

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

Integrating Proteasome Inhibitor Plus Either Third-Generation IMiD or Histone Deacetylase Inhibitor-Based Regimens into Relapsed/Refractory Multiple Myeloma Management

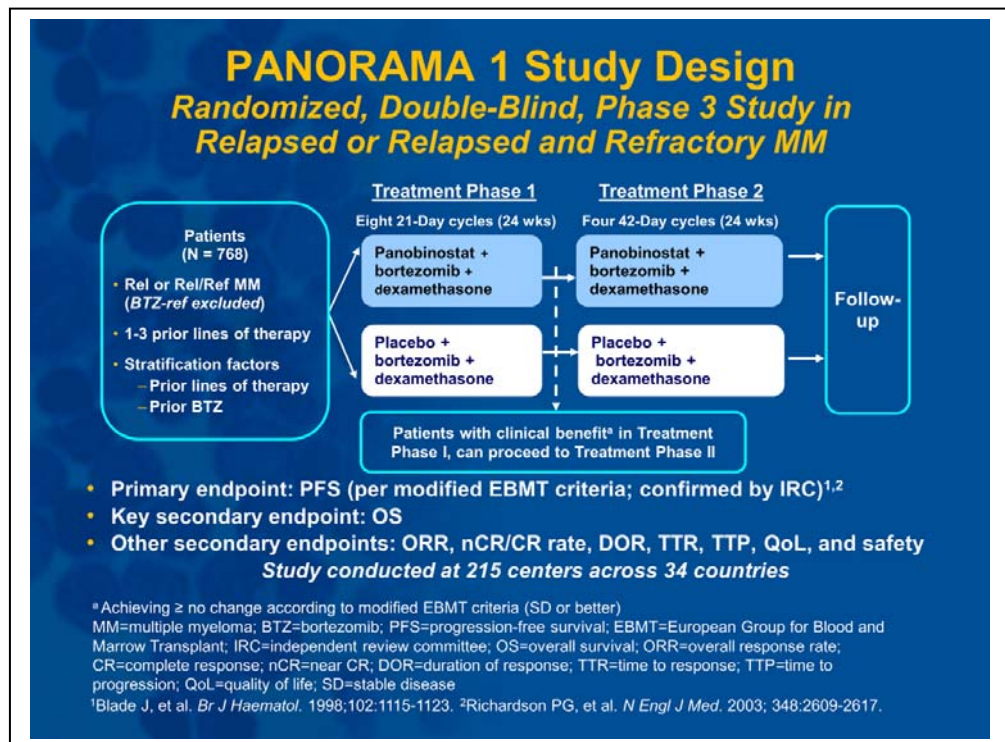
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Welcome to *Managing Myeloma*. My name is Antonio Palumbo, and I am a physician working at the Myeloma Unit of the University of Torino, Italy. Today, I am going to discuss integrating proteasome inhibitors plus either third-generation IMiDs or histone deacetylase inhibitor-based regimens for relapsed/refractory multiple myeloma.

We are now going to discuss three major new agents – proteasome inhibitors, histone deacetylase inhibitors, and the third-generation IMiD, pomalidomide. First of all, I would like to start by showing you the data from the PANORAMA study. Basically, this is a randomized study for patients with relapsed/refractory myeloma, who have had one to three prior lines of therapy or early salvage

regimens. This is a combination that includes panobinostat plus bortezomib and dexamethasone, and it has been compared with bortezomib and dexamethasone as the standard of care in terms of salvage regimens. You see here that there are two phases. Phase one consisted of eight 21-day cycles, followed by phase two, which used four 42-day cycles, and this, I think, is

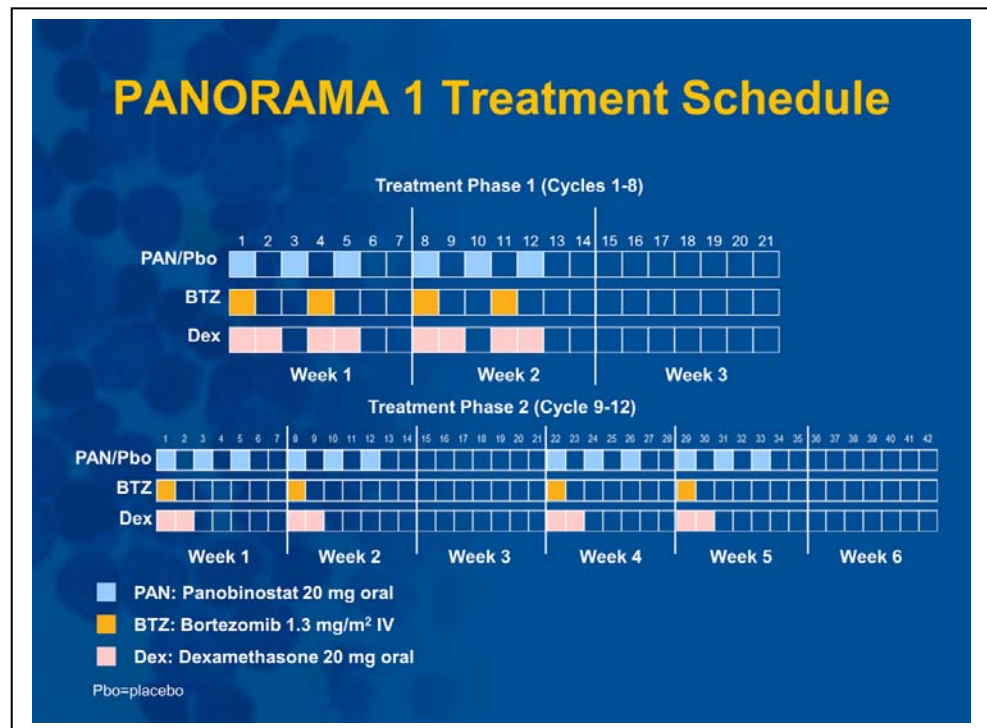


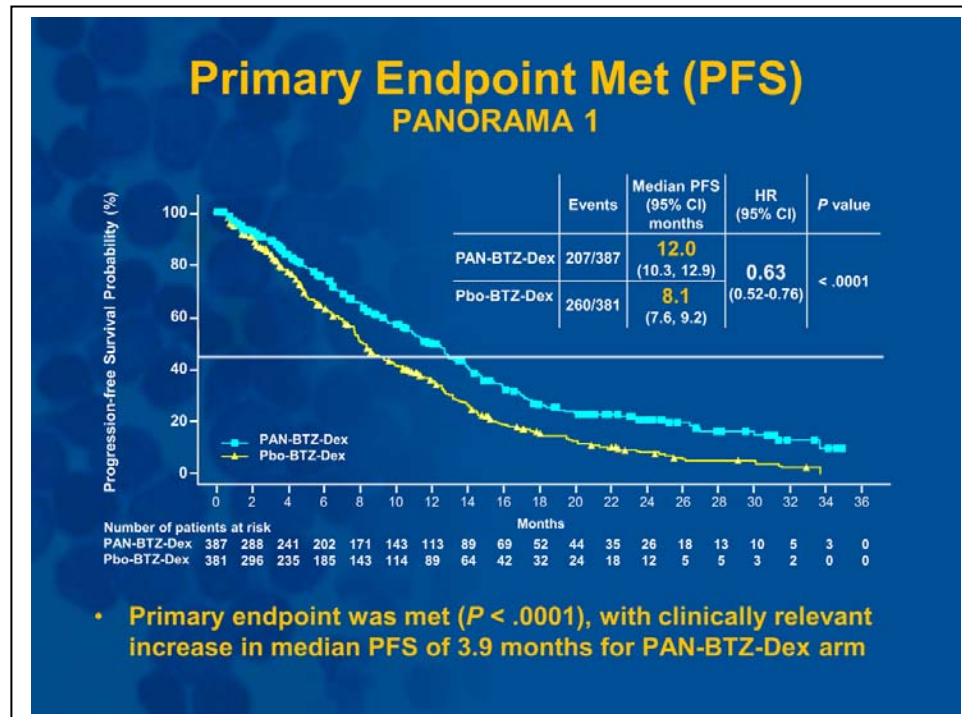
also important to highlight, as it demonstrates how we could use this regimen in different patients.

In this slide, we go into more detail about how to use this combination that includes panobinostat in two phases, one and two, and you can see here two different schedules that you could use in different patients, once again according to the definition of fit versus frail patients. We can see the dose of panobinostat is 20 mg on days 1, 3, 5, 8, 10, and 12, every 21 days, with bortezomib given twice weekly on days 1, 4, 8, and 11, and

dexamethasone given at the standard dose of 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12. This could be considered the most intense regimen. Note that panobinostat should always be used every other day. The dose of panobinostat could be less than 20 mg, especially if the patient begins to experience side effects; it could be 15 mg, and bortezomib could be weekly, as opposed to twice weekly, and even the dose of dexamethasone can be reduced.

In phase 2, you will see another less intense approach, with panobinostat given on days 1, 3, 5, 8, 10 and 12, every 21 days. Remember that the dose of panobinostat can be reduced to 15 mg, or even 10 mg, but here, bortezomib is given weekly, and dexamethasone is given at a 40 mg dose, weekly. Remember these two opportunities: when panobinostat is given on a 3-week basis, with 2 weeks on and 1 week off, the dose can go from 20 mg to 15 mg, and bortezomib and dexamethasone can both go from a twice-weekly dose to a weekly basis.

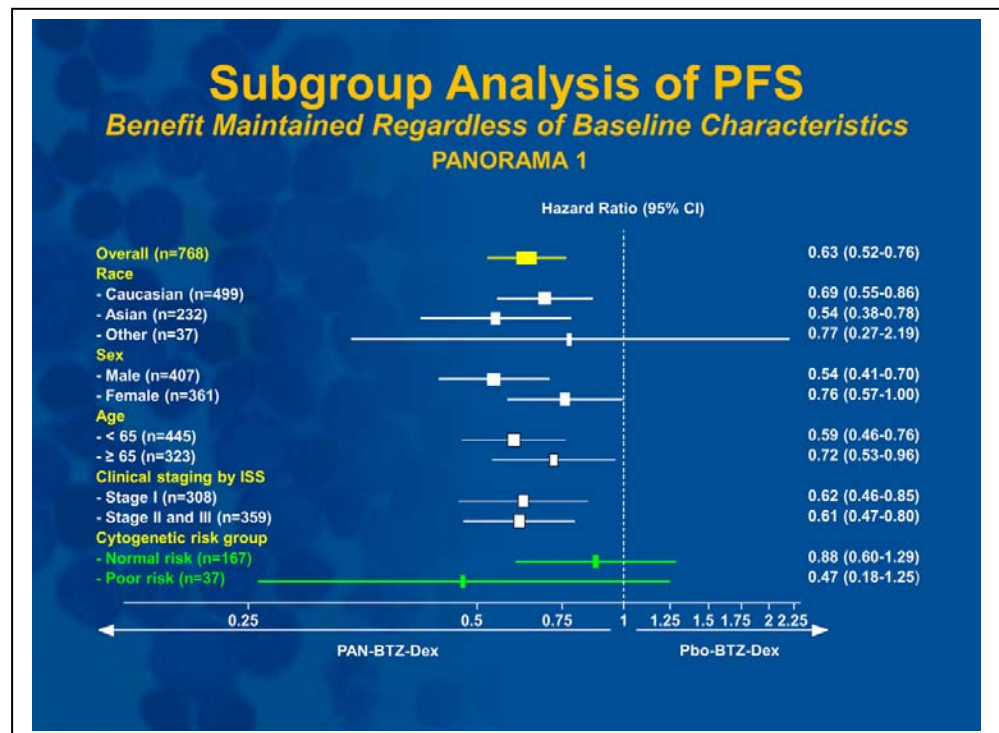


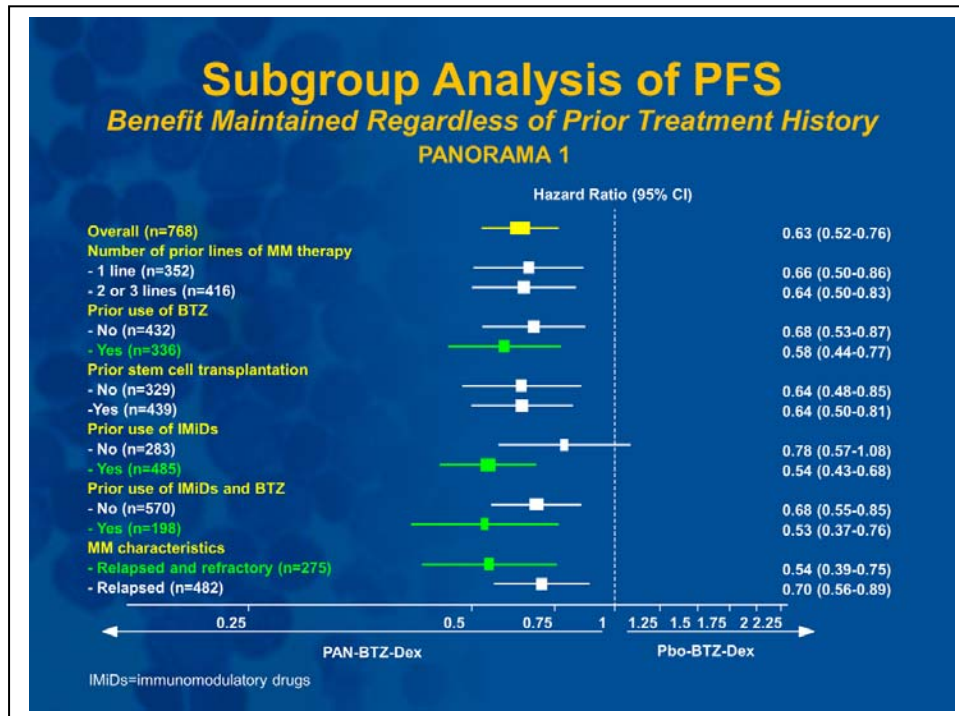


In this slide, we see the primary endpoint of progression-free survival, and this primary endpoint has been reached with an improvement in median progression-free survival that increased from 8 to 12 months, with a hazard ratio of 0.63, and a P value of less than 0.0001. Basically, this is a clear advantage for the use of this HDAC inhibitor, which is also a completely new

agent with a completely new mechanism of action. Certainly, this could be considered, especially when we are facing a condition of partial resistance to bortezomib.

In this forest plot, we define the subgroup analysis of progression-free survival. As you can see, there were no major differences from the different subgroups, although younger patients do better than older patients. This dosage of panobinostat might create some side effects, in terms of GI toxicity and thrombocytopenia, which is why it was also suggested to use a lower dose of 15 mg, and eventually, if that dose is well tolerated, to increase to 20 mg. The advantage is also present in both stage 1, as well as stage 2 and 3 disease, so I would say that there appears to be no major differences between high-risk or standard-risk patients with this regimen.

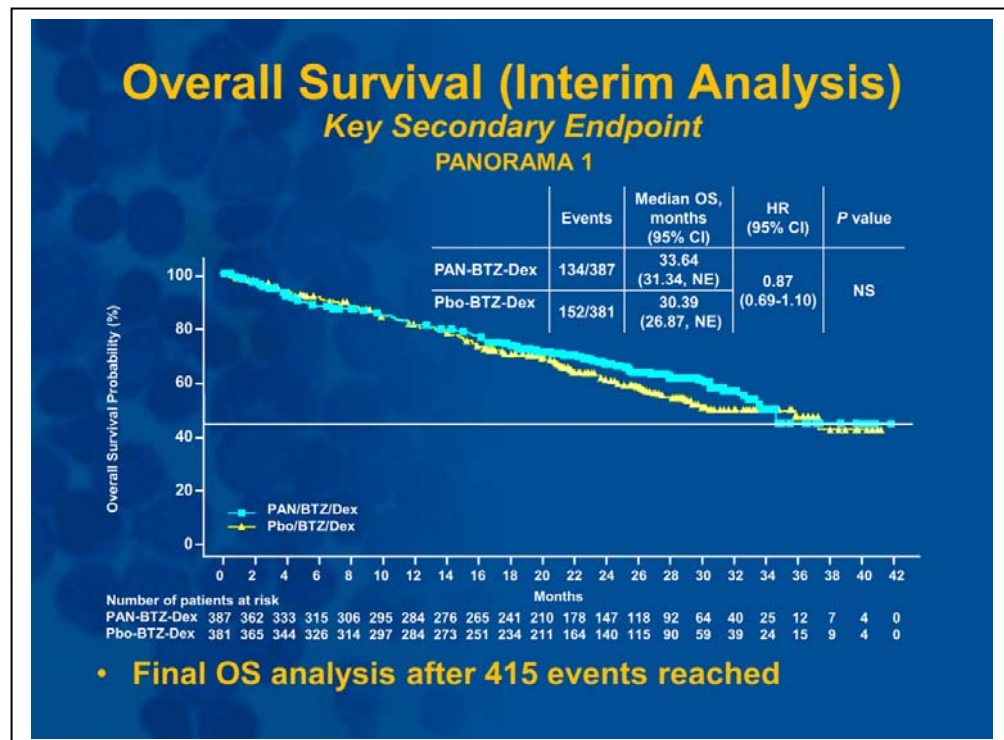




In this slide, we also see the advantage in progression-free survival is independent of the number of lines of therapy the patient has received. In this study, patients who had only one prior line of therapy had the same benefit in PFS as patients who had two or three prior lines of therapy. There was also no major difference in PFS for patients who had been previously treated with bortezomib versus those who had

not, although patients who had prior treatment with bortezomib seem to have an even greater advantage. Similar outcome were also seen for prior stem cell transplantation, for prior use of IMiDs, and for different characteristics in a relapsed or refractory condition.

In this slide, we see the overall survival data. This is early data, and not yet mature enough for a final analysis in this study, but, at present, we see no major differences in terms of overall survival when we compare the three-drug combination of panobinostat, bortezomib and dexamethasone, versus bortezomib and dexamethasone alone.



In terms of response rate, here you can see a combination of complete response (CR) and near CR rates of 27% for the three-drug combination versus 15% for bortezomib and dexamethasone alone, with a *P* value of 0.00006. This is a major difference, almost doubling the CR rate in patients using the three-drug combination that includes panobinostat.

From an efficacy point of view, there is certainly a major advantage with panobinostat as a compound with a completely new mechanism of action. Clearly, this is a way to overcome bortezomib resistance.

Efficacy: Response

PANORAMA 1

	PAN-BTZ-Dex (n = 387)	Pbo-BTZ-Dex (n = 381)	<i>P</i> value
ORR (PR or better) [95% CI]	60.7% [55.7, 65.6]	54.6% [49.4, 59.7]	.087
CR/nCR rate [95% CI]	27.6% [23.2, 32.4]	15.7% [12.2, 19.8]	.00006*
Median DoR [95% CI]	13.1 mos [11.8, 14.9]	10.9 mos [9.2, 11.8]	N/A
Median TTR [95% CI]	1.5 mos [1.4, 1.6]	2.0 mos [1.6, 2.8]	N/A
Median TTP [95% CI]	12.7 mos [11.8-14.9]	8.5 mos [7.7-9.7]	N/A

*Post-hoc analysis

- **CR/nCR rate was nearly doubled vs control arm (sCR in PAN arm 2%, vs 0% Pbo arm)**
- **Clinically meaningful improvements in median DoR and TTP**

PR=partial response; sCR=stringent complete response

Non-Hematologic AEs

Grade 3/4 Diarrhea and Asthenia/Fatigue Observed

PANORAMA 1

	PAN-BTZ-Dex (n = 381)		Pbo-BTZ-Dex (n = 377)	
Preferred term – %	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhea	68.2	25.5	41.6	8.0
Peripheral neuropathy ^a	60.6	17.6	67.1	14.6
Asthenia/fatigue	57.0	23.9	40.6	11.9
Nausea	36.2	5.5	20.7	0.5
Peripheral edema	28.6	2.1	19.1	0.3
Decreased appetite	28.1	3.1	12.5	1.1
Constipation	26.8	1.0	32.6	1.1
Pyrexia	26.0	1.3	14.9	1.9
Vomiting	25.7	7.3	13.0	1.3
Cough	21.3	1.0	18.6	0

- **Discontinuation due to diarrhea (4.5%) and fatigue (2.9%) on PAN arm**

^aCombined incidence of hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy.

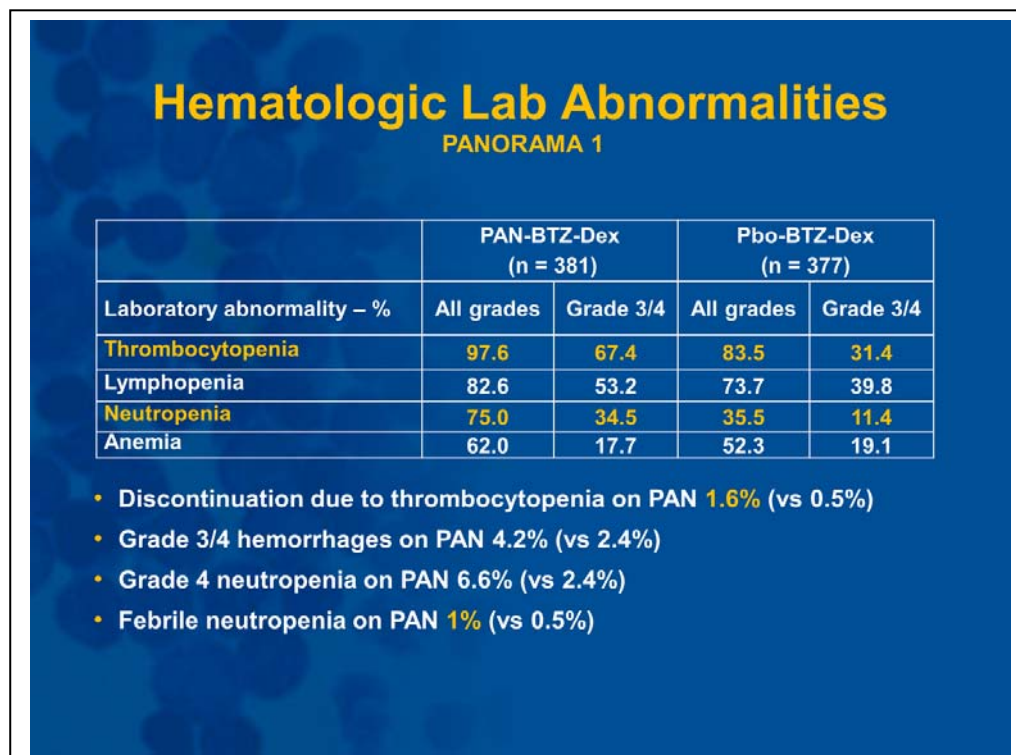
In this slide, you can see the non-hematologic side effects that were reported. Here, the issue we probably have to pay more attention to is diarrhea, as I was saying before, with a GI toxicity that increases from 8% with the two-drug combination to 25% with the three-drug regimen. So here, in my opinion, the

major suggestion is to start with a lower dose, even 10 mg at the first cycle, to see if that is well-

tolerated and then, certainly if the patient tolerates the lower dose, to increase to 15 mg in the second cycle, and then subsequently to 20 mg. So, when we're faced with a patient with comorbidities, when we do not feel confident to immediately start with a full dose, this dose escalation may represent a way to limit the major issue related to GI toxicity.

Peripheral neuropathy is as expected, at 17%, but this is mainly due by the twice-weekly infusion, so once again, a once-weekly infusion could certainly overcome this issue. Grade 3–4 fatigue was present in 23% of patients versus 12% in the bortezomib-dexamethasone arm. All other side effects are basically in the same range, and no major increase has been detected with the three-drug combination.

Here you can see the hematologic toxicities reported, and once again, we see the other major side effect of this combination, thrombocytopenia: 67% of patients taking the three-drug combination experienced grade 3–4 thrombocytopenia versus half that amount, 31%, for grade 3–4 thrombocytopenia seen in the bortezomib and dexamethasone



alone group. So, once again, to reduce the incidence of thrombocytopenia, at the beginning, you can start with the lower dose and make sure that the patient can tolerate the dose that you're using, and then increase the dose to increase the efficacy of the combination. We saw 34% grade 3–4 neutropenia with the three-drug combination versus 11% in the control arm, and there wasn't a major difference in anemia between the two groups.

So, if I can close on this issue, the main message is that HDAC inhibitors are new class of drug, with a completely new mechanism of action. These drugs are certainly important in patients previously exposed to bortezomib with suboptimal response to bortezomib, and they are clearly effective in terms of progression-free survival. We need to pay attention to GI toxicity and thrombocytopenia, and to start with a lower dose of 10 mg or 15 mg, and eventually reach the maximum dose of 20 mg to reduce the risk of GI toxicity and thrombocytopenia.

We're now going to talk about another major opportunity, and that is Car-Pom-d, the combination of carfilzomib, pomalidomide, and dexamethasone. Something to remember here is that carfilzomib is a second-generation proteasome inhibitor, so we might use it after

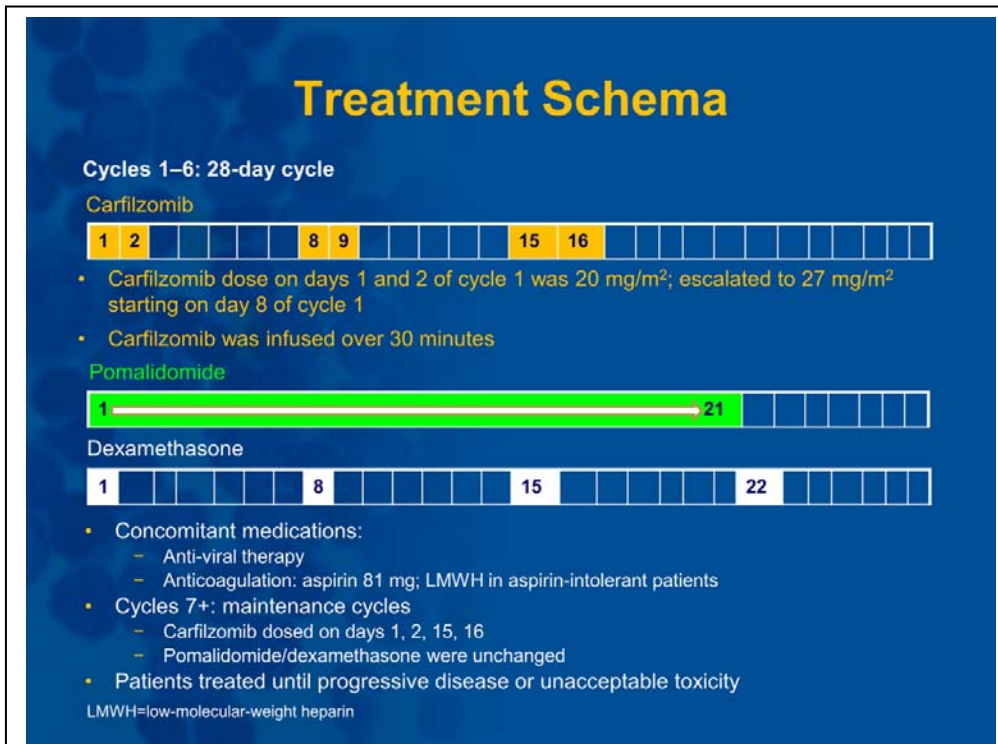
A Multi-Center Phase I/II Trial of Carfilzomib and Pomalidomide with Dexamethasone (Car-Pom-d) in Patients with Relapsed/Refractory Multiple Myeloma

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Academic Myeloma Consortium (AMyC)

bortezomib. On the other hand, pomalidomide is a third-generation IMiD, and can be used after lenalidomide. So, typically, a VRD induction could be followed by carfilzomib, pomalidomide, and dexamethasone salvage. Here, we're moving from the third to the second proteasome inhibitor compound and from the lenalidomide to pomalidomide. Once we use them at diagnosis, we can salvage with carfilzomib and pomalidomide combination.



This is the treatment schema for Car-Pom-d. You can see here that the treatment of carfilzomib is the standard: we do start at a dose of 20 mg, on days 1 and 2 of cycle 1 only, and thereafter, we move to a standard dose, the 27 mg/m² that can be used thereafter without any change. Carfilzomib

should be delivered on days 1, 2, 8, 9, 15, and 16; so, twice-weekly for 3 weeks, with the last week without treatment, and so the cycle is every 24 days. The number of cycles can be delivered continuously throughout the different cycles. Pomalidomide should be used at the usual dose of 4 mg, from day 1 to 21, with 1 week without treatment, once again on the 28-day basis. Dexamethasone can be given at its typical weekly dose, at 40 mg or 20 mg, according to age and toxicity, on days 1, 8, 15, and 22, every 28 days. We could even split the dose of dexamethasone and use a lower dose, so that, instead of 40 mg on day 1, you give 20 mg on days 1 and 2. By splitting the dose of dexamethasone, this combination could be even better tolerated. The treatment is given until progression or, of course, unacceptable toxicity.

This is the key inclusion criteria for this study. Of course, these patients were heavily treated, and they needed to be refractory, defined as less than 25% response or progressing during therapy or within the 60 days after completion of the previous regimen. So, usually, pomalidomide needs to be used after lenalidomide, after there is proof that the lenalidomide is not working any longer; this means a response that is less than 25% progression during therapy or progression within 60 days from the stop of the previous regimen.

Key Inclusion Criteria

- Relapsed and/or refractory multiple myeloma
- All patients must have received prior lenalidomide therapy and have been determined to be refractory
 - Refractory defined as $\leq 25\%$ response or progression during therapy or within 60 days after completion of a regimen
 - Patients must have had full or maximally tolerated dose of lenalidomide administered for a minimum of at least two completed cycles of therapy
- Measurable disease
- ECOG 0–2
- Adequate hematologic, renal, liver, and cardiac function

Prior Therapies Received

Therapy, n (%)	
Prior stem cell transplant	44/74* (59%)
Prior bortezomib**	66/74* (89%)
Prior lenalidomide	79/79 (100%)
Lenalidomide-refractory	79/79 (100%)

* Five patients did not have complete prior therapy data available

** Includes multiple bortezomib combinations

**29 of 32 (91%) patients in the phase I portion were bortezomib-refractory

And you can see that here that these patients were clearly very, very heavily pre-treated: 60% of patients received a prior stem cell transplant, 90% of patients received prior bortezomib, and, of course, as defined by inclusion criteria, 100% were refractory to lenalidomide.

In this slide, we see the treatment-

related hematologic adverse events. Carfilzomib is probably one of the best drugs to use in a combination, because its hematologic toxicity is very limited. So, for a patient in an advanced stage of disease with a low platelet count, it is not certain whether we can increase the risk of

thrombocytopenia. You can see here, though, that the risk of neutropenia for all grades, or even thrombocytopenia, is around 30%. So, this means that this combination is very, very well tolerated from a hematologic point of view, and certainly, carfilzomib is not adding an extra hematologic toxicity over what can be seen with the use of pomalidomide and dexamethasone alone.

Treatment-Related Hematologic Adverse Events (N=79)

Adverse event	Grade 1, n	Grade 2, n	Grade 3, n	Grade 4, n	All grades, n (%)
Neutropenia	0	4	17	6	27 (34%)
Anemia	1	10	13	1	25 (32%)
Thrombocytopenia	4	7	6	5	22 (28%)
Febrile neutropenia	0	0	3	0	3 (4%)

- Toxicities were generally reversible and manageable

Here you can see the risk of treatment-related non-hematologic adverse events, and once again, the major differences were risk-related fatigue, of all grades, which was 40%, with dyspnea at around 28%, and pneumonia at 10%, which is quite acceptable. Here, I would like to highlight few issues. First, carfilzomib does not have any peripheral neuropathy, so, from this point of

view, if there is a preexisting peripheral neuropathy, it is a clear inclusion criteria and a selection for the Car-Pom-d combination. There is a small signal in terms of the risk of cardiac side effects, which was, in this study, 3%. What is important here is to check the patient's blood pressure before infusion of carfilzomib and 10 minutes after the end of the infusion of carfilzomib, and then 1 to 2 hours after the end of the infusion of carfilzomib. This will allow you to avoid, and to be able to treat the patients who are experiencing, hypertension, and who might then have, in the combination with dexamethasone, an increased risk of some cardiac side effects. So, it is very important to check the patient's blood pressure and treat the hypertension immediately after the infusion of carfilzomib and 1 to 2 hours later, and if there is a clear sign of hypertension, to treat this condition. Other than that, there are no major side effects with this combination, from this point of view. DVT is not a major issue and there are no other major problems, in terms of toxicities.

Treatment-Related Non-Hematologic Adverse Events (N=79)

Adverse event, n	Grade 1, n	Grade 2, n	Grade 3, n	Grade 4, n	All grades, n (%)
Fatigue	10	20	3	0	33 (42%)
Dyspnea	12	9	1	0	22 (28%)
Muscle spasms	11	3	0	0	14 (18%)
Diarrhea	6	5	2	0	13 (16%)
Skin, rash, pruritus	7	1	2	0	10 (13%)
Pneumonia*	0	2	6	0	9 (11%)
Hypocalcemia	5	3	0	0	8 (10%)
Creatinine elevated	3	2	0	1	6 (8%)
Peripheral sensory neuropathy	2	2	1	0	5 (6%)
DVT/PE/VTE*	0	4	0	0	5 (6%)
Cardiac failure, congestive	0	0	2	0	2 (3%)

*1 grade 5 pneumonia event and 1 grade 5 pulmonary embolism event; both treatment-related
DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism

Clinical Activity: Response Rates

Best overall response	N=79
VGPR	21 (27%)
PR	34 (43%)
MR	10 (13%)
SD	13 (16%)
PD	1 (1%)

-ORR = 70%
CBR = 83%

VGPR=very good partial response; MR=minimal response; PD=progressive disease; CBR=clinical benefit rate

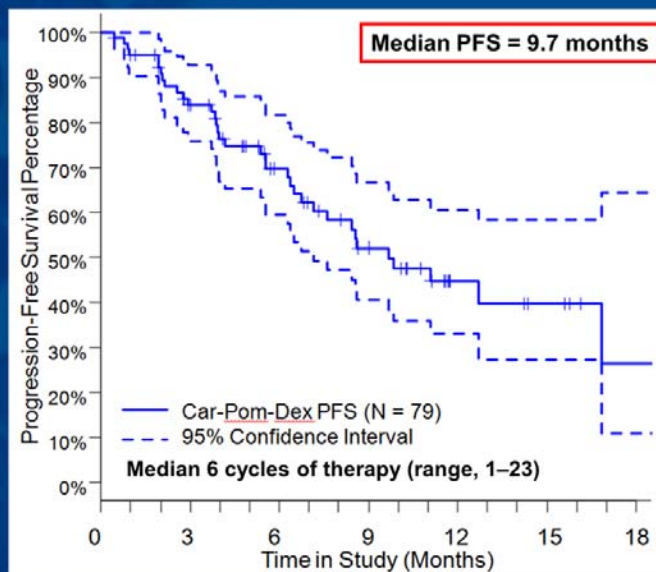
In this slide, we show the clinical activity, which is very interesting, because the response rate was 70%, and, as you know, the response rate of pomalidomide and dexamethasone is around 30%. The response rate of the three-drug combination can be double the two-drug combination, even with a 30% VGPR rate.

Basically, I think

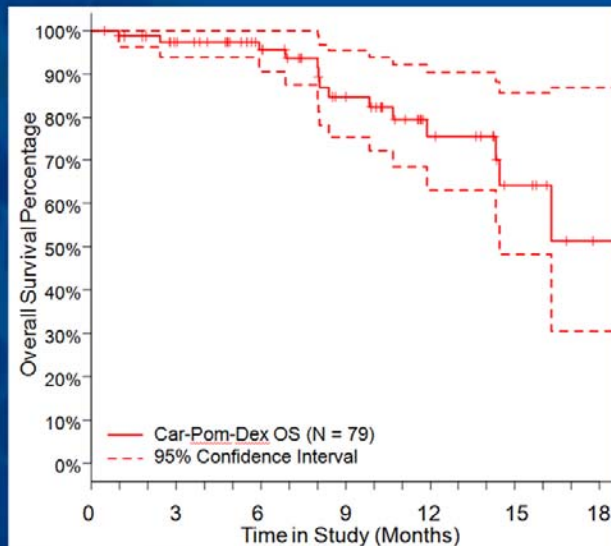
this three-drug combination can double the efficacy that you can see with pomalidomide and dexamethasone, with a clinical benefit that is present in over 80% of those patients.

Here is the progression-free survival with the Car-Pom-d combination in this very advanced stage of disease; the median number of previous treatment regimens in these patients was five. So we're talking about patients with a very advanced stage of disease, and, as you can see, the median progression-free survival was almost 10 months....

Progression-Free Survival



Median Overall Survival Not Reached at 18 Months



...with a median overall survival that has not yet been reached at 18 months.

So, certainly, we can conclude that this three-drug combination is the optimal salvage after VRD. It combines the new proteasome inhibitor and an IMiD together, to maximize the efficacy of a salvage regimen. We should clearly define that, with a VGPR rate of 27%, a progression-free survival of 10 months, and a duration of response of almost 18 months, this might represent one of the optimal regimens to use in not-so-late stages of disease, in the early phase of the salvage.

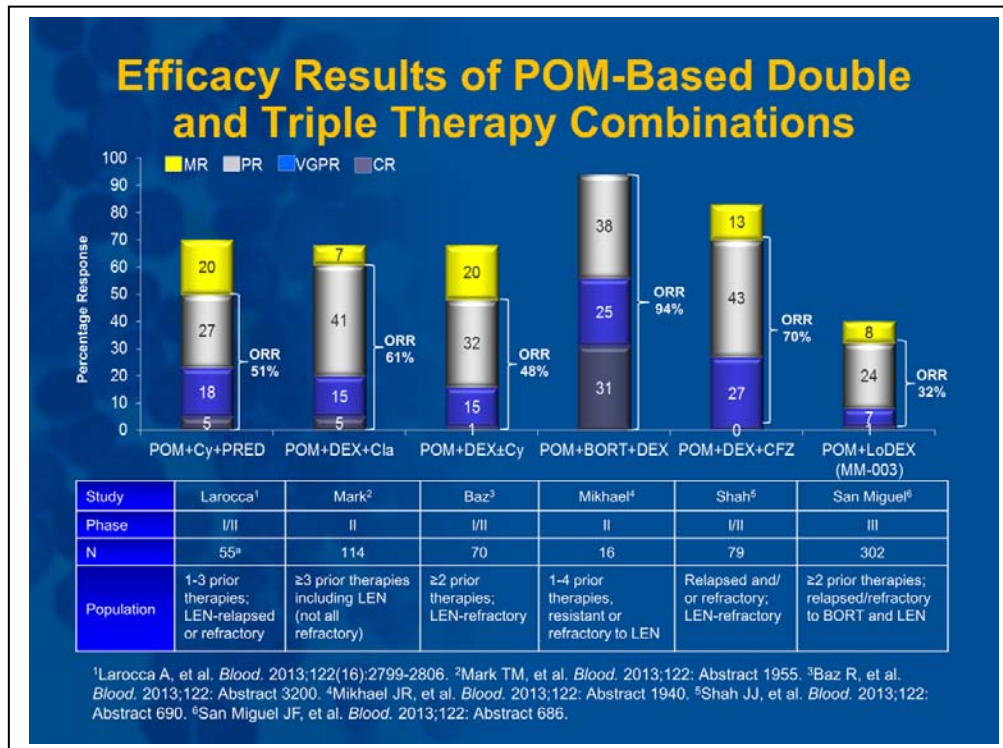
Conclusions

- The combination of Car-Pom-d is highly active in this heavily pretreated, lenalidomide-refractory patient population
 - Patients had received a median of 5 prior lines of therapy; 49% of patients had high/intermediate risk cytogenetics at baseline

▪ ≥ VGPR	27%
▪ ORR	70%
▪ CBR	83%
▪ DOR (median)	17.7 months
▪ PFS (median)	9.7 months
▪ OS (median)	>18 months

- Response rates, PFS, and OS were preserved independent of FISH/cytogenetic risk status
- The regimen was well tolerated with no unexpected toxicities
- Enrollment is nearly complete in this phase II trial; subsequent dose escalation of carfilzomib in less heavily treated patients with 1–3 lines of prior therapy is planned

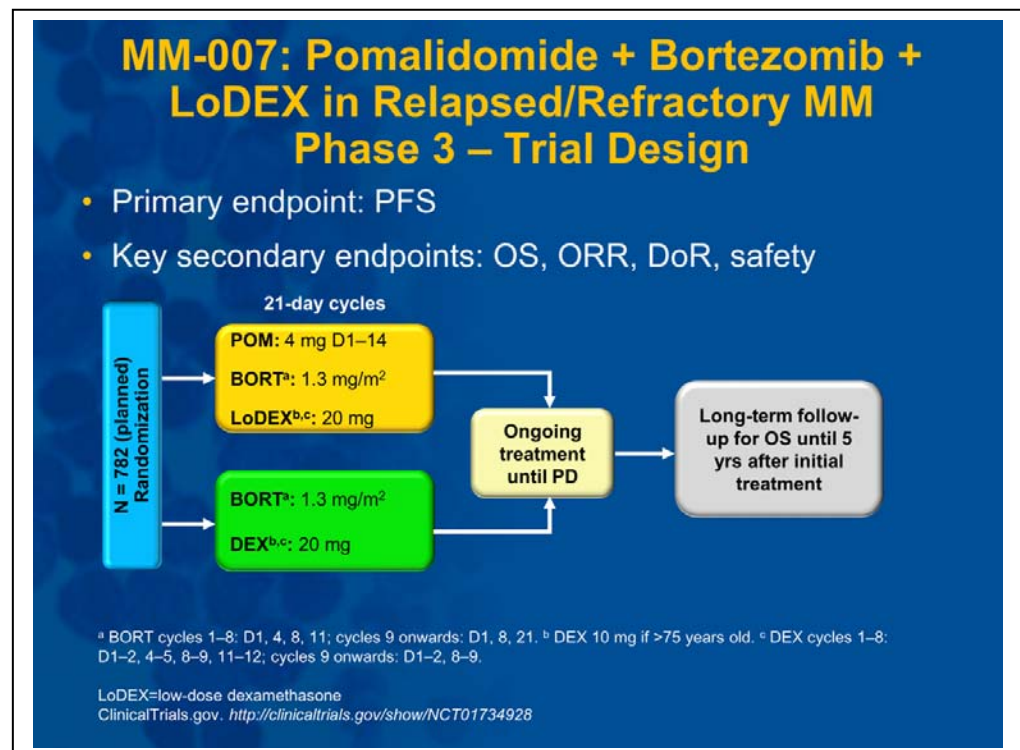
Car-Pom-d=carfilzomib-pomalidomide-dexamethasone; FISH=fluorescence in situ hybridization



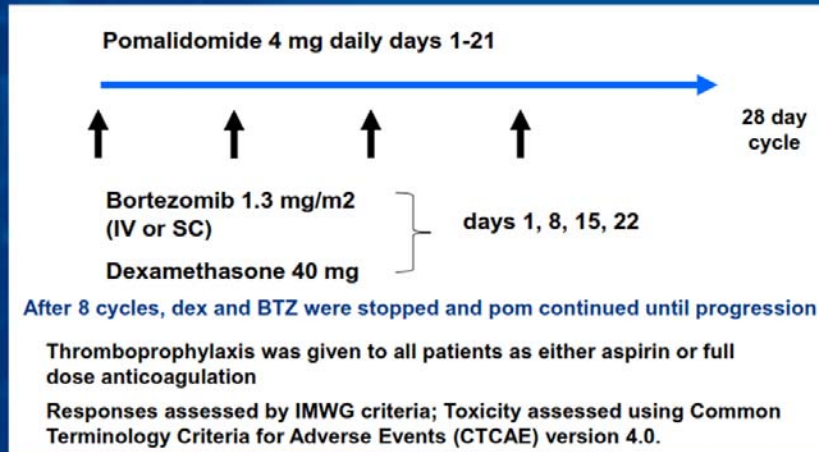
Now, to change gears, we'll move to the combination of bortezomib, pomalidomide, and dexamethasone. As you can see in this slide, the three-drug combination is clearly increasing the efficacy of bortezomib and dexamethasone, and certainly, the combination of pomalidomide, bortezomib, and dexamethasone

is the best among the three-drug combination with an overall response rate of almost 90%.

This slide summarizes how we use this combination of pomalidomide, bortezomib, and dexamethasone. We use pomalidomide at 4 mg, from days 1 to 14, and bortezomib at the usual dose, with low dexamethasone on a 21-day cycle.



Treatment



Lacy MQ, et al. *Blood*. [ASH Annual Meeting Abstracts] 2014;124(21):abstract 304.

This slide summarizes another way to deliver this combination. In this approach, you can use a 28-day cycle with weekly infusions of bortezomib on days 1, 8, 15, and 22, and the usual dose of pomalidomide 4 mg on a daily basis from days 1 to 21, with the usual weekly infusion of dexamethasone 40 mg. This treatment schema

is probably slightly better, with a reduced risk of peripheral neuropathy; I would certainly prefer this schema. One question is how to differentiate between the choice of carfilzomib versus bortezomib. Certainly, bortezomib can be used if the patient has had no previous exposure to bortezomib, or had an excellent previous response to bortezomib; otherwise, certainly, carfilzomib or panobinostat might represent a better choice following a previous exposure to bortezomib.

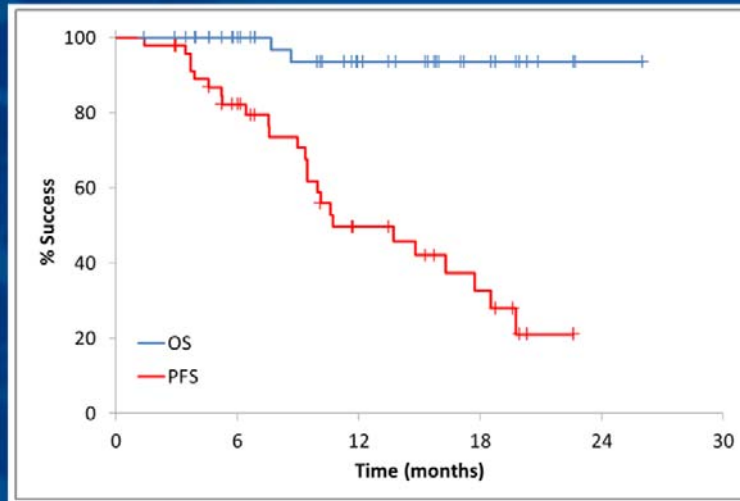
These are the outcomes data, and, you can see a 45% VGPR rate. The study did have small numbers, but certainly, a 45% VGPR rate is an important achievement.

Patient Outcomes

	N=47
Response Rate	85%
No. of Responders	40
sCR	3
CR	6
VGPR	12
PR	19
	45% VGPR+
Overall Survival, median	NA
%Event Free at 6 mo	100%
%Event Free at 12 mo	94%
Progression Free Survival, median	10.7 mo (95%CI: 9.4-18.5)
Duration of Response, median	13.7 mo (95%CI: 8.5-16.8)

Lacy MQ, et al. *Blood*. [ASH Annual Meeting Abstracts] 2014; 124(21):abstract 304.

OS and PFS

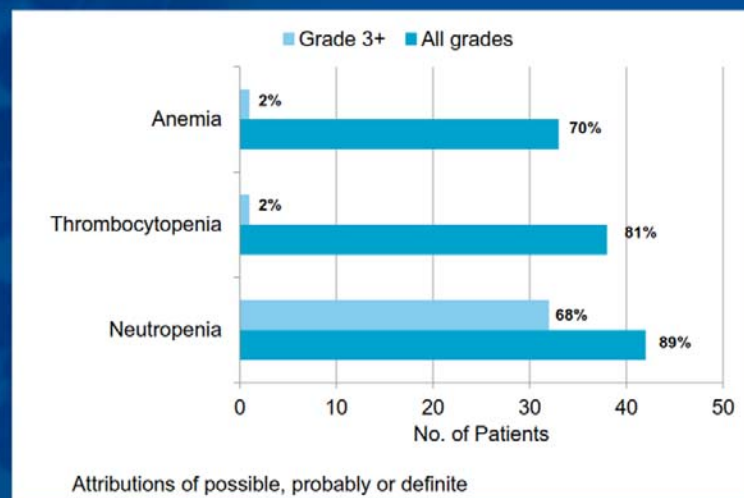


Lacy MQ, et al. *Blood*. [ASH Annual Meeting Abstracts] 2014;124(21):abstract 304.

And here, you can see both the progression-free survival is once again in the range of 1 year, with an overall survival that is very good but certainly also too early to define.

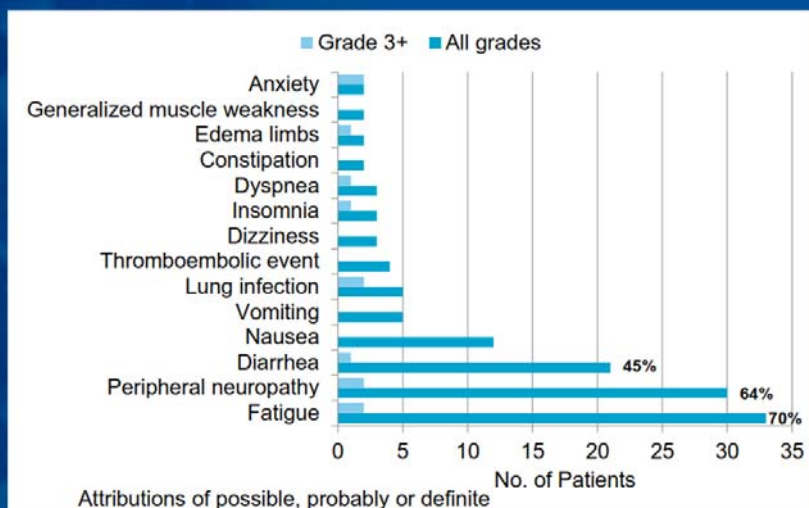
This slide summarizes the reported hematologic toxicities, across all grades. These are, as you can see here, very limited to some extent. These patients were not so highly exposed to previous regimens, and thrombocytopenia of grade 3–4 is around 2% to 3%, although there is some grade of some thrombocytopenia in 80% of all patients.

Hematologic Toxicity



Lacy MQ, et al. *Blood*. [ASH Annual Meeting Abstracts] 2014;124(21):abstract 304.

Non-Hematologic Toxicity



Lacy MQ, et al. *Blood*. [ASH Annual Meeting Abstracts] 2014;124(21):abstract 304.

If we look at the reported non-hematologic toxicities, once again, we see what we usually see: peripheral neuropathy is present in 60% of patients, with other reported non-hematologic malignancies that include fatigue, and diarrhea, as well. Certainly, this is a safety profile that is not so different from what we

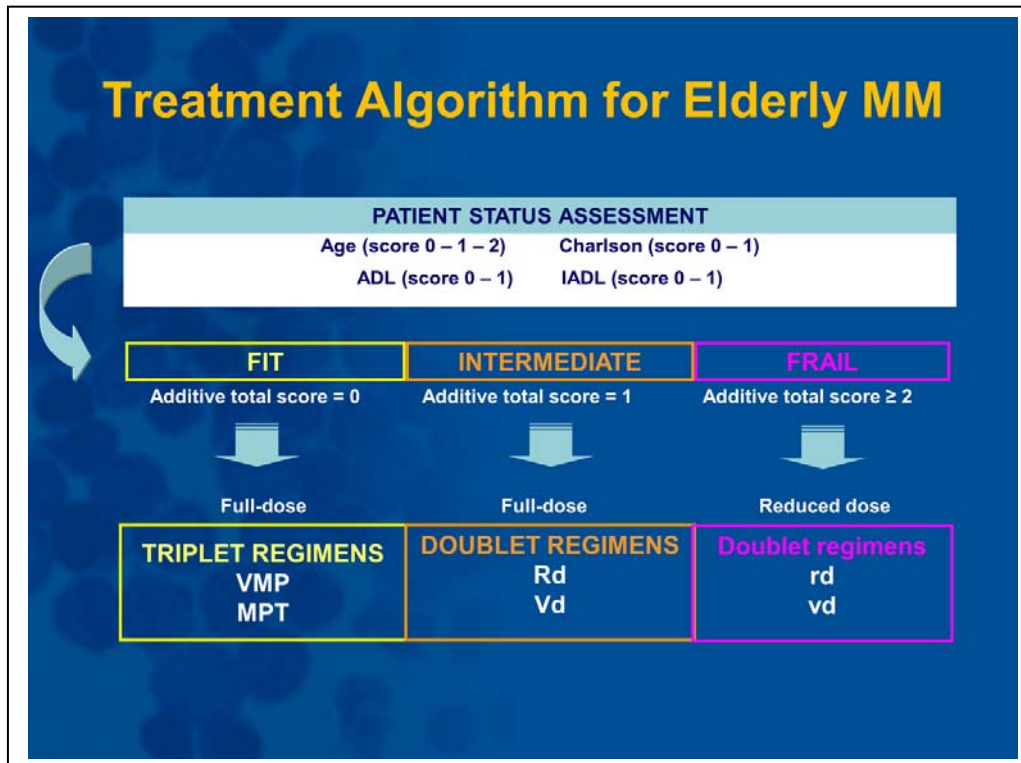
see with the combination of bortezomib, lenalidomide, and dexamethasone.

To close, we need to put a small emphasis on the need to define the fit versus the frail patients. We are aware that, without comorbidities, we become frail at the age of 80. We start to be frail at younger ages with comorbidities, so it is important to have the cutoff of 80 years of age in mind, and to check whether the patient has some other comorbidities, because the presence of some other comorbidities are certainly the sign of the frail condition.

New Treatment Algorithm for Elderly MM

Patient status assessment		
Age		
ADL		
IADL		
Charlson comorbidity score		
FIT	INTERMEDIATE FIT	FRAIL
Age <80 yr	Fit >80 yr	Unfit >80 yr
ADL 6	ADL 5	ADL ≤4
IADL 8	IADL 6-7	IADL ≤5
Charlson 0	Charlson 1	Charlson ≥2
Go-go	Moderate-go	Slow-go
Full-dose regimens Dose level 0	Reduced-dose regimens Dose level -1	Reduced-dose Palliative approach Dose level -2

ADL=activity of daily living; IADL=instrumental ADL
Palumbo A, et al. *Blood*. 2011;118:4519-4529.



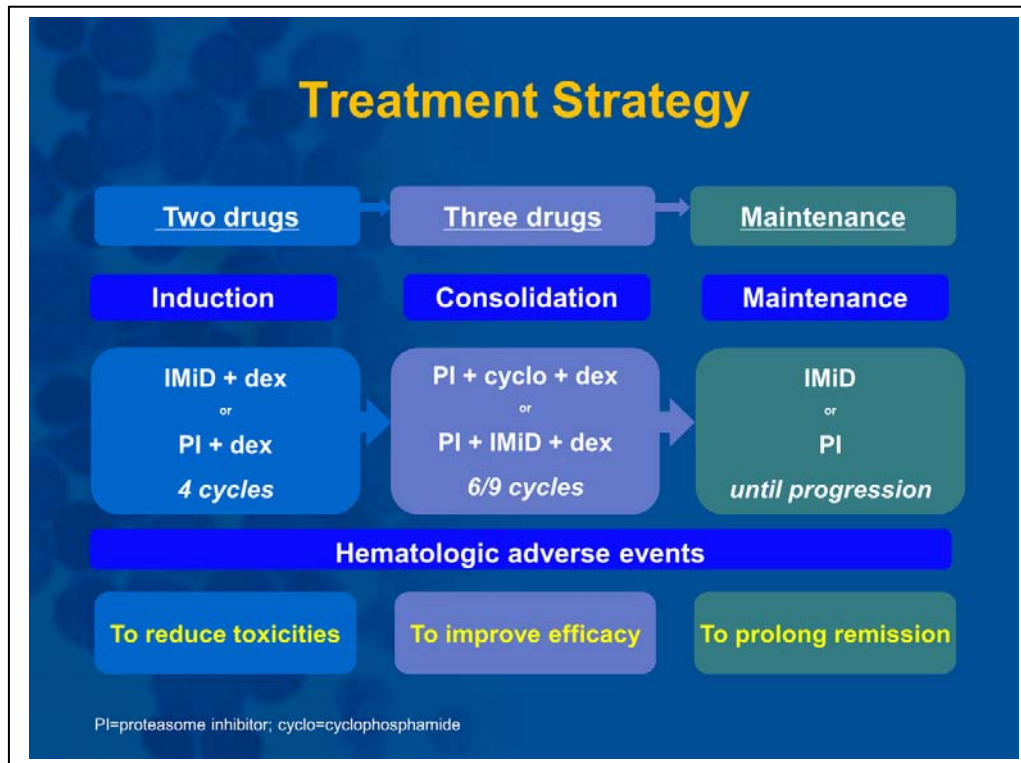
If we are in a frail condition, as you can see in this slide, we probably want to adjust our treatment, and we have two options. Option one is to move from a three-drug combination to a two-drug combination.

As you can see in this slide, a second option is to use the three-drug combination, but to reduce the dose of lenalidomide from 25 mg to 15 mg, bortezomib on a weekly basis from 1.3 mg/m² to 1 mg/m², carfilzomib from 27 mg to 20 mg, and panobinostat from the dose of 20 mg to 15 mg or even 10 mg. So, keep in mind that when we are facing a frail condition, we probably need to reduce the dose, to avoid and reduce the risk of toxicity.

Treatment Algorithm

DOSE LEVEL 0	DOSE LEVEL -1	DOSE LEVEL -2
Lenalidomide 25 mg/d d 1-21 / 4 wks	15 mg/d d 1-21 / 4 wks	10 mg/d d 1-21 / 4 wks
Thalidomide 100 mg/d	50 mg/d	50 mg/every other day
Bortezomib 1.3 mg/m ² d 1,8,15,22 / 5 wks	1.0 mg/m ² d 1,8,15,22 / 5 wks	1.3 mg/m ² d 1,15 / 4 wks
Melphalan 0.2 mg/kg/d d 1-4 / 5 wks	0.15 mg/kg d 1-4 / 5 wks	0.10 mg/kg d 1-4 / 5 wks
Prednisone 2 mg/kg/d d 1-4 / 5 wks	1.5 mg/kg/d d 1-4 / 5 wks	1 mg/kg/d d 1-4 / 5 wks

Palumbo A, et al. *N Engl J Med*. 2011;364:1046-1060.



Another issue that it is important and should be highlighted: when we are in a grey zone, we might start immediately with the two-drug combination, let's say pomalidomide and dexamethasone, and then, later on, to add the third agent, when we see that the two-drug combination is well-tolerated.

Once again, this is a way to reduce toxicity and maximize efficacy. So, we start with the two drugs, and after two to three cycles, we move to a three-drug combination to increase the efficacy and, to some extent, reduce toxicity.

To close, look at the therapeutic algorithm today. Basically, the induction is a three-drug combination of bortezomib and an IMiD: bortezomib, lenalidomide and dexamethasone plus transplant for the younger, and without transplant for the elderly; and we move to the two-drug combination for the frail condition. Certainly today, we have to keep in mind what we already have discussed during this presentation, that the moment we move

Future Therapeutic Algorithm

	Young	Fit Elderly	Frail Elderly
Diagnosis	VRD/VCD – ASCT	VRD/VCD	Rd
PI based Therapy	Carf-Rd	Carf-Rd	Ixa-Rd
MoAb based Therapy	Elo-Rd/Dara-Rd	Elo-Rd/Dara-Rd	Elo-Rd/Dara-Rd
Pom based Therapy	POM-BORT-LoDEX	POM-BORT-LoDEX	POM-LoDEX
HDAC based Therapy	Panob-Vd	Panob-Vd	Panob-Vd

ASCT=autologous stem cell transplant


from bortezomib, we move to carfilzomib, then we move to panobinostat, and we are looking, one after the other, for the drug that can overcome the previous resistance to a proteasome inhibitor. On the other hand, we move from lenalidomide to pomalidomide, once again to overcome the previous resistance to an IMiD.

So, in the treatment schema, if we start from VRD, you can certainly then move to a combination regimen that includes pomalidomide from one side, and a combination that includes carfilzomib or panobinostat on the other side. Keep in mind that we also now have a new option that includes the monoclonal antibodies, elotuzumab or daratumumab; these might represent an additional option for the salvage regimen. So, we have to choose between next-generation proteasome inhibitor-based therapy, monoclonal antibody-based therapy, and HDAC inhibitor-based therapy that can be also combined with IMiDs such as lenalidomide and pomalidomide.

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

Managing Myeloma's Regimen Protocols

- To support you in using the most appropriate therapies for your patients with multiple myeloma, *Managing Myeloma* has worked with clinical experts to develop this protocol series. Each protocol focuses on the latest information from clinical trials on prescribing, administering, and monitoring a new agent or regimen. In these practice resources, you'll find comprehensive, referenced guidance in the safe and effective use of therapies for your patients with this disease.



http://www.managingmyeloma.com/mtr/regimen-protocols