that carfilzomib is going forward now combined with lenalidomide and dexamethasone versus lenalidomide and dexamethasone in a full approval for relapsed myeloma clinical trial called the ASPIRE trial which we expect to hear about certainly during 2014 and its final data. [Onyx, 2014] In addition, this combination carfilzomib-lenalidomide-dexamethasone has been moved forward and is even being studied because of its tolerability being favorable in earlier stage clinical trials, even in smoldering myeloma. [Vij, 2012b; NCT01572480] So, we definitely have the first second-generation active proteasome inhibitor after bortezomib.

Moving Towards an all Oral Therapy – Ixazomib Citrate

I would just like I mentioned, I find even more exciting, honestly, the opportunity to have an oral proteasome inhibitor, so-called ixazomib citrate (MLN9708). This is a son of bortezomib if you will, a boronic acid-based proteasome inhibitor, but this one is oral and has now just finished phase I clinical trials under two schedules (Figure 4 and 5).[Richardson, 2014; Richardson, 2013; Kumar, 2014b;Offidani, 2014]

Figure 4 Chemical Structures of Ixazomib Citrate pro-drug (MLN9708) (A) and the Bioavailable metabolite Ixazomib (MLN2238) (B). [Offidani, 2014]

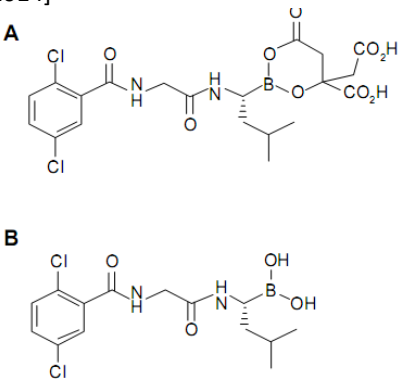


Figure 5. Main Bortezomib and Ixazomib Citrate (MLN9708) Pharmacokinetic and Pharmacodynamic Parameters [Offidani, 2014]

Parameter	Bortezomib	MLN9708
Subunits inhibited	β5, β1	β5
β5 dissociation half-life (minutes)	110	18
Binding kinetics	Slowly reversible	Reversible
C_{max} (ng/mL)	548	10,500
AUC_{0-24h} (h · ng/mL)	4,422	9,660
Vd (L/kg)	4.3	20.2
AUE_{0-24h} (%L · h)	1,170	718
Route of administration	IV/SC	Oral/IV

Abbreviations: C_{max}, maximum concentration; AUC, area under the concentration versus time curve; Vd, volume of distribution; AUE, area under the effect versus time curve; IV, intravenous; SC, subcutaneous.

The agent has a half life of 3 to 4 days [Richardson, 2013] and so it was given either once a week [Kumar, 2014b] or twice a week [Richardson, 2014] as a single agent without steroids in relapsed/refractory myeloma, and in both of these schedules, there was something like a 20% response rate, and these responses were durable and did include in some cases patients whose myeloma was resistant to bortezomib. Excitingly as we have just mentioned with carfilzomib, there were not many adverse effects. In particular, the neuropathy that is attendant to bortezomib use was not a major feature here, and just as we mentioned for carfilzomib, so it is true here. Ixazomib citrate has been combined with lenalidomide and dexamethasone in the relapsed setting ongoing ixazomib-lenalidomide-dexamethasone (IRD) versus lenalidomide-dex (LD) Phase III clinical trial for approval, [NCT01564537] but also, as initial therapy, the same triplet, IRD has shown very promising activity with nearly universal responses of significant extent as well and very tolerated. [Kumar, 2012b] IRD is being evaluated in a phase III trial for the treatment of newly diagnosed multiple myeloma patients (NCT01850524) and additional combination therapies with ixazomib are ongoing in clinical trials across the life cycle of the disease. [Offidani, 2014] So, the opportunity here is as I see it and I would love to hear what you both think about this, but to me, the opportunity to give a very active all oral agent regimen in combination to our patients with myeloma is honestly a dream we have all been pursuing for many years. So any thoughts on this new agent and the excitement that it brings?

Sandra Kurtin, NP: Well, I will start. This is Sandy and I think this is a wonderful thing. I see a little bit of a good news-bad news. I think we still struggle with the whole oral adherence and really putting the onus on staying on therapy in the hands of the patient and the caregiver, and I think we still need to do a better job of creating programs to help with that and I think what we try to do in our setting is emulate the IV therapy. [Deutsch, 2014; Eliasson, 2011] In other words, you could easily write a prescription and send someone off for a month, which would not be advised, but rather emulate the weekly visits in the early parts of therapy. We know that most people on oral therapy come off drugs in the first 2 months, [Deutsch, 2014] and we know that in this drug, it took that long to really see maximum depth of response. [Richardson, 2013; Richardson, 2014] So, I think what we need to do as we roll this out, hopefully, in general use is really give people sound guidelines on how do you get people through those early months of therapy? The only other thing that I would mention is the issue of rash, and it has been interesting in the lenalidomide data, both in myeloma and other disease states, that rash actually has been one of the leading causes for people to discontinue therapy, and I do not know that we really understand the rash. [Kumar, 2012b] It does not appear to be an allergic rash. It tends to be more immunomodulatory in nature. So I think that will be another challenge for us as we put this out to our colleagues.

Dr. Kenneth Anderson: And Don, have you had experience with ixazomib in either the single-agent or combination strategy so far?

Dr. Donald Harvey: We have. We were able to join the paper that Dr. Richardson just published on the twice-weekly oral regimen, and ixazomib has a lot of fascinating properties in addition to the ones you have mentioned already. [Richardson, 2014] It is a pro drug [Figure 4], and while there is some GI toxicity with it, the nature of the pro drug helps it to be hydrolyzed rapidly upon absorption and in my opinion also allows the GI toxicity to be a bit less than it might be with other direct proteasome inhibitors, and so that is the fascinating part of this drug. The other thing is that, as you mentioned, the long half-life allows for once-weekly dosing which is helpful for turning this disease more and more into a chronic and hopefully curative therapy. [Richardson, 2013; Richardson, 2014] If you look at the emerging drugs, we are beginning to talk about new oral therapies which are going to be required to turn cancer into a chronic disease. Similarly, monoclonal antibodies, if you think about their use in places like Crohn's disease and rheumatoid arthritis. [US FDA, 2014; Meier, 2013] Those are chronic diseases, and so, I think we can see the drugs that we are beginning to see come to the forefront more and more, but the ixazomib is a great partner in a lot of ways. I think as Sandy mentioned the rash can be concerning, and particularly as you combine it with lenalidomide, rash may become a bit more challenging to manage, [Kumar, 2012b] but overall, at least in our experience, the rash has been generally self-limiting and the topical therapies have been enough in our trials and our hands to be able to manage it, but it is I think a really exciting time for oral proteasome inhibition.

Dr. Kenneth Anderson: Wonderful, I will just echo that. I personally have many patients who have been participating in the trials as well and they really like the all oral regimen, and also, this has allowed maintenance therapy to be tested with this oral proteasome inhibitor, at least in a preliminary way, and I personally have someone who is out now over 4 years on maintenance ixazomib therapy. A phase II trial is evaluating IRD post-ASCT consolidation with randomization to either ixazomib or lenalidomide maintenance therapy [NCT02253316] and a phase III trial is evaluating ixazomib maintenance therapy after ASCT [NCT02181413] Since it is oral and relatively well tolerated, it is an ideal candidate to at least be evaluated as a maintenance, and we do know more and more in myeloma that the concept of continuous therapy honestly demonstrated most to date by lenalidomide has made a major difference in progression-fee and overall survival. [Facon, 2013] In one ongoing phase II trial for newly diagnosed multiple myeloma patients who did not undergo transplant, Ixazomib is given twice weekly with lenalidomide plus dexamethasone for one year followed by ixazomib maintenance given until disease progression or unacceptable toxicity [NCT01383928]. So, maybe here, we have a very user-friendly proteasome inhibitor option to be tested as a maintenance as well.

Histone Deacetylase (HDAC) Inhibitor: Panobinostat

So, why don't I move on now because in addition to the new second-generation proteasome inhibitors we have the histone deacetylase inhibitors also making their way into the myeloma treatment paradigm, and vorinostat type 1-2 broad HDAC inhibitor was the first to be tested in myeloma as a single agent and then in combination with lenalidomide-dexamethasone, but in a big Phase III trial with bortezomib versus bortezomib in relapsed/refractory myeloma. And that clinical trial has actually already been published and showed that bortezomib given to block a proteasome and in this case the HDAC inhibitor vorinostat given to block the other path of protein degradation called the aggresome, [Dimopoulos, 2013] that combination was more active in terms of higher response rates than bortezomib alone. That was very exciting, but the progression-free survival advantage was less than 1 month because this broad histone deacetylase inhibitor vorinostat has side effects including diarrhea, low-platelet counts, and fatigue. So, what is new and very current is the so-called PANORAMA clinical trial where another type 1-2 broad HDAC inhibitor called panobinostat has been given together with proteasome inhibitor bortezomib, again predicated upon the idea that it can block the aggresome and proteasome at the same time, and this clinical trial was just reported, and there is a 4-month progression-free survival advantage in this particular clinical trial where panobinostat and bortezomib were given together versus bortezomib alone. [Richardson, 2014b; San-Miguel, 2014] The side effects again were of the same kinds in terms of diarrhea, low platelet count, and fatigue, and this

successful trial I think was resulting in a major way from dose and schedule that seemed to be tolerated better than in the vorinostat trial. The panobinostat HDAC inhibitor was given every other day, three times a week for 2 weeks out of a 3-week cycle. So, there were six doses in 1 cycle, and with this it was better tolerated and could result in this 4-month progression-free survival advantage. I think it is important to say though that even with this about a third of patients had to discontinue treatment because of adverse effect. There is plenty of room to try to get more tolerated HDAC inhibitors. The concept has been proven as valid and I think this will add to our treatment paradigm a new class of agents. So, maybe I can ask Sandra. Have you had any experience with using panobinostat?

Sandra Kurtin, NP: We have, and I think for us you established or you developed a level of comfort with some of these toxicities. They are not really that different than many of the other drugs that we are currently using in myeloma. I think for instance in thrombocytopenia you get this what I call moderate asymptomatic cytopenia as you develop a level of comfort with people that have low but stable and asymptomatic platelet counts, but again, that can be concerning in the general population and really have had nobody developing frank bleeding or other problems. I think the GI toxicities have been a little bit more of a challenge primarily from a patient perspective. So, working with our dieticians and other people to try to find ways to mitigate that, I think, is key to keeping people on their therapy.

Dr. Kenneth Anderson: Okay and Don have you had experience at your center with these clinical trials?

Dr. Donald Harvey: Yes, we have. Certainly, panobinostat as mentioned can be challenging, and there are occasionally patients who come in constipated and diarrhea may actually be welcome to them to be honest, but some certainly we have got to be very careful of management of diarrhea and other and fatigue in helping the patients to understand that those may be adverse events that could be challenging but can certainly be managed.

Dr. Kenneth Anderson: Right. We will watch with eager anticipation the progress in the area, panobinostat is being now combined with the immunomodulatory drugs, lenalidomide and dex [NCT01651039], with bortezomib plus lenalidomide and dexamethasone [NCT01440582; NCT01965353], and also with ixazomib plus dexamethasone [NCT02057640], and then, there are some more selective HDAC inhibitors in clinical trials. [e.g. NCT01583283; NCT01742988; NCT01129193] One of them is called ricolinostat [NCT01583283] with the hope that the tolerability might be improved and so the efficacy might benefit as well. In any event, we are excited because this is the first HDAC inhibitor, first in class, the new class of agents that we hope to use in myeloma.

> ***Update:*** *The U.S. Food and Drug Administration approved panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma on February 23, 2015. In November 2014, the FDA's Oncologic Drugs Advisory Committee advised the agency that, based on the data reviewed, the drug's benefits did not outweigh its risks for patients with relapsed multiple myeloma. After the meeting, the company submitted additional information supporting panobinostat's use for a different indication: patients with multiple myeloma who have received at least two prior standard therapies, including bortezomib and an immunomodulatory agent.*
>
> *The safety and efficacy of panobinostat in combination with bortezomib and dexamethasone was demonstrated in 193 clinical trial participants with multiple myeloma who received at least two prior treatments that included bortezomib and an immunomodulatory agent. Participants were randomly assigned to receive a combination of panobinostat, bortezomib and dexamethasone, or bortezomib and dexamethasone alone.*
>
> *Study results showed participants receiving the panobinostat combination saw a delay in their disease progression (progression-free survival) for about 10.6 months, compared to 5.8 months in participants*

treated with bortezomib and dexamethasone alone. Additionally, 59 percent of panobinostat-treated participants saw their cancer shrink or disappear after treatment (response rate), versus 41 percent in those receiving bortezomib and dexamethasone.

Panobinostat carries a Boxed Warning alerting patients and health care professionals that severe diarrhea and severe and fatal cardiac events, arrhythmias and electrocardiogram (ECG) changes have occurred in patients receiving panobinostat. Because of these risks, panobinostat is being approved with a Risk Evaluation and Mitigation Strategy (REMS) consisting of a communication plan to inform health care professionals of these risks and how to minimize them.

The most common side effects of panobinostat were diarrhea, tiredness, nausea, swelling in the arms or legs, decreased appetite, fever, vomiting and weakness. The most common laboratory abnormalities were low levels of phosphorus in the blood (hypophosphatemia), low potassium levels in the blood (hypokalemia), low levels of salt in the blood (hyponatremia), increased creatinine, low platelets (thrombocytopenia), low white blood cell counts (leukopenia) and low red blood cell counts (anemia). Healthcare professionals should also inform patients of the risk of bleeding in the gastrointestinal tract and the lungs, and liver damage (hepatotoxicity).

The FDA granted panobinostat priority review and orphan product designation. Priority review provides for an expedited review of drugs that are intended to treat a serious disease or condition and may provide a significant improvement over available therapy. Orphan product designation is given to drugs intended to treat rare diseases.
[FDA News Release. FDA Approves Farydak for Treatment of Multiple Myeloma. Release Date February 23, 2015. Last accessed at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435296.htm on July 7, 2015.]

Monoclonal Antibodies: Elotuzumab (anti-CS1) and Daratumumab and SAR650984 (anti-CD38)

Elotuzumab (anti-CS1, SLAMF7)

So, let's finish off with the discussion of the monoclonal antibodies in myeloma which I think arguably are the most exciting advance in our field for a long time. Immune therapies have been tested in myeloma for decades, but this is now finally it seems delivering on the promise of immune modalities. In particular, elotuzumab, which is directed at the antigen SLAMF7, has been validated preclinically as a target in myeloma, and the humanized antibody called elotuzumab directed at this antigen as a single agent achieved stable disease but really not responses in relapsed/refractory disease. [Zonder, 2012; Hsi, 2008; Tai, 2008; Tai, 2009] Fortunately, the immunomodulatory drug lenalidomide combined with this and any other antibody can really enhance antibody-dependent cellular cytotoxicity, [Collins, 2013] and this has resulted in the case of elotuzumab in going from stable disease as the best response to a single-agent antibody trial to lenalidomide, dexamethasone, and elotuzumab resulting in an 80-90% response rate in relapsed myeloma. [Lonial, 2012; Richardson, 2012] Even more excitingly, these responses are lasting 33 months in the Phase II clinical trial and include patients whose myeloma has 17p deletion or high-risk genetics. [Richardson, 2012] So, clearly, this is a major advance, high response rates that are durable and the ability has been quite remarkable in our center.

Daratumumab and SAR650984 (anti-CD38)

I will mention just quickly the two CD38 antibodies, and then we can discuss all three perhaps, but CD38 is an antigen that is strongly expressed on myeloma cells but certainly expressed on other cells as well. It was originally described on activated T-cells over 3 decades ago, and it is also on activated immune effector cells as well as endothelial cells, and half of hematopoietic progenitor cells. [Quarona, 2013; Malavasi, 1992] Nonetheless, two different CD38 monoclonal antibodies, daratumumab and the SAR antibody, have gone forward as single agents in relapsed/refractory myeloma and shown remarkable activity in the range of 30-40% responses as single agents,

even in advanced myeloma. And then, each of these, daratumumab and the SAR antibody, have been combined with lenalidomide-dexamethasone for the same reasons, to increase antibody dependent cellular cytotoxicity and again, the response rates, although the data is earlier and the durability all are seen to be markedly enhanced. [Lokhorst, 2014; Martin TG, 2014a; Plesner, 2014; Martin, 2014b] I guess what I am saying in summary is I do believe strongly that all three of these antibodies will be eventually approved for treatment of patients with myeloma, and the exciting thing is they appear to be active even when, for example, 17p deletion is present which translates into a nonfunctional P53. This has been a real problem for us in terms of using conventional or novel targeted therapies, but maybe the immune monoclonal antibody approaches will be even active in these patients. The FDA granted elotuzumab breakthrough therapy designation for use in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received one or more prior therapies in May 2014 based on the Phase II data. [Bristol-Myers Squibb, 2014] Phase 3 trials of elotuzumab using the 10 mg/kg ± lenalidomide and dexamethasone are ongoing in newly diagnosed MM including ELOQUENT-1; CA204-006; NCT01335399 and in R/R MM ELOQUENT-2; CA204-004; NCT01239797. An additional trial, SWOG 1211 is the first national and intergroup study targeting the high-risk (HR) MM population. A randomized phase I/II trial was designed to evaluate the efficacy of incorporating novel agents into first-line therapy for HRMM patients comparing lenalidomide, bortezomib and dexamethasone (RVD) with or without addition of elotuzumab (Elo). Clinical trial information: NCT01668719. The US Food and Drug Administration (FDA) has also granted Breakthrough Therapy Designation for daratumumab for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double refractory to a PI and IMID in Spring of 2013. [Genmab A/S Press Release, 2013] Studies exploring the efficacy of daratumumab are ongoing with 7 open and recruiting or not yet recruiting at this time. Notable, a phase 3 randomized study comparing daratumumab + lenalidomide and dexamethasone with lenalidomide and dexamethasone alone in RR MM (NCT02076009) a phase 3 study examining the addition of daratumamab to bortezomib and dexamethasone in patients with RR MM (NCT02136134) and in newly diagnosed, previously untreated patients, a randomized, open label phase 3 study comparing daratumubab plus bortezomib, melphalan and prednisone (VMP) to VMP alone [NCT02195479]. Two SAR studies remain active, but new studies have not yet been registered with clinicaltrials.gov.

So, Don, I know you have had experience. Dr. Sagar Lonial has been one of the leaders of the trials in this area, but do you not think this is quite an exciting advance?

Dr. Donald Harvey: I really do. It is fascinating as you mentioned earlier to think about the concept of manipulating the immune system beyond those really older and nastier drugs like interferon and others that were tried in maintenance, and elotuzumab has been a great story in many instances, and certainly, Dr. Lonial, as you mentioned, has been a leader within this. I find this fascinating from a clinical pharmacology perspective that the dosing of elotuzumab at 20 mg/kg appears to be inferior to the lower dose of 10 mg/kg, suggesting a potential hysteresis effect, but the tolerability of this drug over the long term has been quite good. [Richardson, 2012] There are very rare infusion reactions that were seen early in the development of this drug but with substantial and very effective premedication, those have really come to approach zero, and the duration of responses and duration of activity of this drug in combination with lenalidomide in the trial Sagar published has been really, really pretty phenomenal. [Lonial, 2012]

Dr. Kenneth Anderson: Right, and again Sandra, have you had opportunity to care for patients that have received any of these antibody therapies?

Sandra Kurtin, NP: Just the elotuzumab. We have not used the daratumumab, and I think I would just echo the same. I think once you refine the premedication regimen and you have a hypersensitivity management protocol in place it is not unlike the other monoclonal antibodies that we have used for so many years in lymphomas, and so, I agree it is a very exciting addition and something that we have to come along for a long time for myeloma patients.

Dr. Donald Harvey: Dr. Anderson, I have a question for you. How do you see these drugs being developed with competition for resources and competition for trying to understand where these drugs will fit in the relapsed/refractory setting and moving them into potentially front line? How do you see all that playing out over the next few years?

Dr. Kenneth Anderson: It is a wonderful question, and it is a very happy problem to consider. What we have all said is we really have multiple agents in different classes that are active, and we can study in our preclinical lab and animal model as how to combine them in the best ways, but we have rapidly done this also in clinical trial. So we already know that lenalidomide and bortezomib or honestly pomalidomide and carfilzomib, but an immunomodulatory drug and a proteasome inhibitor in most cases are additive or synergistic in preclinical and clinical trials. We have just commented all of us that the immunomodulatory drugs markedly enhance the antibody activity. So, there is a combination that is very active and again that is right now in the relapsed patients, but very quickly Don to just get to your point, I think we are going to have combinations of agents used earlier and earlier, first as initial therapy for active myeloma and then perhaps even earlier into what we now call smoldering disease, but I think the trend is going to be to put an immunomodulatory drug together with a proteasome inhibitor, and my bet would be that one or all of these monoclonal antibodies will be tested after approval in the more advanced patients. They will be tested as part of combinations in the initial treatment. [NCT02195479; NCT01668719; NCT01335399] So we will have an IMiD, proteasome inhibitor and monoclonal antibody for example as a combination, and it may be within the next 2 to 3 years we will develop a combination therapy not unlike CHOP-rituxan or bendamustine-Rituxan, for example, in some of our lymphomas or some of the combinations that have been curative in Hodgkin disease or testicular cancer but get to a combination of three or four classes of drugs which will really have overwhelming response rate and extent in myeloma. [Raje, 2014] What I am saying is the opportunity to achieve unprecedented states of response, minimal residual disease negativity by using these new more potent classes of drugs together and honestly creating what we hope first will be a chronic illness and then ultimately hopefully a cure. I think the other thing I will quickly say is we understand that myeloma is very heterogenous genetically even from the start, and we have learned from our own conventional chemotherapy studies and also from our colleagues in infectious disease that when you start with clonal heterogeneity or genetic heterogeneity and you want to treat effectively and avoid the emergence of drug resistance, whether it be bacteria virus, such as in tuberculosis or HIV, but in particular in cancer, I think using these combinations that are very active very early to deal with this genetic heterogeneity that is there at the outset and to prevent the evolution will really make a profound impact. I hope you are of the same view.

Table 3: Ixazomib, Panobinostat, Elotuzumab, and Daratumumab and SAR650984: Regimens and Outcomes.
Please **review this important information** on these regimens and outcomes.

Sandra Kurtin, NP: Absolutely.

Dr. Donald Harvey: Absolutely. The ideas of maintenance, the blurring of the lines between induction and maintenance is kind of a fun thing to think of as the tolerability of these drugs to get so much better that instead of chopping up phases of care perhaps we are going to simply have "This is your regimen for a very extended period of time."

Dr. Kenneth Anderson: Yes, I could not agree. It is on the one hand to have active agents in patients who really had no options is a major opportunity now, and on the other hand, and Sandra so stressed this, that these agents are by and large quite tolerated. So, we have the opportunity to not use them as single agents but to use them as combination. So I think the future is extraordinarily promising both for patients and caregivers alike.

Sandra Kurtin, NP: And I would agree with that wholeheartedly and I think our next challenge given as you say the happy problem we have in having all of these agents is to somehow develop a way to provide a little bit more consensus and guideline on how we sequence them and do that intelligently based on individual disease profiles and some of the individual attributes of the patients. So I think that may be our next challenge as a group. [Raje, 2014]

Dr. Kenneth Anderson: Yes, I could not agree more, and the opportunity to achieve that very goal has never been greater either. We have the ability to genomically characterize the patients now at an unprecedented level and we have also the opportunity to understand scientifically how these medications work individually and together. So, hopefully, when we combine those two databases, understanding the patient's profile better than ever and then understanding which combinations of agents are likely to work best, we will really impact the course of myeloma in a major way. Why don't I summarized by just saying I think we have had a very palpably exciting conversation here. For those of us who have watched myeloma treatment over the years, there has never been a more exciting time. The opportunity for science to improve diagnosis, prognosis, and treatment has never been better, and the ability to impact patients' lives and maintain quality of life has never been greater as well. I think I would like to thank *Managing Myeloma* for having this opportunity to share this exciting news with you as I like to say the past 10 to 15 years has been incredibly positive in myeloma with extension multifold of patient survival, but my view is the future is even brighter still.

Dr. Donald Harvey: Absolutely and thank you all for the opportunity to discuss this.

Sandra Kurtin, NP: Absolutely. Thank you.

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