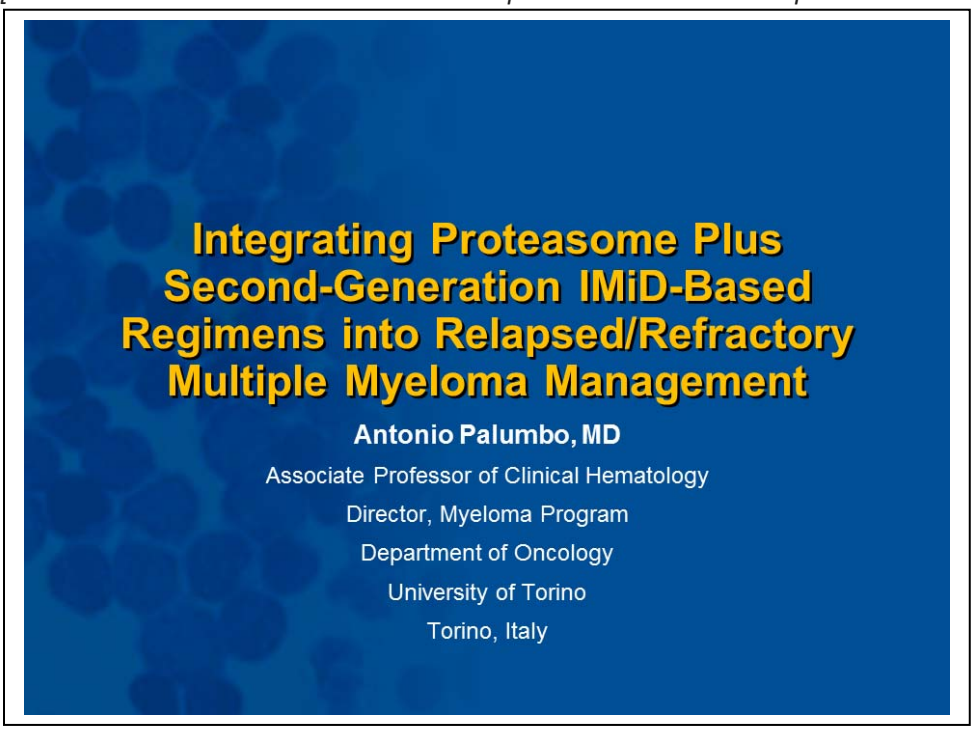
Integrating Proteasome Plus Second-Generation IMiD-Based Regimens in Relapsed/ Refractory Multiple Myeloma Management

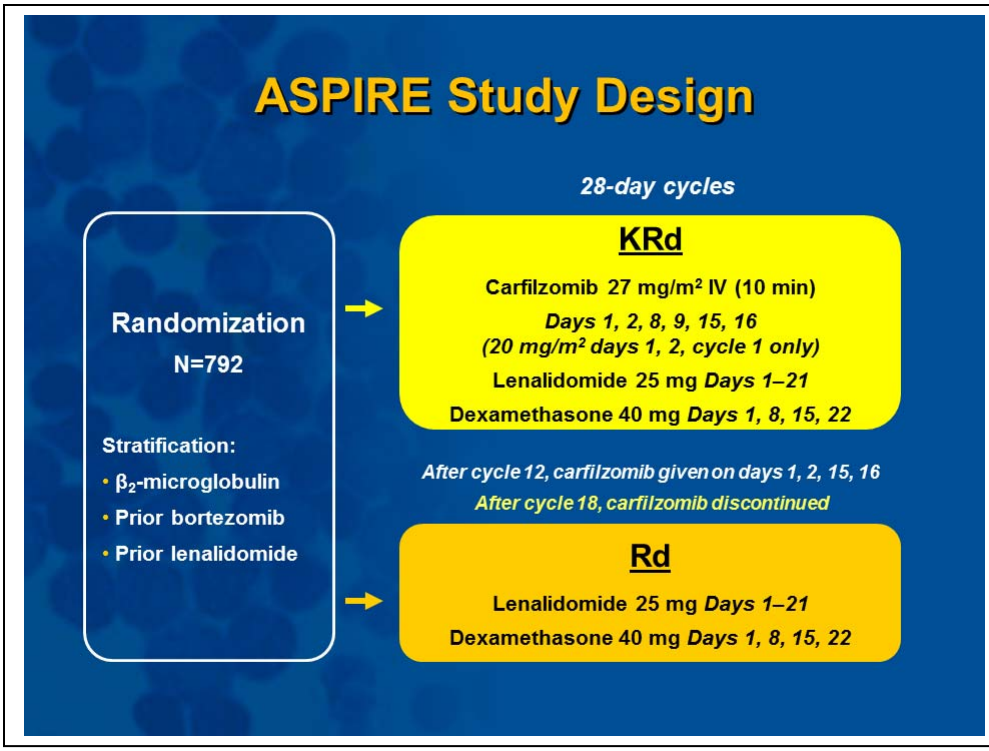
Presented by Antonio Palumbo, MD

[Editor's note: Dr. Palumbo's video transcript has been edited to improve readability]

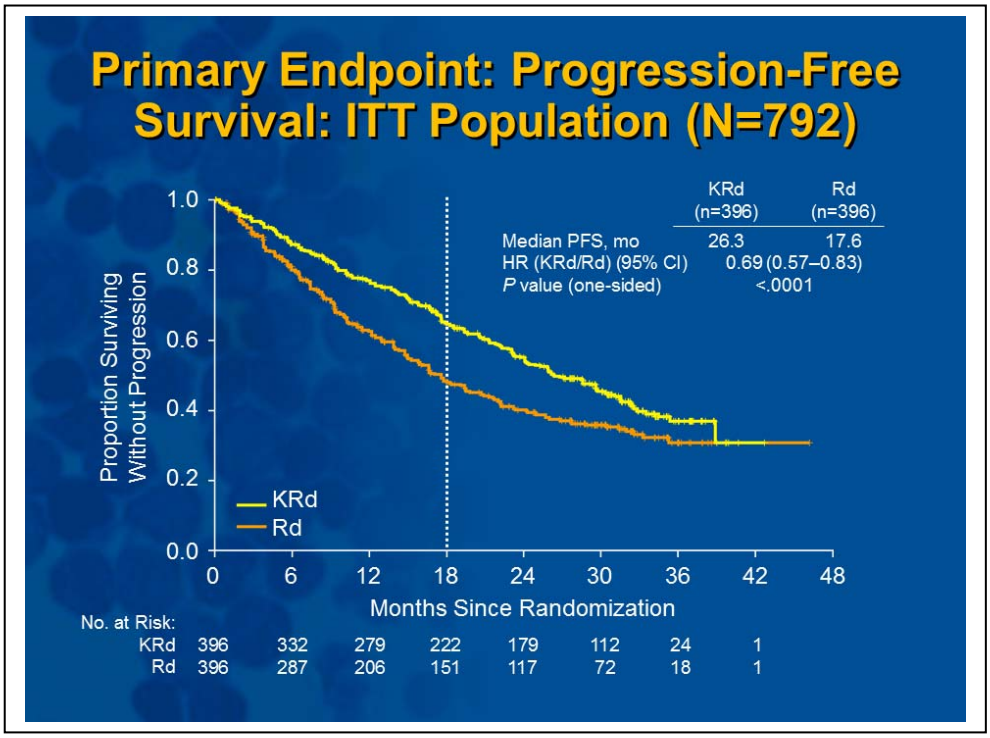


Welcome to *Managing Myeloma.* My name is Antonio Palumbo, and I am a physician working in the Myeloma Unit at the University of Torino, Italy. Today, I am going to discuss few issues related to integrating proteasome inhibitors and second-generation IMiD-based regimens into relapsed/refractory multiple myeloma.

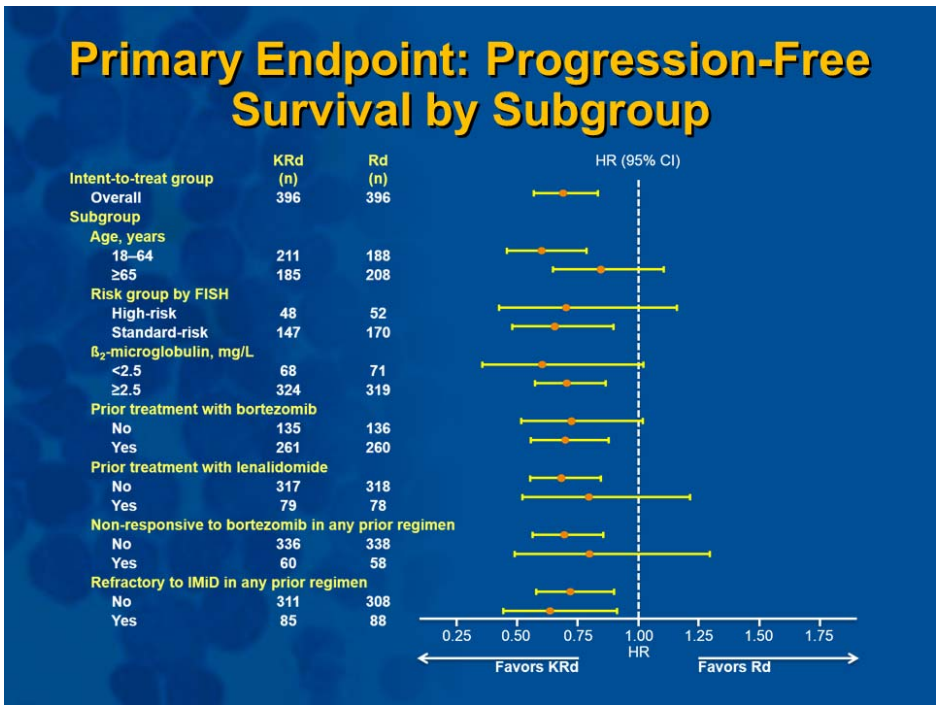
How can we combine these two agents in the treatment of multiple myeloma? The first topic I will discuss is the new data from the combination of carfilzomib plus lenalidomide and dexamethasone. The study, which was called the ASPIRE study, was developed in patients with 1 to 3 prior lines of therapy. Here we're talking about first and second salvage regimens, and the schema that has been used in this study involves carfilzomib at the dose of 27 mg/m^2. It is important to remember that this dose needs to be reduced to 20 mg/m^2 on days 1 and 2 in cycle 1 only. So, we start at 20 mg/m^2 and then increase the dose up to 27 mg/m^2, and this is the standard dose we use. The infusion occurs on days 1, 2, 8, 9, 15, and 16 of every 28-day cycle. This infusion is done intravenously in approximately 10 minutes, and we combine it with lenalidomide at the dose of 25 mg per day on day 1 through day 21; so, three weeks on and one week



off. This is combined with dexamethasone at the dose of 40 mg on days 1, 8, 15, and 22 — basically, on a weekly basis. If the dexamethasone is not well tolerated, the dose can be reduced from 40 mg to 20 mg, especially in subjects over the age of 75.



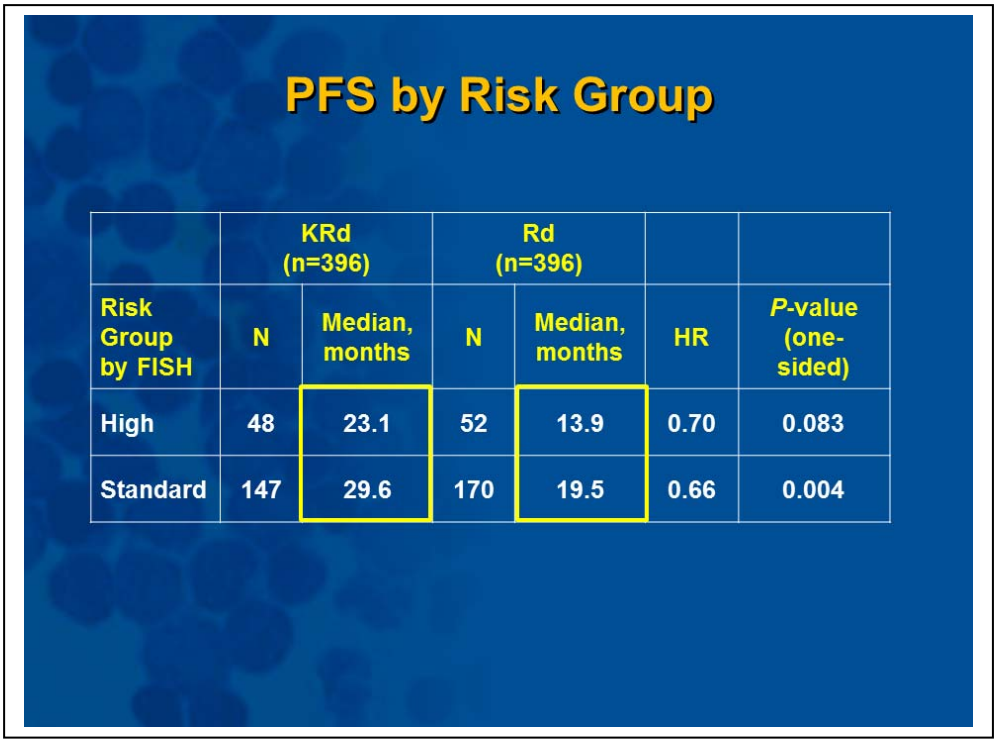
In this slide, we see the results of the ASPIRE study. The primary endpoint was progression-free survival, and this study showed a remarkable median progression-free survival of 26 months, compared to 17 months in the control arm, which consisted of patients who received lenalidomide and dexamethasone only. So, the addition of the third agent — in this case, the second-generation proteasome inhibitor carfilzomib — did increase median progression-free survival by approximately 9 months. This is quite important, because current available regimens usually have a median progression-free survival of about one year. This is the first time that, by adding a third agent, we were able to improve median progression-free survival from 1 year to 2 years. As you can see here, the ratio was 0.69, with the p-value of less than 0.0001.



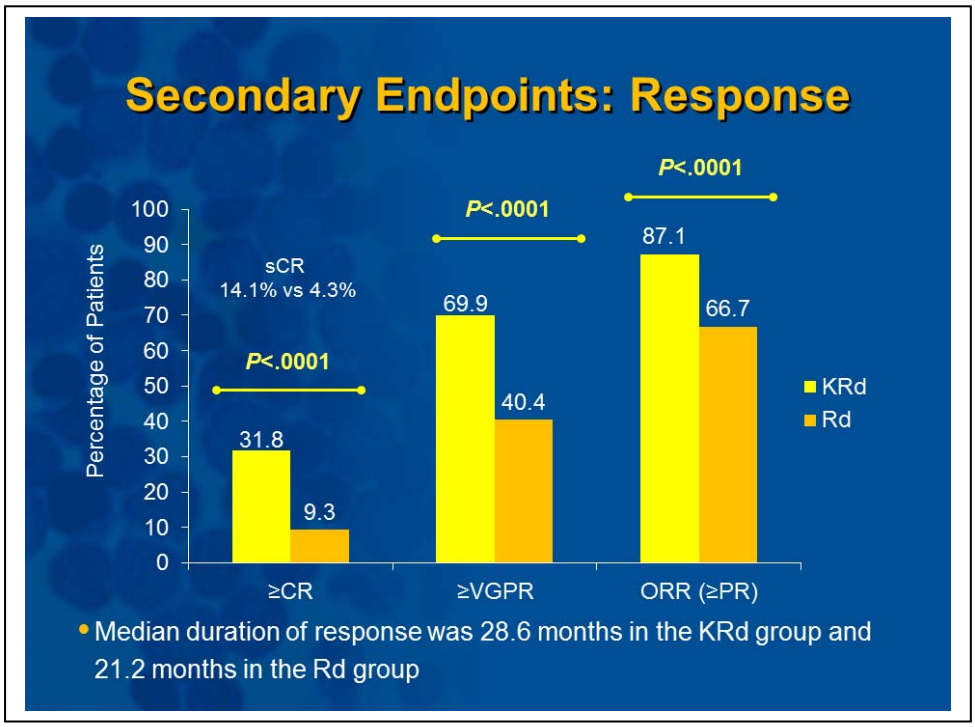
In this slide, we highlight progression-free survival by subgroups, and you can see that all of the subgroups did show the benefit of adding this third agent. In the risk groups defined by FISH, there was an equal improvement in both high-risk and

standard-risk patients. You can also see improvement in the beta-2 microglobulin, in both patients with less than and more than 2.5 mg/L beta-2 microglobulin.

A very important point here concerns the results that were seen when patients who had received prior treatment with bortezomib were compared with patients who had not previously received bortezomib. The result that we see here implies that the previous treatment with bortezomib can be rechallenged by the use of carfilzomib. The actual numbers here are not so important. Prior treatment with lenalidomide also showed an improvement, according to whether or not patients had received prior treatment with lenalidomide. This was the same for patients who were refractory to an IMiD in any prior regimen, and you can see that the data favors the use of carfilzomib in combination with lenalidomide and dexamethasone.

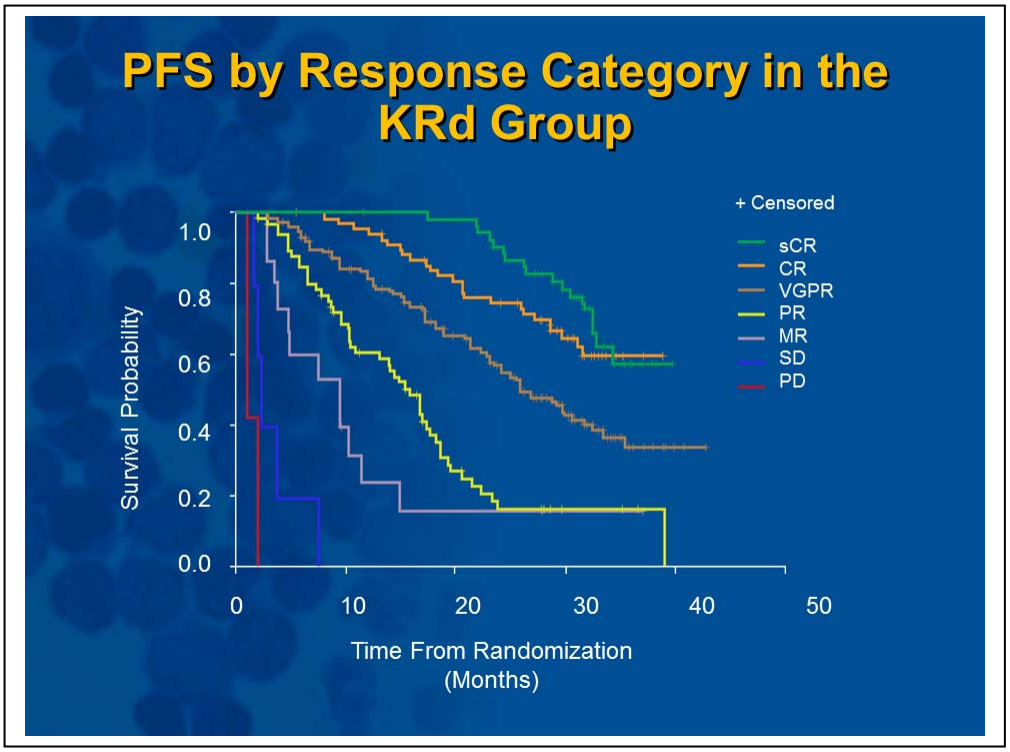


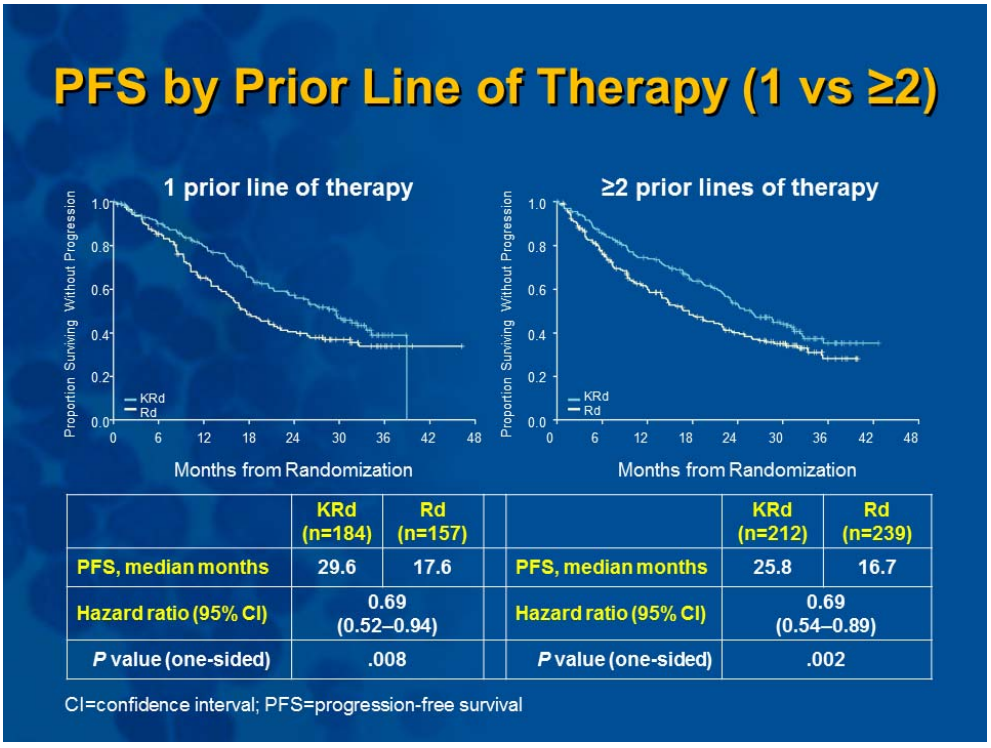
In this slide, you can see that there is an improvement in terms of progression-free survival, both in patients with high risk as defined by FISH or standard risk as defined by FISH. You can see that the median PFS in the high-risk population was 23 months versus 13 months, and in the standard population, the median progression-free survival was 29 months versus 19 months. This highlights the fact that, in both high-risk and standard-risk patients, we see a reduced risk of progression of around 30% with the addition of carfilzomib.



This slide makes a very important point: with this regimen, for the first time, we saw a complete response (CR) rate of 30% in relapsed/refractory patients. Usually, the standard CR rate is around 30% with combination therapy that includes a proteasome inhibitor, an alkylating agent, or an IMiD in a newly diagnosed patient. But we saw in the ASPIRE study that we have the opportunity to achieve the same proportion of CR rate in relapsed/refractory patients with the use of carfilzomib in combination with lenalidomide and dexamethasone. Similarly for the very good partial response (VGPR) rate, we saw a 70% GPR for the three-drug combination, versus 40% for the two-drug combination. I would also like to highlight something that is important: in addition to the difference in CR and VGPR rates, the action is absolutely quicker with carfilzomib. The tumor reduction is probably the fastest that you can obtain currently with the various agents we currently have available, so this is especially something to consider when you have a patient with symptomatic disease and you need to get rid of the tumor very quickly. Certainly, this is one of the best available regimens.

In this slide, you can see progression-free survival according to the different response rates, and you can see that, the higher the CR rate you obtain, and the more profound cytoreduction that you obtain, the better the patient's median progression-free survival will be. In this graph, PFS was almost 3 years in patients who achieved CR or stringent CR, and is approximately 30 months for patients who achieved the VGPR rate. This is important because of course, if you are moving from 40% to 70% VGPR rate, you will certainly increase the proportion of patients who might even reach 3 years of progression-free survival in a relapsed setting.





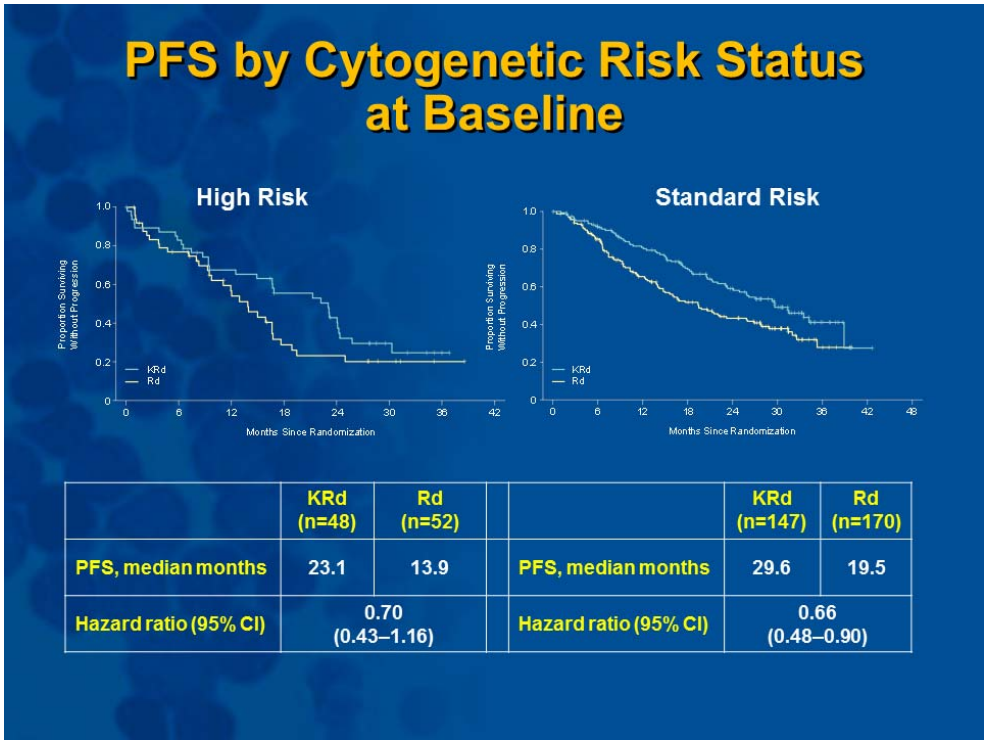
	KRd (n=184)	Rd (n=157)		KRd (n=212)	Rd (n=239)
PFS, median months	29.6	17.6	PFS, median months	25.8	16.7
Hazard ratio (95% CI)	0.69 (0.52–0.94)		Hazard ratio (95% CI)	0.69 (0.54–0.89)	
P value (one-sided)	.008		*P* value (one-sided)	.002	

CI=confidence interval; PFS=progression-free survival

This slide highlights the difference in PFS according to the number of prior lines of therapy, with one versus two or more. As you can see, the difference is clearly very well maintained. If you have only one prior line of therapy, or if you have two or more prior lines of therapy, the hazard ratio is basically 0.7 in both groups. The median

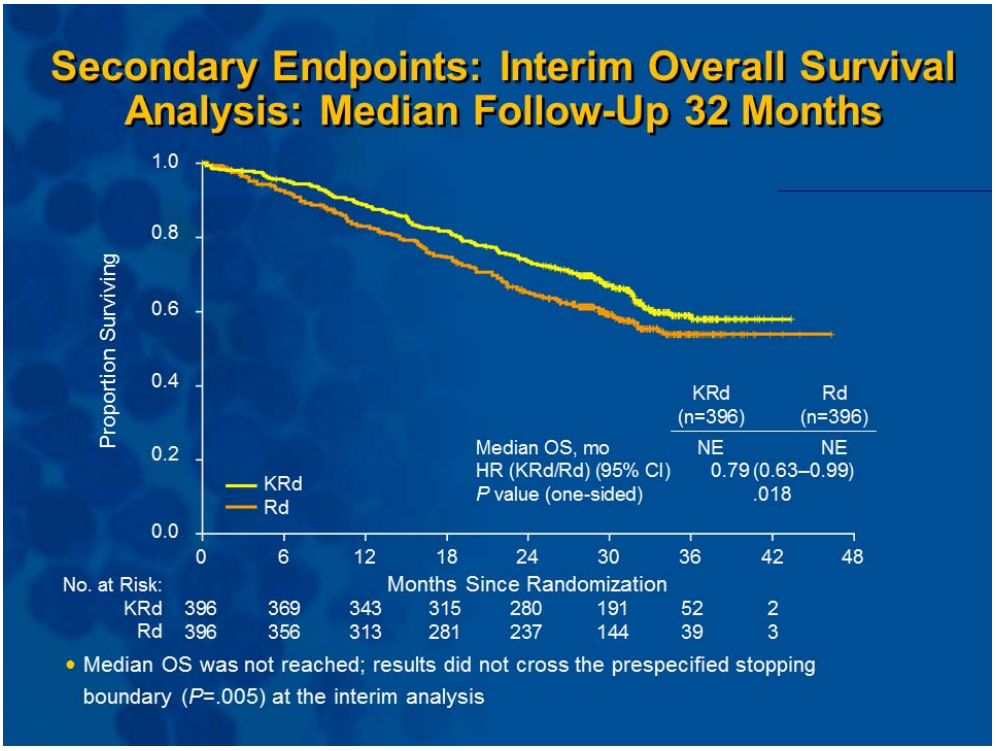
progression-free survival is 29 months with one prior line, versus 25.8 with two or more prior lines of therapy. This clear shows that, as we saw before, even in patients who have already had two or more prior lines of therapy, the use of a second-generation proteasome inhibitor, a new compound, clearly shows the efficacy independently from the number of prior lines used before.

You can see another important message in this slide, which looks at the differentiation of high-risk versus standard-risk patients. Once again, you can see that the addition of carfilzomib reduced the risk of progression in both groups by approximately 30%, regardless of risk status.

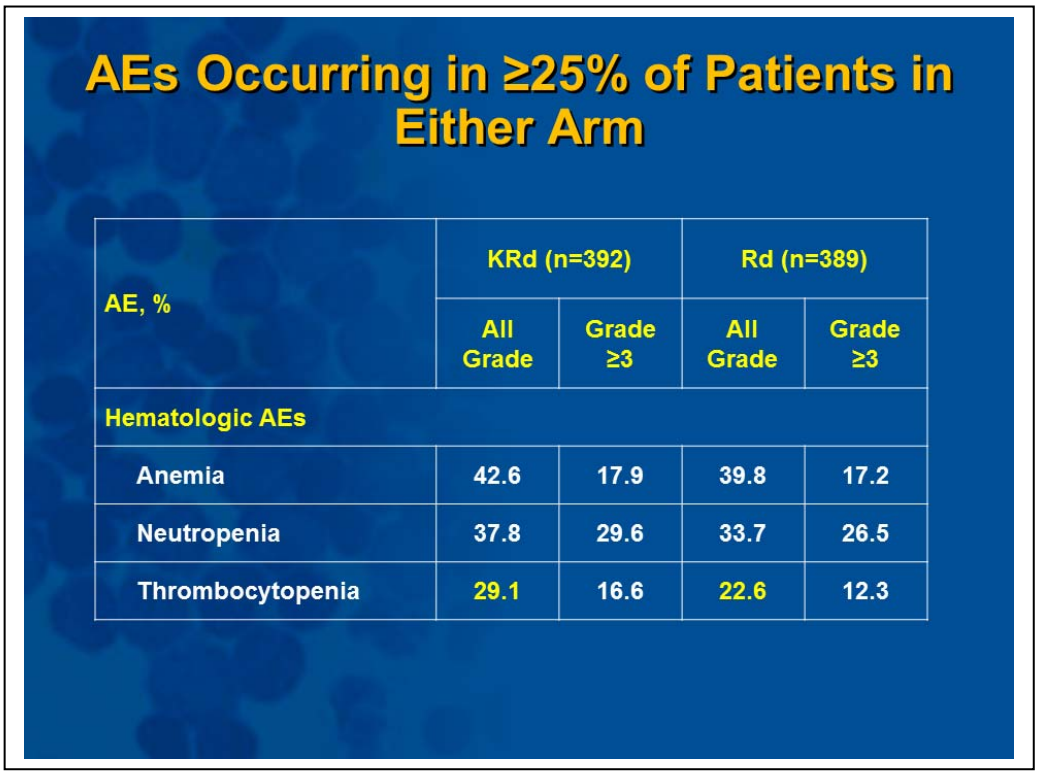


	KRd (n=48)	Rd (n=52)		KRd (n=147)	Rd (n=170)
PFS, median months	23.1	13.9	PFS, median months	29.6	19.5
Hazard ratio (95% CI)	0.70 (0.43–1.16)		Hazard ratio (95% CI)	0.66 (0.48–0.90)	

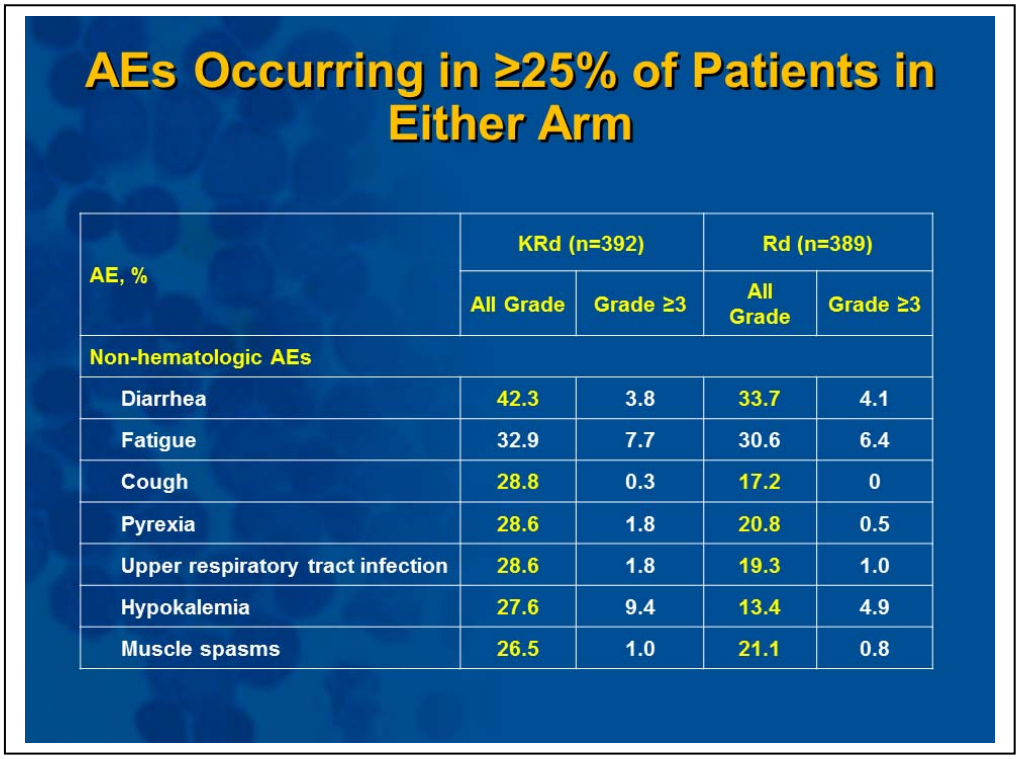
The follow-up, we can see in this slide, was fairly short. It wasn't long enough, but certainly, we can begin to see an advantage with the addition of carfilzomib, in terms of median overall survival with a hazard ratio of 0.79 and *p*-value of 0.01. So, we can clearly see a difference, even in terms of overall survival, and even if the follow-up is probably not mature. In fact, neither of the curves are reaching the median at



present, but there is already a significant trend in terms of improved overall survival for the combination, including carfilzomib, lenalidomide, and dexamethasone.

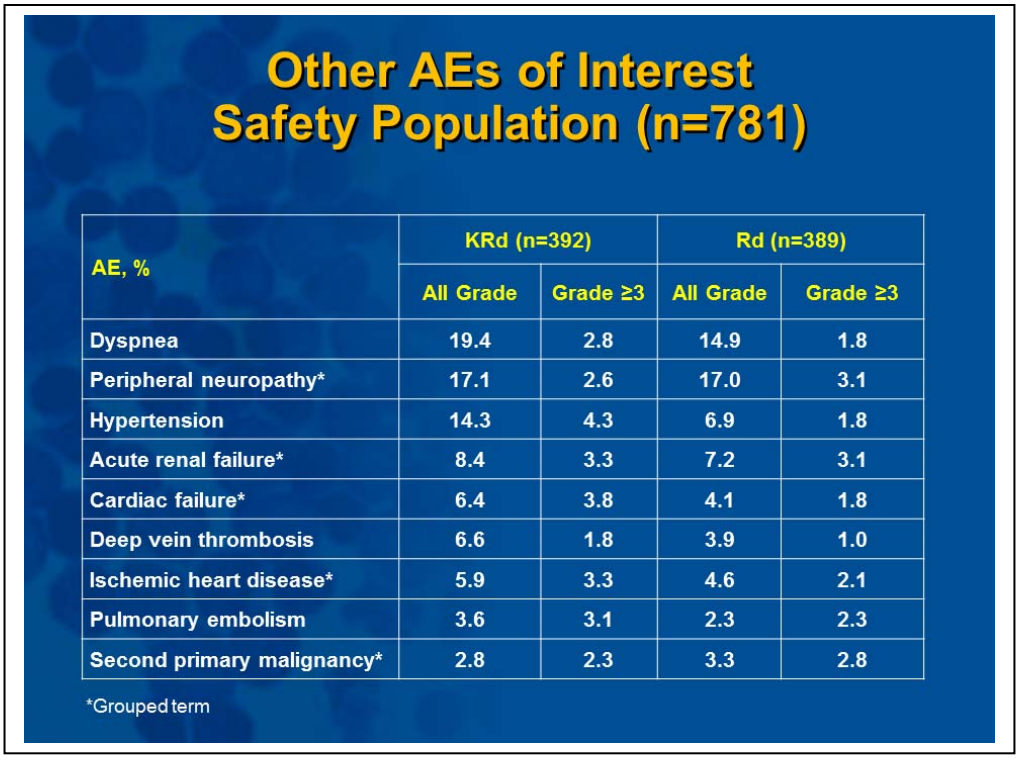


Now, a few practical issues: we've already mentioned that, in terms of dosing, we need to use a dose of 20 mg for only the first two infusions, and then we need to move to 27 mg on the subsequent infusion, usually with a twice weekly schedule. Something that is very important to highlight, in terms of the safety of this compound, is that, in terms of hematologic toxicity, it is very well tolerated. One of the major advantages of carfilzomib is that is does not increase the hematologic toxicity over the three-drug combination. You can clearly see from this slide that grade 3 or 4 anemia was seen in 17.9% of patients in the KRd arm, versus 17.2% for Rd. Neutropenia was 29% for KRd versus 26% for Rd. Thrombocytopenia, which is, to some extent, one of major limitations of bortezomib in terms of hematologic toxicity, is 16% versus 12%. So, you can see here that the addition of the third agent is not increasing the hematologic toxicity of the combination. This is very important in relapsed/refractory patients, because these are the patients who will start to have some kind of thrombocytopenia, where the hematopoiesis is reduced by previous chemotherapy. So, the ability to use a combination with no significant increase in hematologic toxicity is quite important.



AE, %	KRd (n=392)		Rd (n=389)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Non-hematologic AEs				
Diarrhea	42.3	3.8	33.7	4.1
Fatigue	32.9	7.7	30.6	6.4
Cough	28.8	0.3	17.2	0
Pyrexia	28.6	1.8	20.8	0.5
Upper respiratory tract infection	28.6	1.8	19.3	1.0
Hypokalemia	27.6	9.4	13.4	4.9
Muscle spasms	26.5	1.0	21.1	0.8

This slide highlights some of the non-hematologic adverse events and you can see here the difference in grade 3 or 4 non-hematologic toxicities seen with this regimen. These are very limited, with the usual differences in terms of infections; for example, you can see here that diarrhea is 3 versus 4, fatigue is 7 versus 6, and upper respiratory infection is 2 versus 1. You don't see any major non-hematologic side effects.



AE, %	KRd (n=392)		Rd (n=389)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Dyspnea	19.4	2.8	14.9	1.8
Peripheral neuropathy*	17.1	2.6	17.0	3.1
Hypertension	14.3	4.3	6.9	1.8
Acute renal failure*	8.4	3.3	7.2	3.1
Cardiac failure*	6.4	3.8	4.1	1.8
Deep vein thrombosis	6.6	1.8	3.9	1.0
Ischemic heart disease*	5.9	3.3	4.6	2.1
Pulmonary embolism	3.6	3.1	2.3	2.3
Second primary malignancy*	2.8	2.3	3.3	2.8

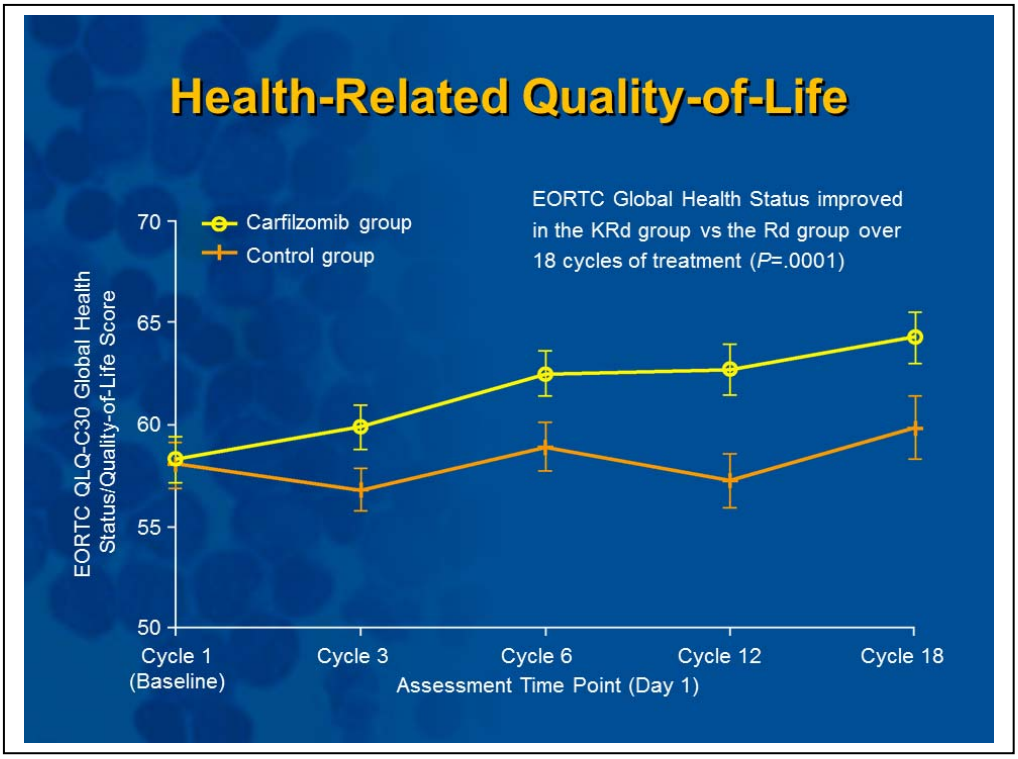
*Grouped term

I think it's important to highlight this next point. This slide summarizes adverse events of major interest. What is the difference, and to which of these should we pay some attention? First of all, peripheral neuropathy: this is another major advantage in comparison to bortezomib, as the risk of peripheral neuropathy in KRd is identical to Rd. Peripheral neuropathy of all grades is 17.1% in KRd versus 17.0% in Rd. Peripheral neuropathy grade 3 or 4 is 3% in KRd versus 3% in Rd. So, peripheral neuropathy and thrombocytopenia

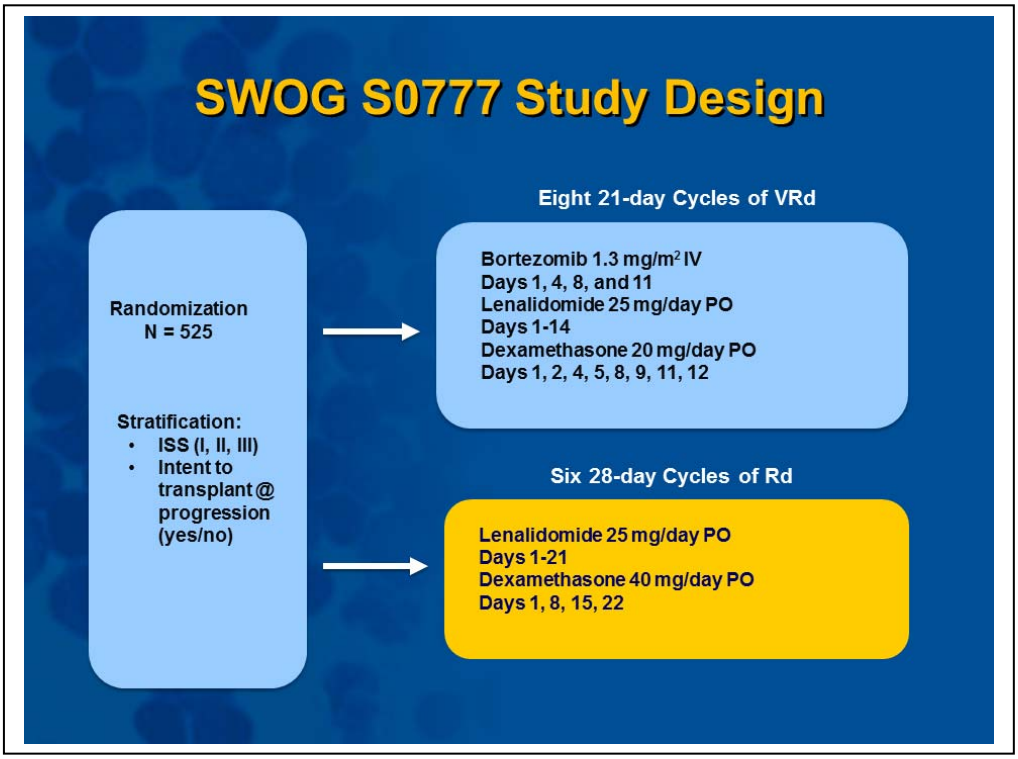
are two conditions by which you have a selective indication for this compound, in addition to the opportunity to have a 30% CR rate today, which is unprecedented in relapsed/refractory patients.

On the other hand, what we should probably pay more attention to is hypertension. You can see the incidence of hypertension with KRD is 14% versus 7% with Rd, and this is something you need to monitor for during the infusion. I would certainly check the patient's blood pressure before beginning the infusion, again 10 minutes after the end of the infusion, and then 1 or 2 hours after the end of the infusion. Some of these patients may develop hypertension; even though it will only last only 1 or 2 days, we still must look at this potential risk factor, because this is probably one of the best ways to avoid and eventually predict some cardiac side effects.

In terms of cardiac failure, there is a difference between KRd and Rd, but, once again, it is minimal, with 3.8% for KRd versus 1.8% for Rd. Deep vein thrombosis is again very limited, 1.8% versus 1%, as is pulmonary embolism at 3.1% versus 2.3%. There is certainly no signal in terms of a major increase in incidence of either deep vein thrombosis or pulmonary embolism. Also, in terms of a second primary malignancy, the numbers for KRd are identical to Rd, so there is no major increase in terms of second primary malignancy. My message here is primarily focused on blood pressure, in that we need to check the patient's blood pressure during the infusion to avoid potential hypertension which, when combined with dexamethasone, might create the basis for some cardiac failure.

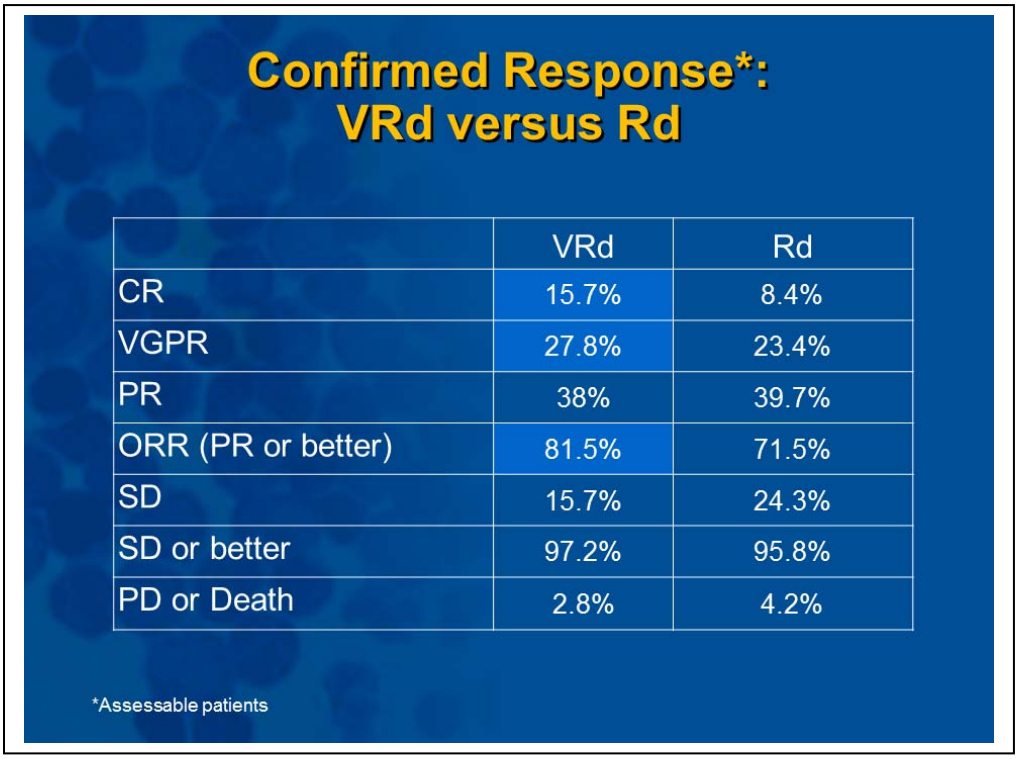


Another very important message concerns quality of life. As you can see here, the difference in terms of quality of life is quite relevant. We do not always see this type of graph for quality of life. You can see how quickly the tumor is reduced in the KRd group, and this translates immediately into a major difference in terms of quality of life. This is also sustained from cycle 3 through cycle 18, and is something that is not always evident in other studies.

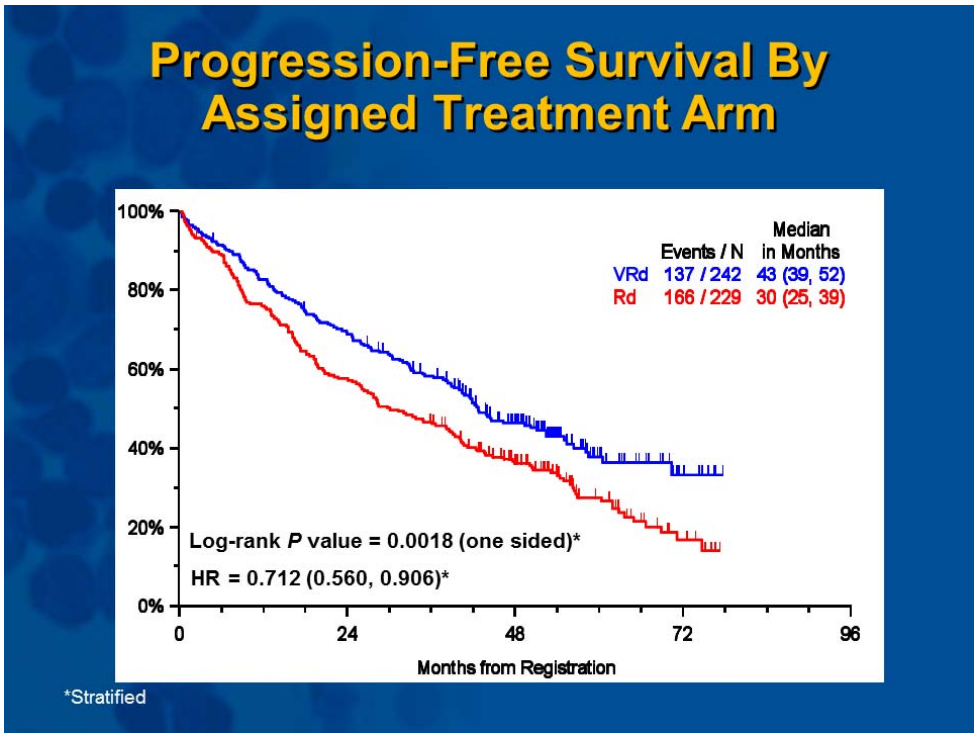


Now, we do have another opportunity, which is, of course, the combination of bortezomib, lenalidomide and dexamethasone, or VRd. In this regimen, bortezomib is usually given in 21-day cycles, with infusion of 1.3 mg^2/L on days 1, 4, 8, and 11. Lenalidomide is always given at the dose of 25 mg/day on days 1 through 14, and dexamethasone is given at the dose of 20 mg of days 1, 2, 4, 5, 8, 9, 11, and 12. This is the typical dose of VRd, and how can we differentiate VRd from KRd? Certainly, carfilzomib might represent an improvement, as the rate of CR is certainly increased, there is no risk of peripheral neuropathy, and there is a slight increase in terms of cardiac events. Based on this, you can differentiate that, of the two regimens, bortezomib could probably be considered, to some extent, the first choice, and carfilzomib the next re-challenge, in terms of proteosome inhibitor infusion.

These are some data coming from a study recently presented at ASH by SWOG, and you can see here the difference in newly diagnosed patients – not in the relapsed/refractory setting. As we can see here, in this study, VRd had a 15% CR rate in newly diagnosed patients, versus 8% for Rd, and a VGPR rate of 30% versus 23% in the Rd group.



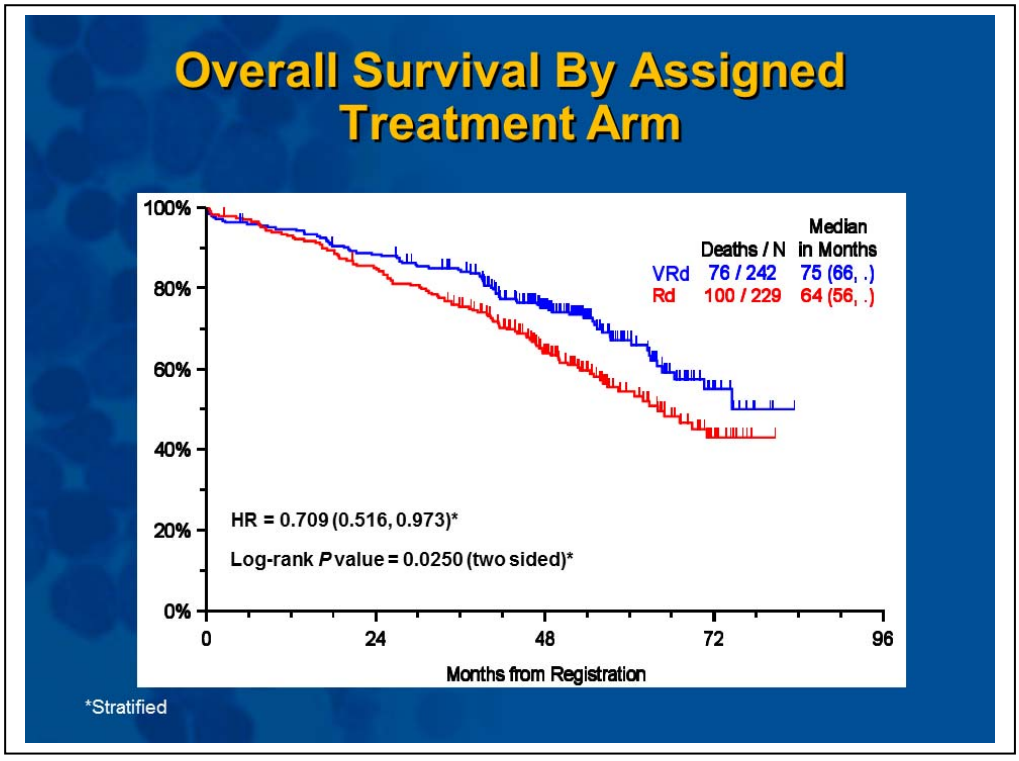
	VRd	Rd
CR	15.7%	8.4%
VGPR	27.8%	23.4%
PR	38%	39.7%
ORR (PR or better)	81.5%	71.5%
SD	15.7%	24.3%
SD or better	97.2%	95.8%
PD or Death	2.8%	4.2%

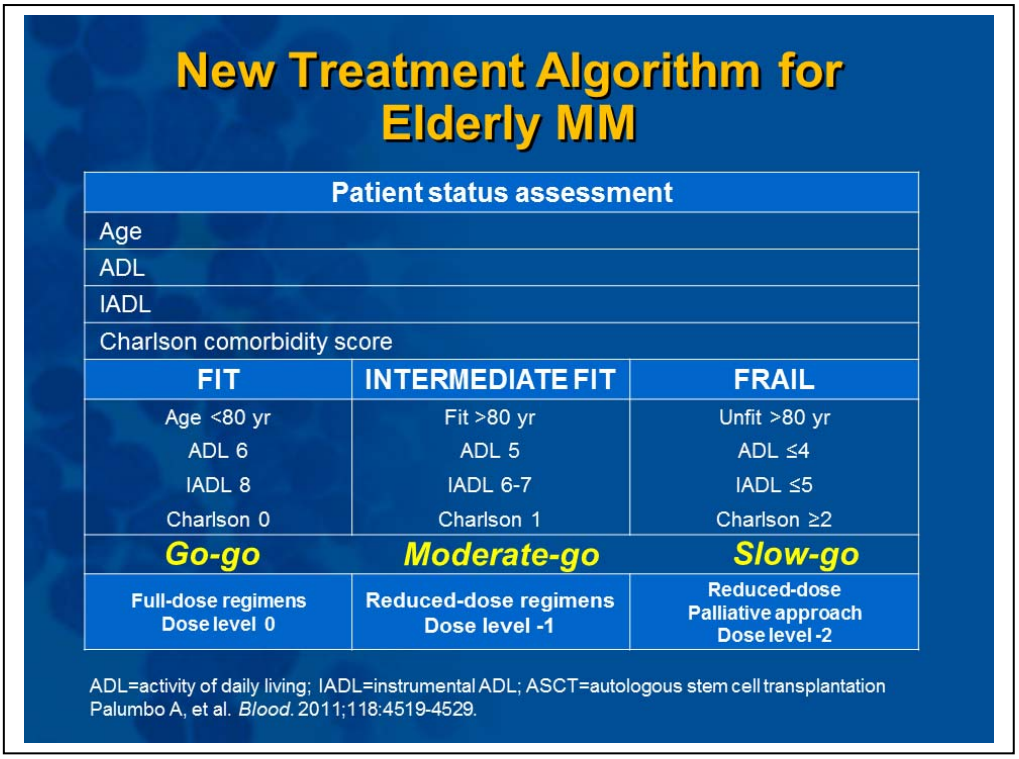


In this study of newly diagnosed patients, this regimen translated into major improvements in terms of progression-free survival, with a median of 43 months for VRd versus 30 months for Rd.

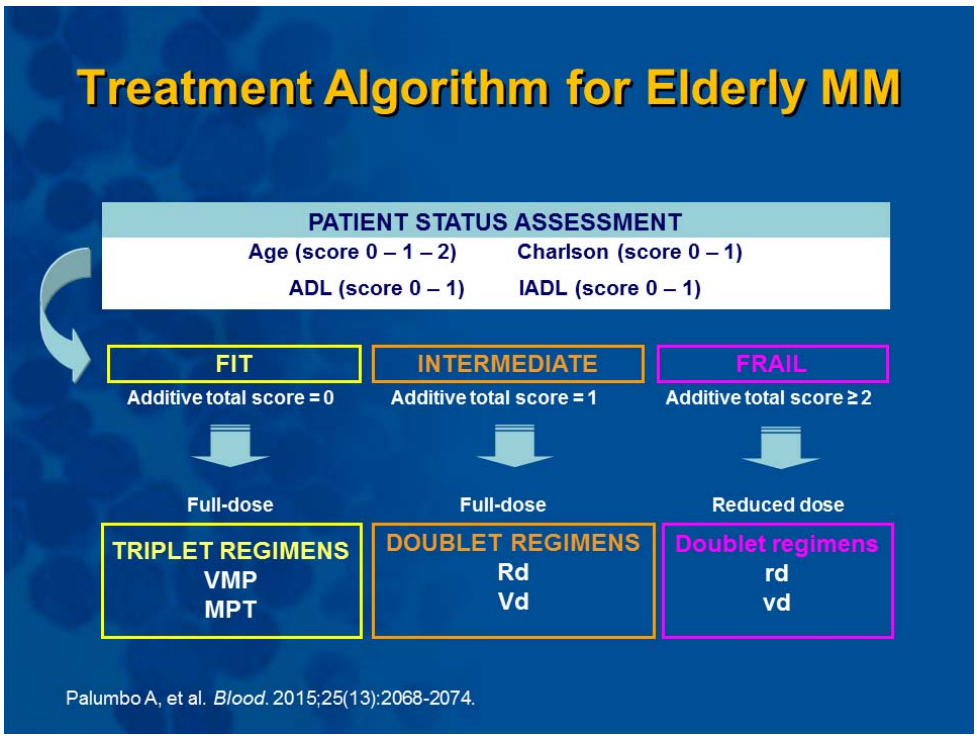
As you can see here, certainly the curves are relevant, with hazard ratio of 0.7. It's also important that we see an improvement in terms of overall survival in the VRd group, as well.

So, these are the two major regimens. Certainly, combinations now should always include a proteasome inhibitor and an IMiD. Carfilzomib does have a higher CR rate compared to bortezomib, with less peripheral neuropathy, but it also has some signal in terms of cardiac side effects. It is probably the best choice for a possible re-challenge after bortezomib infusion.



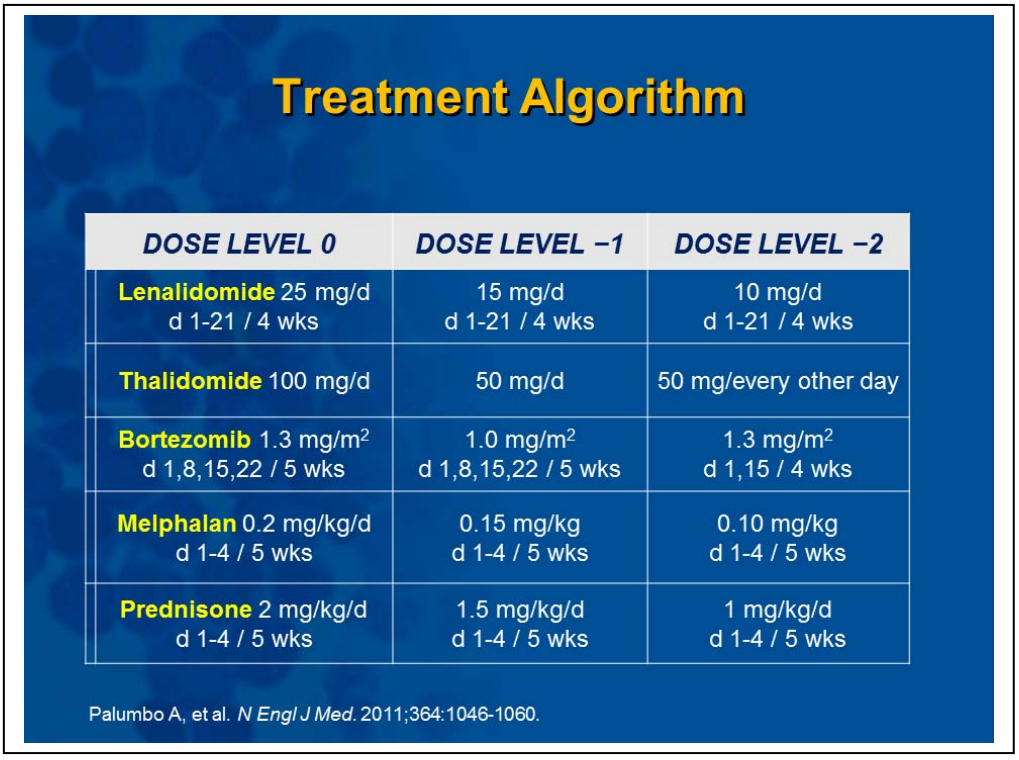


Now, something that I think is always important to remember is dosage and how to approach identifying the most effective dosage for the individual patient. More and more, we're facing patients over the age of 75. More and more, we're facing patients that are not only old, but they're also experiencing some comorbidities. So, what is important is to evaluate the patient first and put together age and comorbidity. The first message is that age is a condition of frailty over the age of 80, not over the age of 75. Someone without any comorbidities is fit up to the age of 80, and becomes frail after the age of 80. Of course, someone becomes frail at a younger age if comorbidities are present. So, these are the two major concepts to remember, 80 years as the cut off in terms of age, and the presence of comorbidities, major comorbidities that can be defined by the Chalrson score, even in the younger patients, even in 60-year-old patients. On the top of that, we must also evaluate two issues, the activities of daily living (ADL) and the instrumental activities of daily living (IADL), sometimes referred to as the brain and the leg condition, which is another way of saying, basically, how much someone is mentally independent and how much someone is physically dependent.

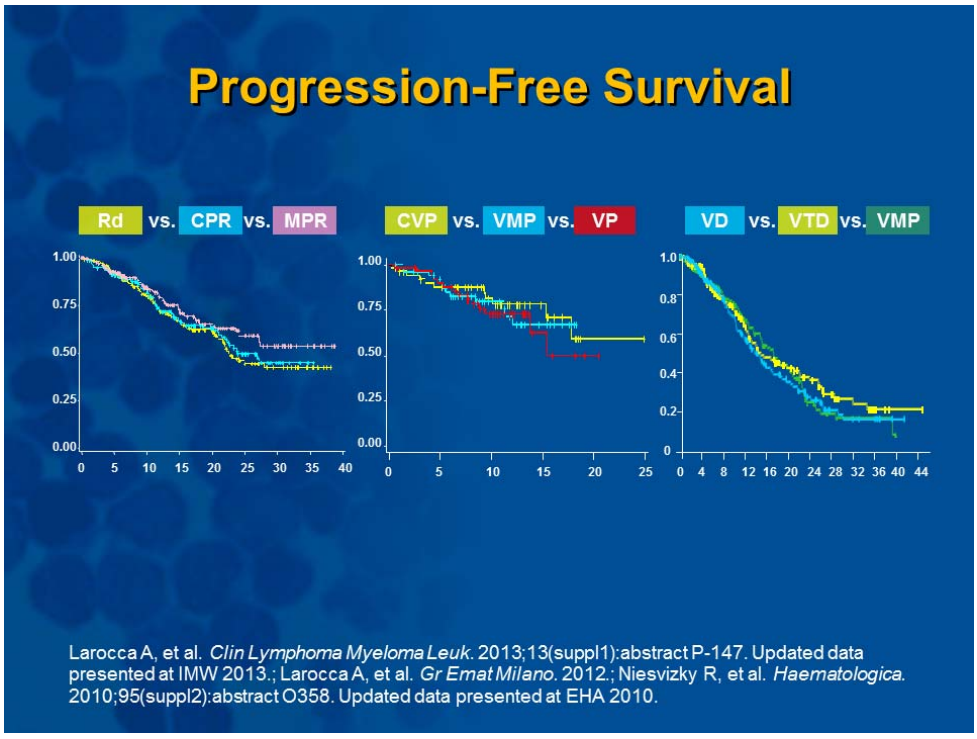


We can manage this condition of frailty in two different ways. One way is to move from a three-drug combination to a two-drug combination, but the other way is also to use a three-drug combination at a lower dose. We should always take in consideration those two options, and certainly, option number one is very simple: we move from a three-drug to a two-drug combination.

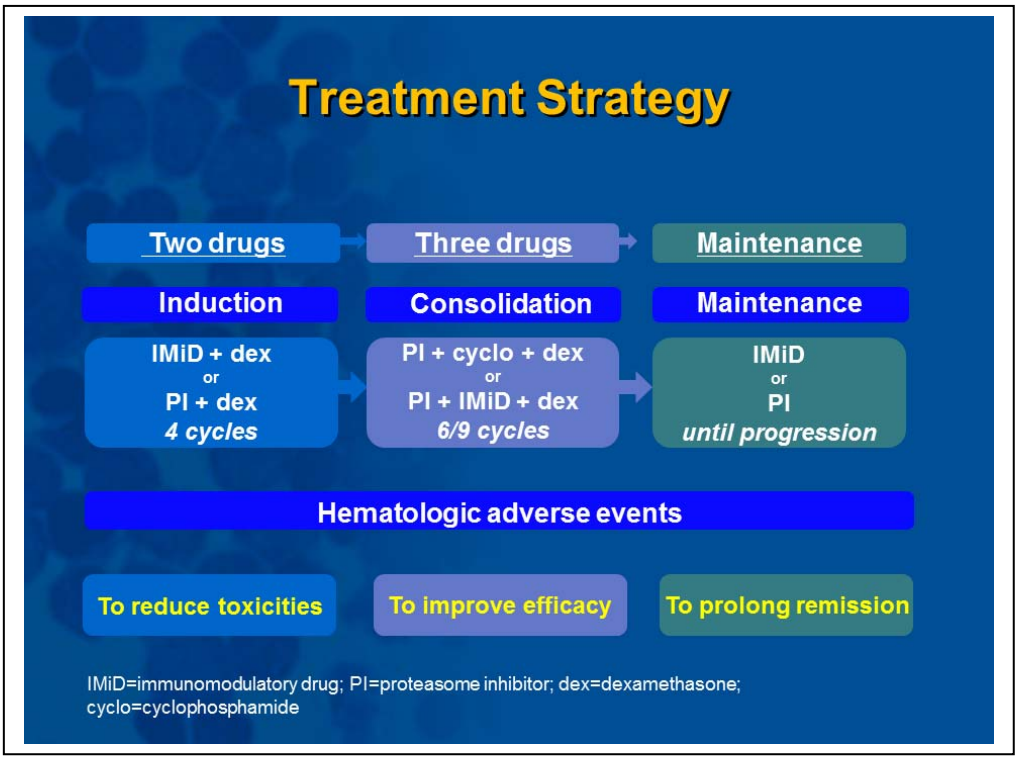
We can see option two in this slide, which is to reduce the dosage. And, here, we have something to consider. The dose of lenalidomide can be reduced from 25 mg to 15 mg. Remember that 50% of the patients over the age of 70 might have a creatinine clearance around 50, and we are already in a dose range of 15 mg. Bortezomib should be reduced from twice weekly to the weekly infusion. This is something that is probably often suggested in patients over the age of 65 who are not in major need of quick tumor reduction. Similarly carfilzomib could also be reduced to 20 mg and this, to



some extent, may represent something to take into consideration. So, always remember that we might face those two conditions, the fit and frail, and that frail patients will require some more caution in the treatment approach.

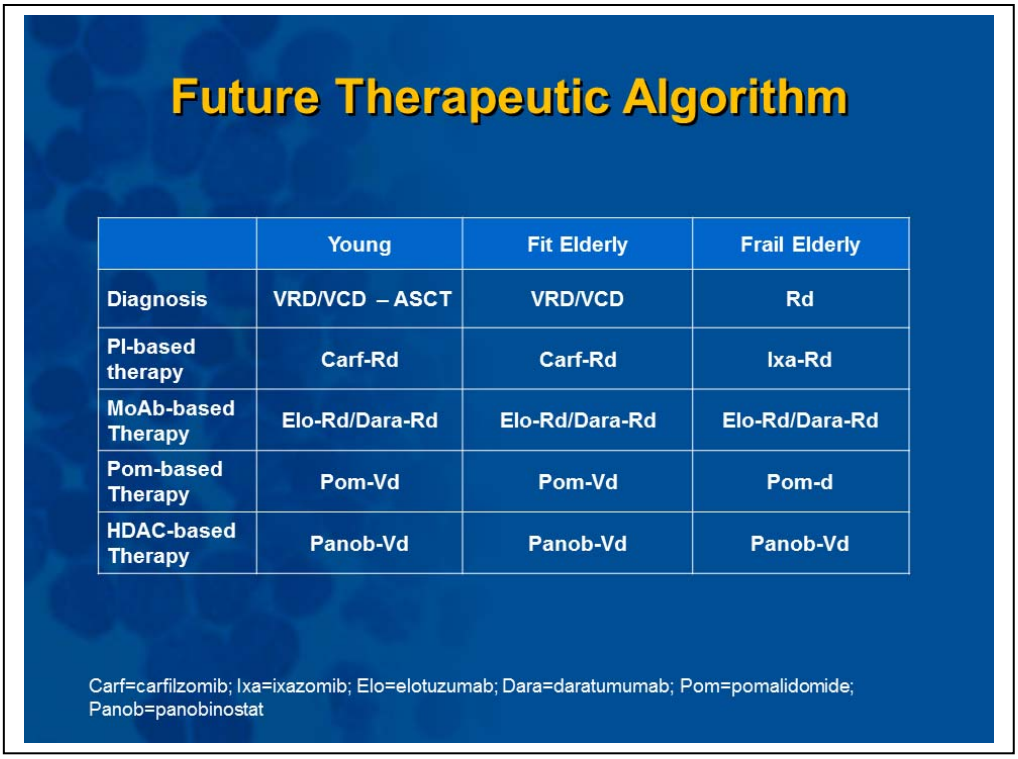


Here are some studies showing the difference between two and three drugs. And you can see here that there is basically no major difference between two and three drug combinations in elderly populations in which a significant proportion of the patients have concomitant comorbidities. One issue that is not always followed but could be considered, is that, when we are in the gray zone between fit and frail, we're not sure whether the patient will be able to tolerate the treatment we are using. We might start with two-drug combination and then, after two to three courses, go from induction to consolidation and add the third agent. It doesn't matter what we might add, but what I think is important is to start with the lower dose intensity for a couple of cycles, to make sure that the patient can tolerate the regimen, and then move into a consolidation state by adding the third agent. I think this is also important, because it is what we basically do with induction and transplantation: we start with a lower dose intensity and then we consolidate. It is also important to remember that in maintenance, it is probably relevant to reduce the dose, to be able to maintain the patient's treatment for a prolonged period of time.



To close, we can see in this slide what is changing today. Basically, we have the treatment schema for our patients, which is probably the combination of a proteasome inhibitor plus an IMiD plus transplant in the so-called young patients, with the same combination but without transplant in the elderly fit patients, and two-drug combination for the frail elderly.

Now, we come to the more complicated topic how to use these regimens in the future in the relapsed/refractory setting. To make this complicated issue very simple, we do have the second-generation proteasome inhibitors, carfilzomib intravenously and ixazomib oral. In the relapsed/refractory setting, we want to once again use the combination of IMiD and proteasome inhibitor, but we also have the availability of the monoclonal antibodies, daratumumab and elotuzumab. And once again, this may represent another therapeutic choice, in case we do not want to use a combination of proteasome inhibitor and IMiD. The other issue that we should also take into consideration is that, as we're moving from bortezomib to carfilzomib, we're also moving from



lenalidomide to pomalidomide. So, in patients with whom we've already been using lenalidomide, in the next therapeutic sequence, we want to introduce pomalidomide as a third-generation IMiD.

Thank you for viewing this activity. For additional resources regarding integrating regimens into relapsed/refractory multiple myeloma management, please view the Regimen Protocol Tool on *ManagingMyeloma.com.* Thank you very much for the attention.