Managing Myeloma

What Are the Current Trials Most Likely to Change Practice?

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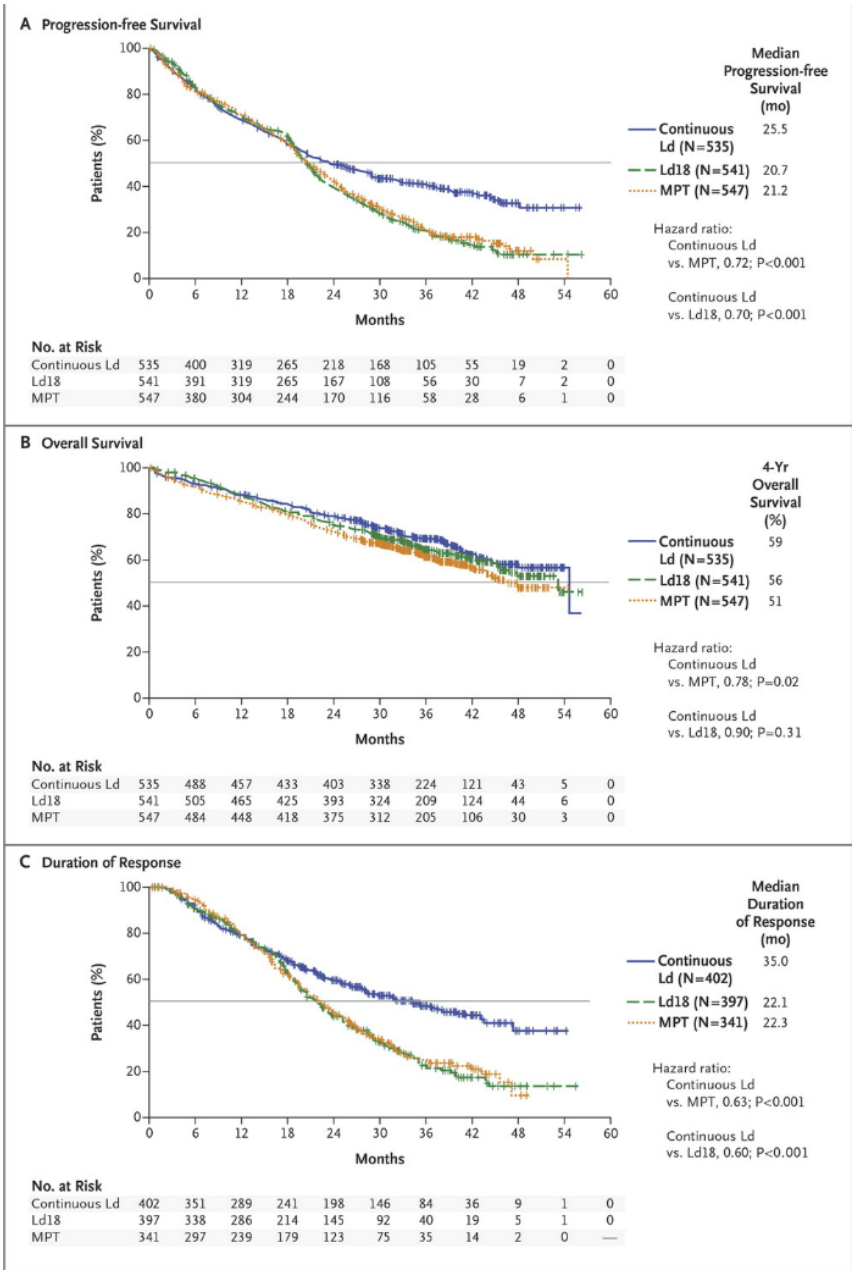
Dr. Raje: Great progress has been made in the treatment of myeloma over the last 10 to 15 years, and I think that we now have the backbone drugs—which are essentially the proteosome inhibitors and the immunomodulatory drugs [IMiDs]—and these have really impacted outcomes where patients are living a lot longer.[1-5] We are now at an exciting time when we are at the threshold of immunotherapies coming a long way, and we will soon have monoclonal antibodies to add to our backbone drugs.[1,6,7] On that note, we have several interesting clinical trials that we can talk about that I do believe are going to be practice-changing in the next couple of years.[1]

The FIRST Trial – Continuous Lenalidomide + Dexamethasone in Newly Diagnosed, Transplant Ineligible Patients

The first study worthy of discussion is called the Frontline Investigation of Lenalidomide + Dexamethasone versus Standard Thalidomide [FIRST] trial.[8] This is also known as the MM-020 trial. This was a large, phase 3, randomized, open-label, 3-arm study with more than 1600 patients randomized in a 3-way randomization in which patients received either continuous lenalidomide-dexamethasone (Ld) up until progression; Ld for a fixed duration of 72 weeks; or melphalan, prednisone, and thalidomide (MPT) for 72 weeks. The trial met the primary end point of progression-free survival (PFS), which was superior in the continuous Ld arm, with a median 25.5 months versus 20.7 in the Ld 72 weeks arm and 21.2 months in the MPT 72 weeks arm (Figure 1).

Figure 1. Kaplan–Meier Estimates of Progression-free Survival, Overall Survival, and Duration of Response.



What was interesting at the interim analysis was that overall survival also favored the continuous Ld arm. The overall survival (OS) rates at 3 years were 70% with continuous Ld, 66% with 18 cycles of Ld (72 weeks), and 62% with MPT (72 weeks); the overall survival rates at 4 years were 59%, 56%, and 51%, respectively. While the difference in overall survival did not cross the prespecified superiority boundary (*P*<.0096), continuous Ld did reduce the risk of death, as compared with MPT (hazard ratio, 0.78; 95% CI, 0.64 to 0.96; *P*=.02). So, based on this trial, Ld has now been approved in the up-front setting by the US Food and Drug Administration [FDA].[9]

This, therefore, is a good reason, Chris, to address a couple of issues that I think would be important to discuss. For example, is continuous use of Ld in terms of real clinical practice doable? What does it mean? Can we really continue patients indefinitely on the recommended dose of lenalidomide? Do we see a drop-off? What are the toxicities? If you can address some of those, that would be great.

Dr. Fausel: Sure, I would be happy to. So, when you look at the grade 3 and 4 toxicities that were reported in the trial, about one-third of the patients who got continuous Ld had infectious complications; about 30% had neutropenia, and between 10% and 20% had anemia and thrombocytopenia (Table 1).

Table 1. Grade 3 and 4 Adverse Events Reported in the FIRST Trial

Event	Continuous Lenalidomide–Dexamethasone (N=532)	Lenalidomide–Dexamethasone for 18 Cycles (N=540)	MPT (N=541)
	number of patients with event (percent)		
Any grade 3 or 4 event*	453 (85)	433 (80)	480 (89)
Hematologic adverse event			
Neutropenia	148 (28)	143 (26)	243 (45)
Anemia	97 (18)	85 (16)	102 (19)
Thrombocytopenia	44 (8)	43 (8)	60 (11)
Lymphopenia	30 (6)	18 (3)	37 (7)
Leukopenia	24 (5)	30 (6)	53 (10)
Nonhematologic adverse event†			
Infection	154 (29)	118 (22)	93 (17)
Cardiac disorder	63 (12)	39 (7)	46 (9)
Pneumonia	43 (8)	45 (8)	31 (6)
Deep-vein thrombosis, pulmonary embolism, or both	42 (8)	30 (6)	29 (5)
Asthenia	41 (8)	33 (6)	32 (6)
Fatigue	39 (7)	46 (9)	31 (6)
Back pain	37 (7)	34 (6)	28 (5)
Hypokalemia	35 (7)	20 (4)	11 (2)
Hyperglycemia	28 (5)	23 (4)	9 (2)
Rash	33 (6)	28 (5)	28 (5)
Cataracts	31 (6)	14 (3)	3 (1)
Dyspnea	30 (6)	22 (4)	18 (3)
Constipation	12 (2)	10 (2)	29 (5)
Peripheral sensory neuropathy	6 (1)	2 (<1)	51 (9)

What sticks out to me in looking at the toxicities as a whole is that there is a trend toward the increasing cardiac toxicity in the continuous Ld arm at 12% compared with 7% in those patients who were only treated for 18 months.

When you look at the breakdown of the secondary malignancies, the continuous Ld patient cohort had 17 total reports of secondary malignancies (3%), 15 of those being solid-tumor malignancies. The patients who got 18 cycles of Ld had 30 total reported secondary malignancies (6%), of which 29 were solid-tumor malignancies. Interestingly, the control arm, MPT, had 27 patients who had secondary malignancies (5%); 12 of those were acute myeloid leukemia or myelodysplastic syndrome.

Dr. Raje: This trial just proved what we have known about the use of lenalidomide in secondary cancers in that melphalan compounds the risk of hematologic cancers.[10-13] I think most of us would argue that we would continue patients on lenalidomide because with lenalidomide-dexamethasone alone, the incidence of second cancers is much lower and the cumulative probability of death from all other causes is much greater than that of developing and dying of second cancers [Figure 2].[13] The combination of melphalan does introduce stem cell toxicity and increased risk of acute leukemias. This was also seen in some of the large, randomized trials in which we used maintenance lenalidomide post–autologous transplant—again, the common theme there being lenalidomide used in the context of melphalan (Table 2 and 3).[11,13]

Table 2. Selected studies focusing on second malignancies after multiple myeloma[11]

Reference	Study design (study period)	No. of patients	Any second malignancy, %	Multiple myeloma to second malignancy, median time	Hematologic malignancy, n (%)	Solid tumor, n (%)
14	Population-based registry study (1986-2005)	8740	6.6	45.3 mo (AML/MDS)	**69 (0.8)**	508 (5.8)
15	Retrospective study, single institution (1997-2008)	589	3	35 mo	6 (1.0)	12 (2.0)
16*	Randomized phase 3 trial, maintenance lenalidomide vs placebo after high-dose melphalan/ASCT	614	5.5 (lenalidomide maintenance); 1 (placebo)	44 mo	Lenalidomide maintenance: † 11 (1.8); placebo arm:† 3 (0.5)	Lenalidomide maintenance:† 12 (2.0); placebo arm:† 3 (0.5)
17*	Randomized phase 3 trial, maintenance lenalidomide vs placebo after high-dose melphalan/ASCT	460	6.5 (lenalidomide maintenance); 2.6 (placebo)	17.5 mo after ASCT	Lenalidomide maintenance:† 8 (1.7); placebo arm:† 0 (0)	Lenalidomide maintenance:† 10 (2.2); placebo arm:† 4 (0.9)
18*	Randomized phase 3 trial, maintenance lenalidomide vs placebo after low-dose melphalan/prednisone with or without lenalidomide	459	3.9 (lenalidomide maintenance); 1.3 (placebo)	25 mo	MPR-R arm:† 7 (1.5); MPR arm:† 5 (1.1); MP arm:† 1 (0.2)	MPR-R: 5 (1.1);† MPR:† 4 (0.9); MP:† 3 (0.7)
19	Retrospective study, single institution (1989-2007)	2418	1.1	NR	26 (1.1)	NR
20	Retrospective study, single institution (1996-2005)	82	12.2	50 mo	10 (12.2)	NR
21	Population-based registry study (1958-1996)	8656	5.5	2.9 y	83 (1.0)	392 (4.5)
22	Retrospective study based on patients from clinical trials (1979-1985)	432	9.2	37 mo (solid tumors) 56 mo (acute leukemia)	17 (3.9)	23 (5.3)
23	Prospective study (NR)	188	3.8	63 mo	7 (3.8)	NR
24	Retrospective study based on patients from clinical trials (1964-1975)	648	1.9	82 mo	12 (1.9)	NR
25	Prospective study (1973-1977)	364	3.8	NR	14 (3.8)	NR
26	Case series (1965-1966)	3	NA	45 mo	3 (NA)	NR
27	Case series (1950-1966)	6	NA	10 y	1 (NA)	NR
28	Retrospective study, multi-institution (1932-1963)	310	2.3	NR	7 (2.3)	NR

MPR-R indicates melphalan/prednisone, Revlimid (lenalidomide), with Revlimid maintenance; MPR, melphalan/prednisone, Revlimid (lenalidomide), without Revlimid maintenance; MP, melphalan/prednisone, without Revlimid maintenance; NR, not reported; and NA, not applicable.
*These results come from interim analyses presented at the American Society of Hematology meeting, Orlando, FL, December 4-7, 2010.
†Updated numbers from presentations at the International Myeloma Workshop in Paris, France, May 3-6, 2011. At this time, the final analyses and written reports have not yet been published at the time this table was published.[11]

Figure 2. Cumulative Probability of the Development of a Second Cancer and of Death from All Other Causes (Excluding Second Cancers).[13]

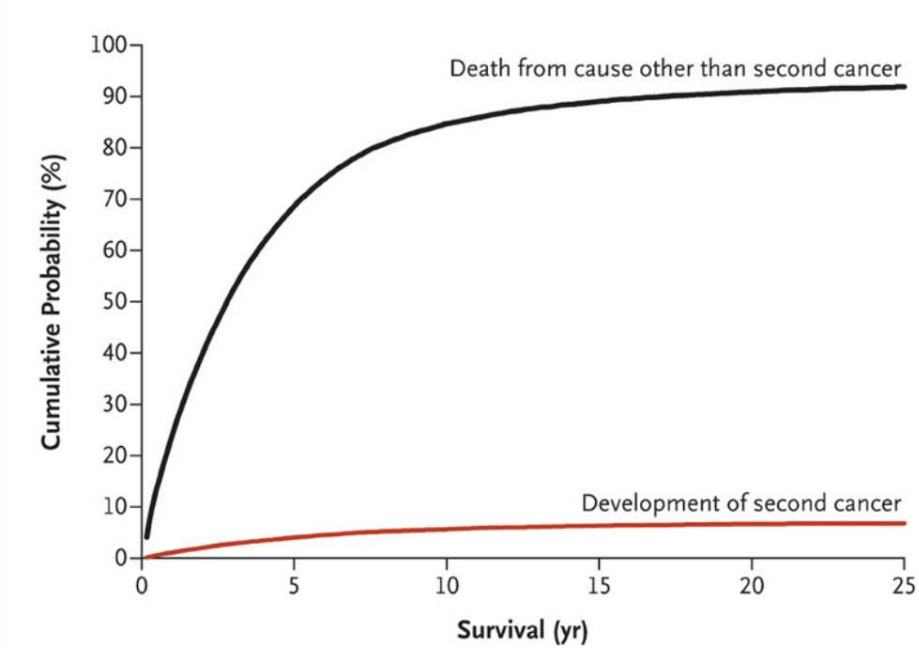


Table 3.Second Primary Malignancy Incidence in Three Large Maintenance Trials of Lenalidomide.

Study (Median follow-up)	Treatment Schedule	% SPM
MM-015 (30 months)	MPL-L/MPL Placebo	7% 3%
IFM 2005-02 (45 months)	L (after HDM-ASCT) Placebo (after HDM-ASCT)	8% 4%
CALGB 100104 (34 months)	L (After HDM-ASCT) Placebo (After HDM-ASCT)	7.8% 2.6%

L=lenalidomide; M=melphalan; P=prednisone; HDM-ASCT=high-dose melphalan with autologous stem cell transplant support

So, melphalan, I do believe, contributes somewhat to this second malignancy incidence, specifically the leukemias and the lymphoid malignancies. But practically speaking, we do like to continue our patients on treatment up until progression, but the reality is patients do have some level of fatigue with all of these drugs. And I am wondering, Tiffany, if you can speak to some of the long-term side effects that we see and how a patient approaches being on treatment indefinitely, specifically in light of the FIRST trial?

> *The level of fatigue [associated with continuous lenalidomide] can definitely be difficult for patients, particularly the older patients…I definitely see improvements in…fatigue when patients are able to get some level of activity—and it does not even have to be 30 to 60 minutes a day. I usually tell them just start up with 10 minutes once a day or twice a day –Tiffany Richards, Nurse Practitioner*

Ms. Richards: I think the level of fatigue can definitely be difficult for patients, particularly the older patients.[29-31] I see in my clinical practice that the older patients have more fatigue compared with the younger patients. That being said, one of the main things that I try to encourage patients to do is to get exercise, because I definitely see improvements in that level of fatigue when patients are able to get some level of activity—and it does not even have to be 30 to 60 minutes a day.[32] I usually tell them just start up with 10 minutes once a day or twice a day and see what happens. And oftentimes, the level of fatigue will improve. They will feel better, and so I really try to encourage patients to do that. Obviously, if patients have neuropathy, then that may be a little bit more difficult, and so then I try to tailor it a little bit based upon what they can do. I think the other thing that can be a little bit problematic with lenalidomide continuously is the diarrhea that can occur long term.[33-35] I have had great success with cholestyramine. In fact, there was a publication that came out in *Blood* by the UK group about the use of bile sequestrants with lenalidomide-induced diarrhea, and we have been using that for about 1.5 years.[36] They have had a lot of great success with that, and it has substantially not only decreased diarrhea, but also improved their quality of life. I was finding that patients were afraid to go out for dinner because they did not want to have the diarrhea that would come within about 30 to 60 minutes after eating. And I think those two are probably the biggest barriers to keeping patients on therapy—and then obviously infection as well.

> *"I think the other thing that can be a little bit problematic with lenalidomide given continuously is the diarrhea that can occur long term. I have had great success with cholestyramine. In fact, there was a publication that came out in Blood by the UK group about the use of bile sequestrants with lenalidomide-induced diarrhea, and we have been using that for about 1.5 years. They have had a lot of great success with that, and it has substantially not only decreased diarrhea, but also improved their quality of life." – Tiffany Richards, Nurse Practitioner*

Dr. Fausel: Tiffany, may I ask how you are dosing the cholestyramine?

Ms. Richards: I just have them take 1 packet a day. And I have them take it every day while they are on therapy.

Dr. Fausel: Have you had to titrate that at all for certain patients? For example, some patients may benefit if they take it before breakfast and before dinner?

Ms. Richards: I have not. Actually, I have found that just with the 1 packet a day that they do really well. They will say, "Okay. It is so much better now. I am down to 1 or 2 stools a day." So, I have not actually had to go up on the dose of the cholestyramine.

Dr. Fausel: Okay, thank you.

Dr. Raje: We have used cholestyramine as well, and I agree completely, Tiffany, it is actually very useful. The other important thing to talk to patients about is using a low-fat diet—which also helps them—and then adding cholestyramine has been incredibly useful. I will add, though, that we typically will not keep patients on the highest dose of lenalidomide because of some of the issues that you have mentioned in the older patient population, like the fatigue and neuropathy, which is not that common but does exist, as well as diarrhea. After you have achieved your maximal response, you can certainly dose-titrate down on the lenalidomide—and lenalidomide, as we know from some of our maintenance studies, does work at much lower dosage, and, in fact, patients can stay on medication longer term. This is at either 10 mg or 15 mg a day.

The ASPIRE Trial – Carfilzomib + Lenalidomide + Dexamethasone vs. Lenalidomide + Dexamethasone and The ENDEAVOR Trial – Carfilzomib + Dexamethasone vs. Bortezomib + Dexamethasone Both in Patients with Relapsed/Refractory Myeloma and ECOG E1A11 Carfilzomib + Lenalidomide + Dexamethasone vs. Bortezomib + Lenalidomide + Dexamethasone in Newly Diagnosed Multiple Myeloma

> *"What was seen in this trial was the fact that up until the ASPIRE trial, we were concerned about some of the toxicities of carfilzomib, cardiac and so on and so forth, but in the clinical trial—which is a multicenter, international trial with more than 700 patients—that signal certainly did not come out, suggesting that the combination of carfilzomib with lenalidomide-dexamethasone seems to be very safe. More importantly, what it also brought up in my mind was even in the relapsed setting, going to combination treatment strategies is probably the right approach based on the fact that there was close to a 9-month progression-free survival difference between the triplet versus the doublet with the lenalidomide and dexamethasone." – Noopur Raje, MD*

Dr. Raje: Moving on, I think we saw a lot of good data last year with the other proteasome inhibitor, carfilzomib, and it did get approved a couple of years back. This past American Society of Hematology [ASH] Annual Meeting and Exposition, the CArfilzomib, Lenalidomide, and DexamethaSone versus Lenalidomide and Dexamethasone for the treatment of Patients with Relapsed Multiple MyEloma [ASPIRE] trial was presented, which was the confirmatory trial for full approval of carfilzomib and the findings have since been published in the *New England Journal of Medicine*.[37] This was a phase 3, randomized, international, clinical trial in which carfilzomib was combined with lenalidomide and low-dose dexamethasone in patients with relapsed myeloma, with the control arm being lenalidomide-dexamethasone alone. What was seen in this trial was the fact that up until the ASPIRE trial, we were concerned about some of the toxicities of carfilzomib, cardiac and so on and so forth, but in the clinical trial—which is a multicenter, international trial with more than 700 patients—that signal certainly did not come out, suggesting that the combination of carfilzomib with lenalidomide-dexamethasone seems to be very safe. More importantly, what it also brought up in my mind was even in the relapsed setting, going to combination treatment strategies is probably the right approach based on the fact that there was close to a 9-month progression-free survival difference between the triplet versus the doublet with the lenalidomide and dexamethasone. Over the last few years, we have had issues with carfilzomib dosing and toxicities, and I am just wondering, Chris, about some of the issues that we have had over the years with carfilzomib, like the cardiac toxicity, and what are the things that one can do to try to mitigate some of those?

Dr. Fausel: So, that is one of the things that I often get worried about in some of my patients who are started out on carfilzomib, because speaking to the results in this trial, 4% of patients had either cardiac failure, grade 3 or 4, and 3% of patients had documented ischemic heart disease grade 3 or greater. So, I think it is really important to be somewhat discriminating as far as what patients you are going to offer this therapy to. Again, many of our patients are older. They have cardiac comorbidities. So, making some sort of determination ahead of time whether the patient is an appropriate candidate for carfilzomib is probably the first step in using good judgment as to whether or not to offer this therapy to patients. As far as some of the other toxicities, we have seen a fair amount of dyspnea associated with this drug, and we have had some patients who are getting single-agent therapy, with the dose escalated up to 56 mg/m^2 per week, which is what was reasonably well tolerated in the phase 1 trial that was published recently in the *Journal of Clinical Oncology*.[38] Other toxicities we are concerned with—we offer these patients antiviral prophylaxis for the reactivation of herpes, as is the case with bortezomib, too. So, we make sure that patients are antiviral prophylaxis, whether it would be acyclovir, famciclovir, or valacyclovir.

"…many of our patients are older. They have cardiac comorbidities. So, making some sort of determination ahead of time whether the patient is an appropriate candidate for carfilzomib is probably the first step in using good judgment as to whether or not to offer this therapy to patients." – Christopher Fausel, PharmD, MHA

"We have also seen some of the cardiac toxicity that you are alluding to, specifically fluid retention. But what we have noticed is if you give the drug a little slower than normal, as opposed to the 10-minute infusion, and if you increase the infusion time, we see a lot less of the fluid retention and the dyspnea. Also, actually managing their fluid balance while they are on carfilzomib really helps patients out." – Noopur Raje, MD

Dr. Raje: We have also seen some of the cardiac toxicity that you are alluding to, specifically fluid retention. But what we have noticed is if you give the drug a little slower than normal, as opposed to the 10-minute infusion, and if you increase the infusion time, we see a lot less of the fluid retention and the dyspnea. Also, actually managing their fluid balance while they are on carfilzomib really helps patients out. Sometimes, they need a little bit of diuretic to go with their carfilzomib treatment, and if you are able to manage some of these toxicities, they do quite well on this treatment. In terms of other things like myelosuppression, Tiffany, do you have a sense of more myelosuppression with carfilzomib as opposed to bortezomib in this case? Besides the schedule, are there any other things that your patients have experienced in terms of how they tolerate the carfilzomib versus bortezomib?

Ms. Richards: I have not really seen that much more myelosuppression with carfilzomib compared with bortezomib. I think patients actually, as far as their platelet counts, maybe do a little bit better with the carfilzomib. As far as the toxicity, we also increased our infusion time to 30 minutes, and then we have also decreased the intravenous fluids to only 250 cc prior to the carfilzomib, and that is it. Since implementing these changes, we have seen a reduction in the degree of dyspnea. So, I think increasing the infusion time, trying to minimize the fluid, and obviously ensuring that you are looking at each patient as an individual to ensure that you are assessing them and reevaluating them. We usually bring them back mid-cycle—particularly with that first cycle—by having them come in on day 3, just to see how they did with the first 2 doses to monitor for any fluid retention and dyspnea that they may have had, so that we can adjust our interventions for days 8 and 9. But I think it is well tolerated. Some patients do get a lot of fatigue, and there are some patients we have had to—once we get a response—go to just days 1, 8, and 15. And in some instances, we have had to reduce the dose of the carfilzomib back down to 20 mg/m^2 because they just were not able to tolerate the 27-mg/m^2 dose. But overall, when we first started using it, I was a little bit concerned about it. But now I have no concerns about it. Obviously, there are some patients who are a little bit nervous about it, but I think as we are using the drug more in a variety of different patients, you learn how to manage the drug and then manage which patients you are going to put on it.

"As we get more used to using these drugs, we learn their toxicities and learn how to modify. And tailoring treatment to the specific patient is so critical in terms of dose adjustments, dropping fluids, increasing infusion times." – Noopur Raje, MD

Dr. Raje: I think that is a really critical point that you have brought up, Tiffany. As we get more used to using these drugs, we learn their toxicities and learn how to modify. And tailoring treatment to the specific patient is so critical in terms of dose adjustments, dropping fluids, increasing infusion times, and so on and so forth. There are a couple of other clinical trials that we are all looking forward to. We do not have data on these as yet. Obviously, the ASPIRE trial,

with carfilzomib/lenalidomide/dexamethasone [CRD] showing remarkable efficacy, is an exciting combination [ClinicalTrials.gov Identifier: NCT01080391].[37] There has never been a head-to-head comparison of bortezomib with carfilzomib in the up-front setting. The ENDEAVOR trial in the relapsed setting has favored carfilzomib [Clinicaltrials.gov Identifier: NCT01568866.[39]

> *"…results from a planned interim analysis showing that the phase 3 head-to-head clinical trial ENDEAVOR evaluating carfilzomib for Injection in combination with low-dose dexamethasone versus bortezomib and low-dose dexamethasone met the primary endpoint of progression-free survival (PFS). Patients with relapsed multiple myeloma treated with carfilzomib lived twice as long without their disease worsening, demonstrating statistically and clinically significant superiority over bortezomib (median PFS 18.7 months versus 9.4 months, HR=0.53, 95% CI, 0.44–0.65). The carfilzomib combination demonstrated superiority over the bortezomib combination for secondary objectives of higher overall response rate and lower neuropathy events. Overall survival data are not yet mature and continue to be monitored"[39] – PR Newswire*

In the up-front setting, there is the Eastern Cooperative Oncology Group [ECOG] E1A11 trial that is ongoing, and this ECOG trial is randomizing patients to bortezomib/lenalidomide/ dexamethasone [RVD] versus CRD as the initial induction treatment. I think, for this trial, it will be interesting to see which of these combinations—whether it is RVD or CRD—will be more effective [ClinicalTrials.gov Identifier: NCT01863550]. But more importantly, I think it gives us the choices of having 2 proteasome inhibitors that are essentially very active when combined with an IMiD. And, again, as you pointed out Chris, depending on the patient profile, you might want to choose one over the other. But, hopefully, this ECOG trial will give us some sense of whether one combination gives you a deeper response versus the other. This trial also has another arm where they are looking at lenalidomide maintenance, so we will have to see. But this, to me, is an exciting trial for which I am looking forward to getting the data on just to try to clarify which induction treatment would be best used.

Table 4: Warnings and Precautions for Carfilzomib and Risk Mitigation[40]

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 5: Adverse Events Seen with Carfilzomib in Multiple Myeloma Trials[40]

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

Oral Proteasome Inhibitor Ixazomib: Phase III Studies, TOURMALINE-MM1 Ixazomib + Lenalidomide + Dexamethasone in Relapsed/Refractory Multiple Myeloma and TOURMALINE-MM2 Ixazomib + Lenalidomide + Dexamethasone in Newly Diagnosed Multiple Myeloma

There is another very interesting proteasome inhibitor that we are using now, and this is the oral proteasome inhibitor, ixazomib. Ixazomib, as you all are aware, has been used both in the up-front setting as well as in the relapsed setting. We have the TOURMALINE-MM1 study [ClinicalTrials.gov Identifier: NCT01564537] and TOURMALINE-MM2 study [ClinicalTrials.gov Identifier: NCT01850524]. Both of these studies have used ixazomib in combination with lenalidomide, one in the relapsed setting, which is TOURMALINE-MM1, and TOURMALINE-MM2, which is the phase 3 trial in newly diagnosed patients with multiple myeloma. Do you want to speak a little bit as to how ixazomib differs from bortezomib, what its half-life is, and how we actually dose it, Chris?

Trial Sponsor Has Announced That the First Interim Analysis of the Phase 3 Study [TOURMALINE-MM1] of Oral Ixazomib in Patients with Relapsed or Refractory Multiple Myeloma Met the Primary Endpoint of Improvement in Progression-Free Survival.[41]

Dr. Fausel: Sure. So, the nice thing about this drug is that it is dosed orally. It provides a little bit more flexibility for patients, and they may not necessarily have to come into a clinic to get their treatment. So, they can conceivably be managed with an all-oral therapy regimen in the outpatient setting, which would be very nice in terms of quality of life. The dosing scheme is interesting because it has a longer half-life, so it can be either given weekly or it can be given twice weekly. In the trial in which it was used in combination with lenalidomide and dexamethasone in the up-front setting, it was given as weekly—so, day 1, 8, and 15 out of a 28-day cycle—and the toxicities appear to be somewhat similar to what we have seen with other proteasome inhibitors [Table 5]. So, there is some myelosuppression. There is thrombocytopenia associated with it. There was about a 6% incidence of peripheral neuropathy that was grade 3 or greater, so it does not look like we are going to avoid that toxicity that has been difficult to manage in some patients receiving bortezomib therapy. So, I think it is going to be a win for patients if the data end up panning out and the efficacy data that we have seen in the smaller trials pan out in some of the larger phase 3 trials.

Dr. Raje: I would agree completely, and I think one of the biggest advantages of ixazomib is the fact that it does not have the same toxicity like bortezomib in the way of neuropathy. So, patients who have neuropathy can go on to ixazomib pretty safely, and it still seems to work in that patient population. And I do think it is going to be a paradigm-shifting trial as you pointed out, Chris, because it is going to be an all-oral treatment. I think the initial data on TOURMALINE-MM1 suggest that it is a positive trial, so, obviously, we are looking forward to the data in

TOURMALINE-MM2 as well because that is in the newly diagnosed. And I think it will fit in very nicely with how we would be able to use proteasome inhibitors in the maintenance setting. Not far behind is the other proteasome inhibitor, the oral proteasome inhibitor, oprozomib, which is undergoing clinical trials as we speak. In the last few minutes, on the new and upcoming clinical trials, I just wanted to turn to you, Tiffany, and ask you about what you think is exciting in the monoclonal antibody world?

Emerging Monoclonal Antibodies: Elotuzumab [anti-CS-1, SLAMF-7] and Daratumumab and SAR650984 anti-CD38

Ms. Richards: I think both elotuzumab and anti-CD-38 antibodies. I am excited to see the result of the phase 3 trials. I think the thing that is neat about the emerging monoclonal antibodies is it gives us a completely different class of drugs to treat our patients with. A lot of the drugs, with the exception of panobinostat, have been newer agents of what patients have already received. So, I think the monoclonal antibodies are really exciting and, hopefully, will change not only how we treat patients, but also improve even further on the overall survival that we have been seeing with the IMiDs and the proteasome inhibitors. So, I think that is a really exciting area, and I am excited to see the phase 3 data. Elotuzumab is being explored in combination with lenalidomide and dexamethasone in relapsed/refractory patients in the ELOQUENT-2 trial [Clinicaltrials.gov Identifier: NCT01239797] as well as in newly diagnosed patients in the ELOQUENT-1 trial [ClinicalTrials.gov Identifier: NCT01335399].

Dr. Raje: Yes. I think monoclonal antibodies have finally come of age in myeloma. We have elotuzumab, and very quickly behind it is daratumumab, 2 completely different targets, one against signaling lymphocytic activation molecule, family member 7 [SLAMF7] and the other one against CD38. And along with daratumumab, you have the Sanofi SAR650984 compound as well. What I think is really interesting about these monoclonal antibodies is they are targeting proteins present on myeloma cells, so they would work in a risk-agnostic manner, so to speak. They do not care about the cytogenetics of the myeloma, and our hope is that they are going to work even in the high-risk patient population. So, going forward, a lot of the clinical trials that we are designing now would be combining these monoclonal antibodies with some of the backbone drugs that we have alluded to already—and in the context of high risk, because the one area where I do think we still need to have a lot of improvement is in patients with very high-risk cytogenic features such as patients having 17p and chromosome 1q abnormalities. It would be great if we could see more data, and it has been quite exciting with the early phase data with some of these monoclonal antibodies [Table 5].

First in Class Histone Deacetylase Inhibitor Panobinostat Recent FDA Approval

Tiffany, you mentioned panobinostat, so I do want to talk a little bit about panobinostat here because it has just gotten its FDA approval after the FDA has re-looked at panobinostat data in both Panobinostat or Placebo With Bortezomib and Dexamethasone in Patients With Relapsed Multiple Myeloma [PANORAMA] 1 and 2 despite a negative vote by the Oncologic Drugs Advisory Committee on PANORAMA 1.[42] Do you want to speak a little bit to the indication and its use, Chris, and what the label would suggest?

Dr. Fausel: So, it is timely because it was just approved, and the approval is specifically in combination with bortezomib and dexamethasone with treatment of patients with multiple myeloma who had 2 prior regimens, which include bortezomib and an IMiD drug. They went back and looked at the progression-free survival in a subgroup of patients from the randomized, placebo-controlled arm with panobinostat in combination with bortezomib and dexamethasone, and they evaluated in prespecified 193 patients who gave their basis of approval. What they found is that the progression-free survival was 10.6 months in the panobinostat arm compared

with 5.8 months in the control, and that is what they used as the basis of their approval for this somewhat-narrow group of patients.[42]

Dr. Raje: I think the histone deacetylase [HDAC] inhibitors and panobinostat certainly have a place in the treatment of multiple myeloma, specifically in the relapsed/refractory setting. The 4-month progression-free survival benefit is real. I do think one has to look at toxicity closely for some of these pan-HDAC inhibitors. What we have seen clinically is a little more thrombocytopenia, a little more gastrointestinal [GI]-related toxicity of these compounds, and when combined with bortezomib, you may, in fact, compound both the thrombocytopenia as well as the GI-related toxicity [Table 5]. So, again, dose adjustment and adequate supportive care will be really helpful in patients who should be getting an HDAC inhibitor along with bortezomib. It is great that we have 1 more new drug in the context of multiple myeloma for our patients with this disease. Again, it has been shown in the high-risk patient population that a combination of panobinostat with bortezomib actually works, based on the PANORAMA 2 data—adding on 1 more new drug in our armamentarium against myeloma.[43]

Dr. Fausel: Can I just add 1 point to that? One thing that I am a little bit nervous with as this drug makes it onto market is there was some cardiac toxicity reported in the trials, and there was about a 20% increase in electrocardiogram changes in the panobinostat-containing arm, and they had an almost-doubled rate of arrhythmias, 12% versus 5% in panobinostat compared with the control. So, as we get more experience with this drug, I think that this is going to be something that we are going to have to keep our eye on.

Ms. Richards: Chris, I do not know if you were aware, but it is actually going to have a Risk Evaluation and Mitigation Strategies [REMS] program attached to it about cardiac toxicity.

Dr. Fausel: Okay.

Dr. Raje: That is great because they did have more deaths on the panobinostat arm as well, and you are right: postapproval use is going to be monitored. The indication for panobinostat use is fairly restricted, and it is going to allow only that patient population with 2 previous salvage treatments, having had previous bortezomib treatment. So, we are going to be able to closely monitor all of this. Also, I do think modifying the dose of panobinostat going forward may be what will be required in the treatment of these patients. So, it is a good thing that we have a REMS program built into this approval strategy. Moving forward now, we have a lot of exciting drugs, and the key would be to combine them judiciously in the future.

Resource
Ixazomib, Panobinostat, Elotuzumab, and Daratumumab and SAR650984: Regimens and Outcomes.
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