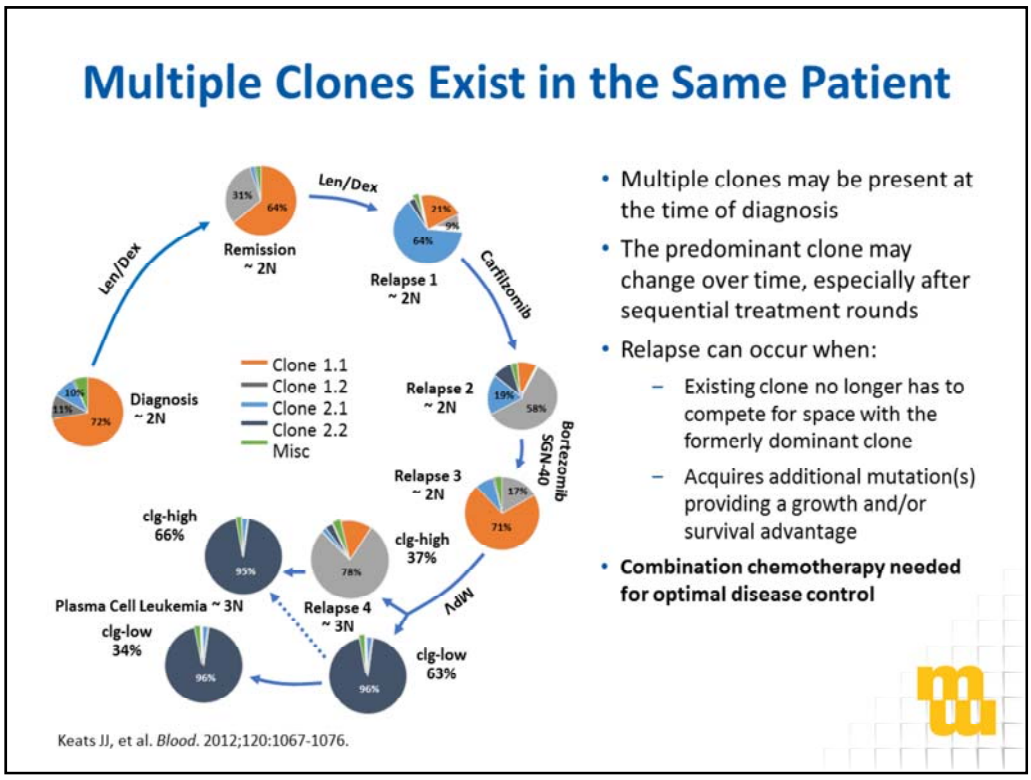
Individualizing Patient Care:
Navigating Drug Sequencing Strategies in Relapsed/Refractory Multiple Myeloma

Welcome to *Managing Myeloma*. I am Dr. Saad Usmani. In today's presentation, I will be discussing individualizing patient care by navigating drug sequencing strategies in relapsed/refractory multiple myeloma (RRMM). Our learning objectives today are: describing the appropriate assessments of the patient- and disease-related factors that impact drug sequencing strategies in RRMM, outline drug sequencing algorithms to guide therapeutic selection in specific patient populations with RRMM, and also recognize investigational strategies for sequencing drugs in RRMM, including the role of cytogenetics and gene expression. Let's begin.

Individualizing Patient Care:

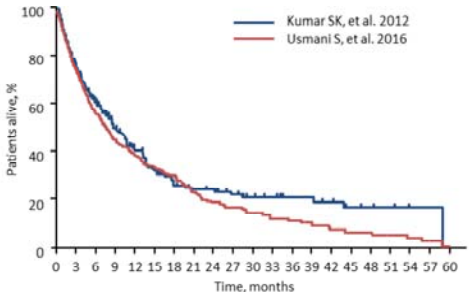
Navigating Drug Sequencing Strategies in Relapsed/Refractory Multiple Myeloma



Multiple myeloma clones exist in the same patient. We have previously believed myeloma to be, from an evolutionary standpoint, a static disease where events are happening sequentially, but we recognize now that the evolution is happening at the same time. There are multiple clones that are proliferating within the same patient and under duress from therapy; over time, different clones will emerge as the dominant clone. The predominant clone at the time of diagnosis may not necessarily be the one that comes back at the time of relapse. This was elegantly shown by Jonathan Keats, almost five years ago, where he looked at genomic sequencing of myeloma patients with sequential therapy. The point that he made with that paper was that, when relapse occurs, different clones may have acquired additional mutations while existing clones may not be as clinically relevant as the dominant ones; making the case for combination chemotherapy to optimally control the relapsed myeloma at that time.

Relapsed/Refractory Disease: Outcomes

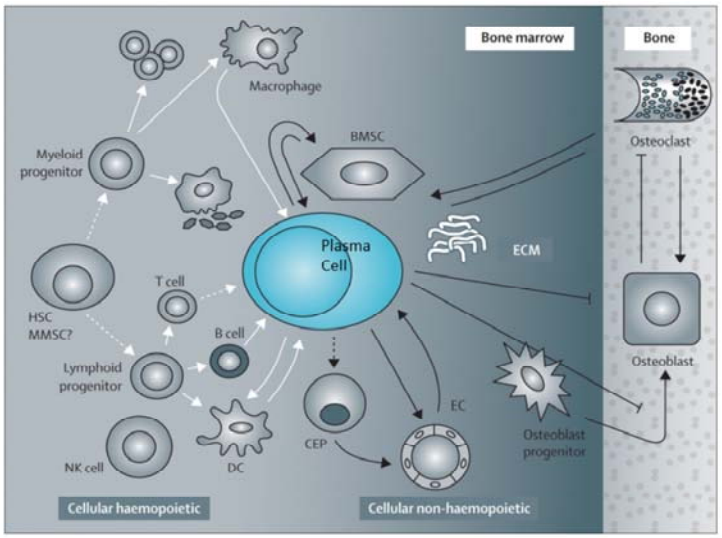
- Despite the introduction of IMiDs and PIs, most patients relapse and outcomes are poor in relapsed or refractory patients[1]
  - Median OS of 9 months in patients refractory to bortezomib and ≥1 IMiD[1]
  - Median OS of 8 months in patients with relapsed or refractory MM who were double refractory or had relapsed after ≥3 prior lines of therapy, including pomalidomide and carfilzomib[2]



IMiDs=immunomodulatory drugs; PIs=proteasome inhibitors; OS=overall survival; MM=multiple myeloma
[1]Kumar SK, et al. *Leukemia*. 2012;26(1):149-157.
[2]Usmani S, et al. *Oncologist*. 2016. doi:10.1634/theoncologist.2016-0104.

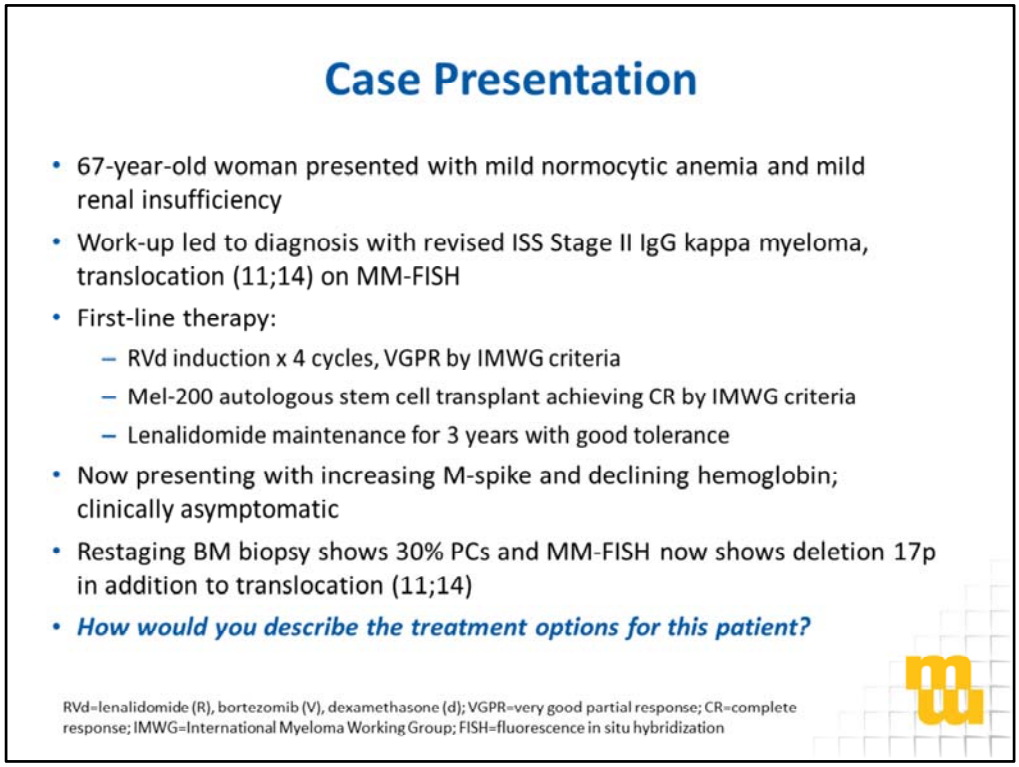
One also has to recognize that the outcomes of relapsed/refractory myeloma patients is poor overall, especially those who become refractory to both proteasome inhibitors (eg, bortezomib) or immunomodulatory drugs. About five years ago, Dr. Shaji Kumar published an experience on those patients showing the median overall survival being about nine months. What we looked at in a subsequent study is, despite the introduction of pomalidomide and carfilzomib in the armamentarium of relapsed/refractory myeloma management, the median overall survival of patients was still about eight months if they are double refractory or have had relapsed disease after three or more prior lines of treatment.

Myeloma Cells Rely on the Bone Marrow Microenvironment for Survival and Proliferation

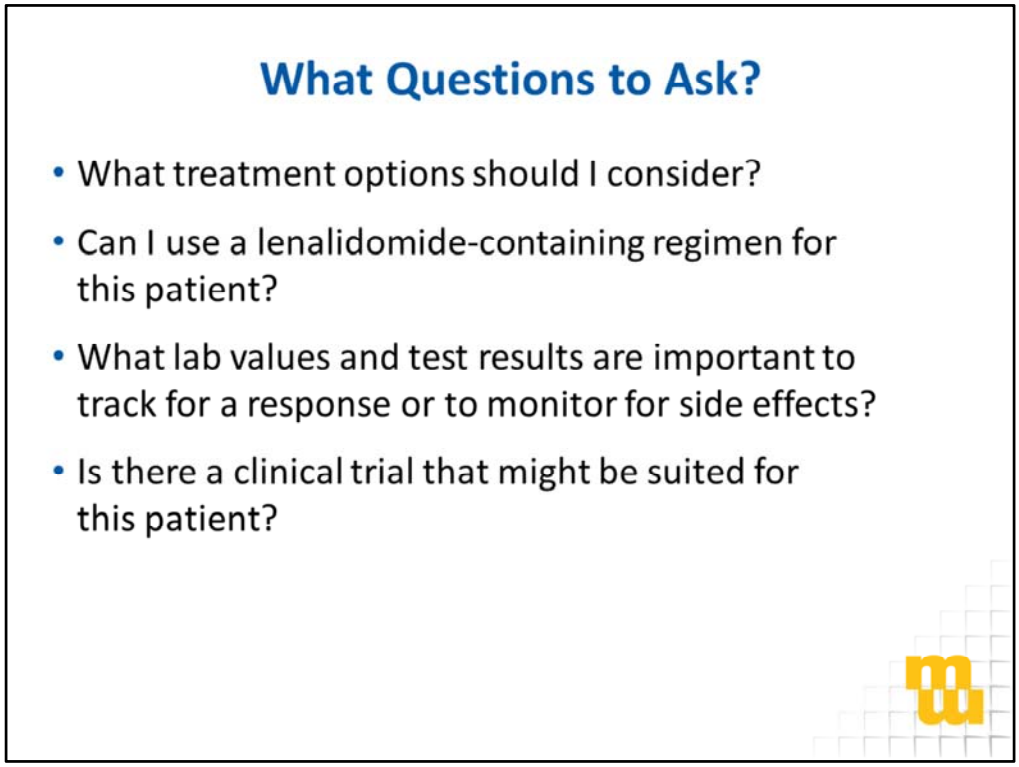


Adapted from Raab MS, et al. *Lancet*. 2009;374(9686):324-339.

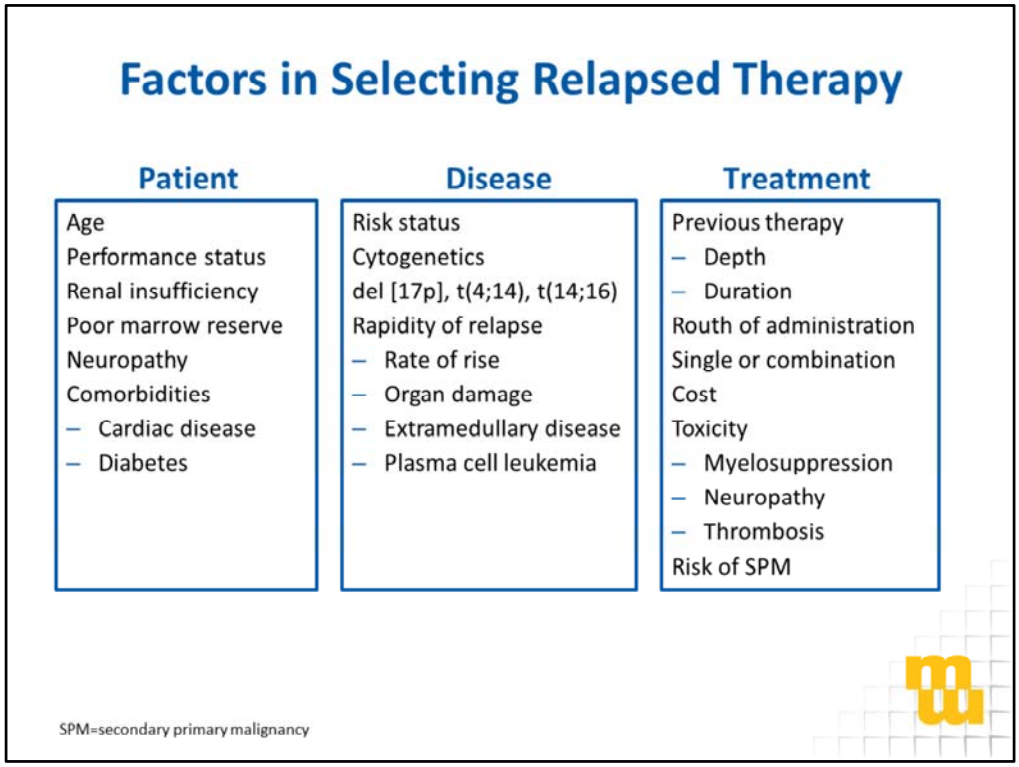
It is not simply about the myeloma cell on its own. The myeloma cell is also relying on its bone marrow microenvironment counterpart – its neighbors – for survival and proliferation. This is where the concept of employing therapies that are not simply just targeting the myeloma cell, but also the tumor microenvironment, the immune repertoire comes into play. The bone marrow stromal cells, the T-cells, B-cells (especially the regulatory T- and B-cells), and DCs play an important role in the survival and proliferation of malignant plasma cells in the bone marrow. We are now thinking of developing strategies that include those mechanisms of action.



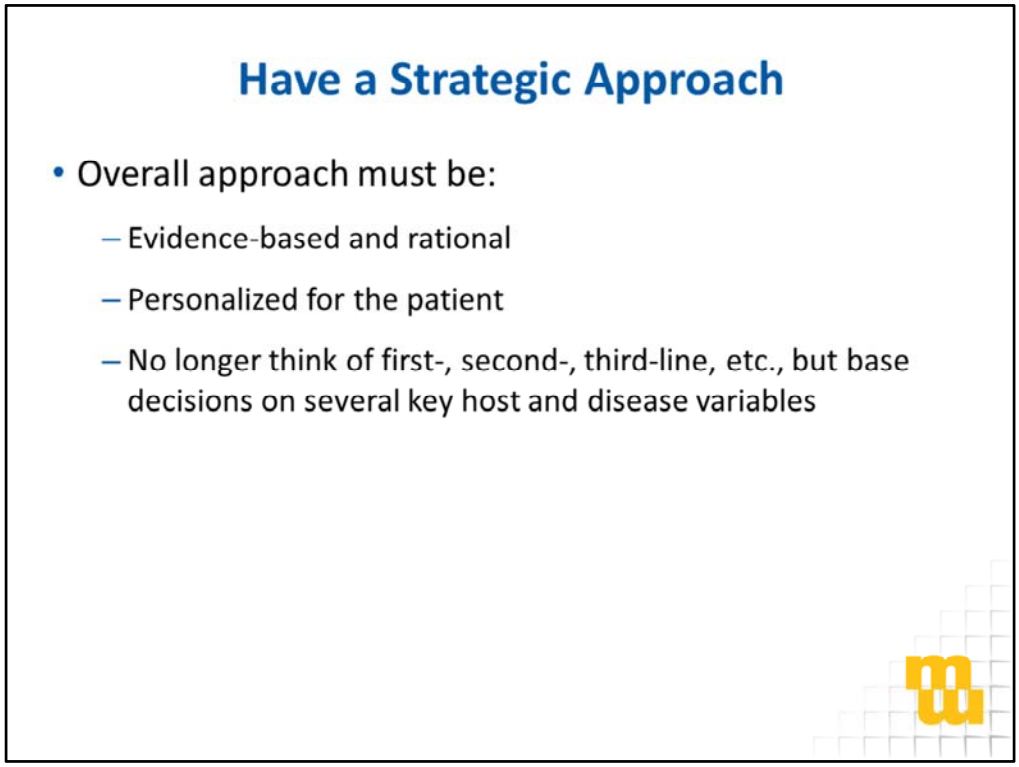
With that I am going to present a case and then try to walk through this case and see if we can come up with a good game plan for this particular patient, who is a typical patient that we would see with the relatively standard risk features. A 67-year-old woman who originally presented with a mild normocytic anemia and mild renal insufficiency to the primary care physician's office. She eventually gets referred to a hematologist when found to have a monoclonal protein. That workup leads to a revised ISS stage II IgG kappa multiple myeloma with translocation 11;14 on FISH panel. The first-line therapy is with RVd for four cycles. The patient went on to achieve very good partial response by IMWG (International Myeloma Working Group) criteria. Then the patient went on to receive Mel-200 and autologous stem cell transplant achieving a complete response by IMWG criteria. This was followed by lenalidomide maintenance for three years with good tolerance. Now the patient is presenting with increasing M-spike and declining hemoglobin; the patient remains clinically asymptomatic right now. The restaging bone marrow biopsy is showing 30% plasma cells and the FISH is now showing deletion 17p in addition to translocation 11;14. "How would you describe the treatment options for this patient?" I am going to walk through the way that we would be thinking about this patient.



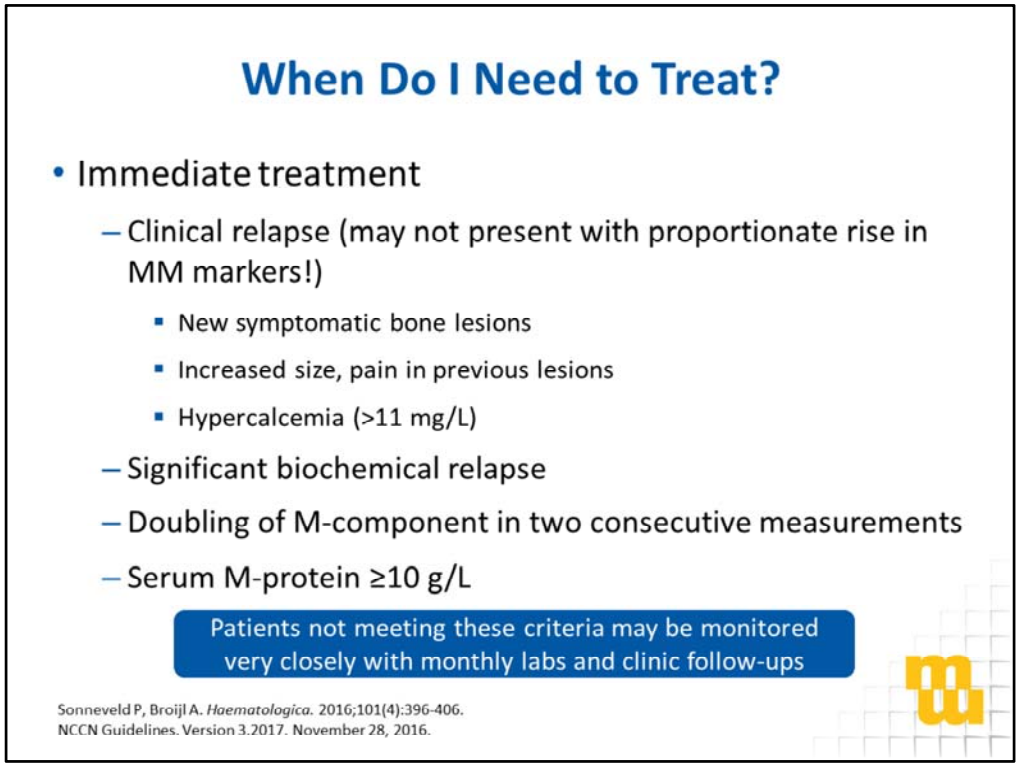
The questions to ask are, obviously, “What treatment options should I consider for this patient?” One very common question is, “Can I use a lenalidomide-containing regimen for this patient?” “What lab values and tests are important to track for the response or to monitor side effects?” “Is there a clinical trial that might be suitable for this patient?”



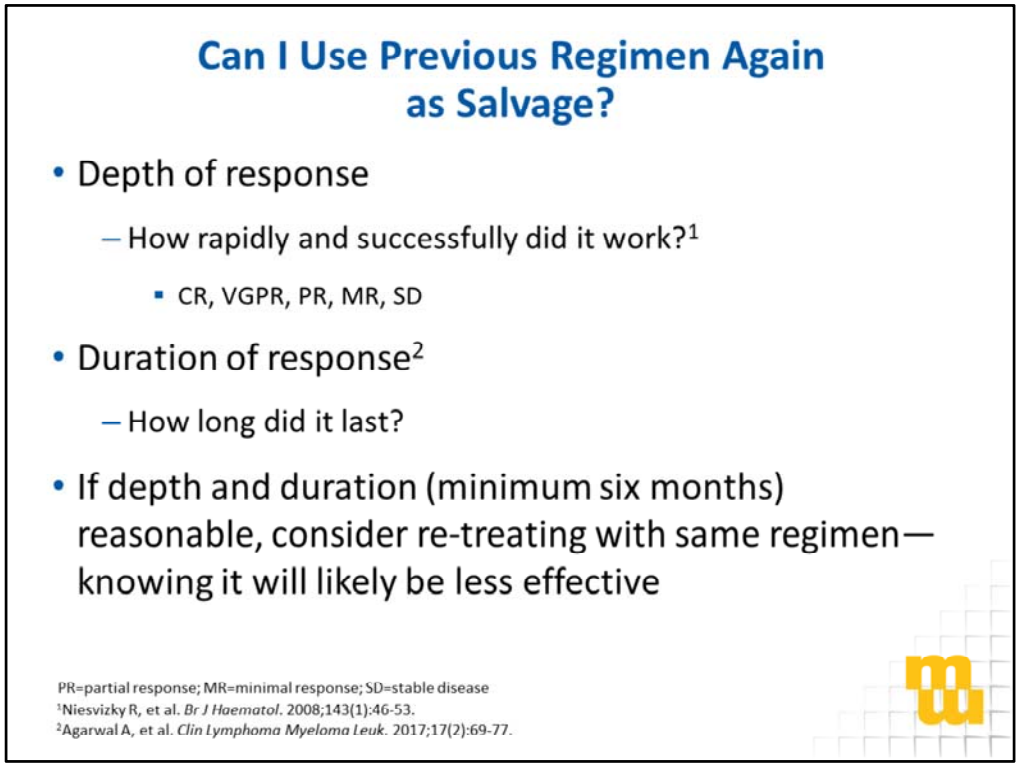
When selecting treatment for a relapsed myeloma patient, we compartmentalize factors that we are considering into: patient-related factors, disease-related factors or treatment-related factors. From a patient perspective: age, performance status, renal insufficiency, poor marrow reserve, presence or absence of neuropathy and the degree, and then other comorbidities that the patient has picked up along the way from the time of diagnosis to now. They may not have had cardiac disease at the time they were diagnosed, but they are now developing cardiac issues or pulmonary issues. They may have had diabetes in the past, and now it is getting worse and they have developed a sequelae of diabetes, or they have developed diabetes which was not there at the time of diagnosis. Then from a disease standpoint, they have risk status, specifically cytogenetics, deletion 17p, translocation 4;14, 14;16. The rapidity of the relapse: how quickly is the disease relapsing, does the patient have organ damage, new bone fractures, extramedullary disease, or presence of plasma cell leukemia at the time of relapse (where the patient is going to require quick cytoreduction)? Then previous treatments: the kind of depth of response they had, the duration of response, what would be the route of administration, and whether the patients are going to benefit from combination chemotherapy. Looking at cost of therapy – as well as access – is going to be important. What kind of toxicities the patient may have had with previous treatments will also help you decide whether you can use the same drugs again or not. The risk of second primary malignancy is something that is emerging in discussions as we pick and choose treatments for our patients.



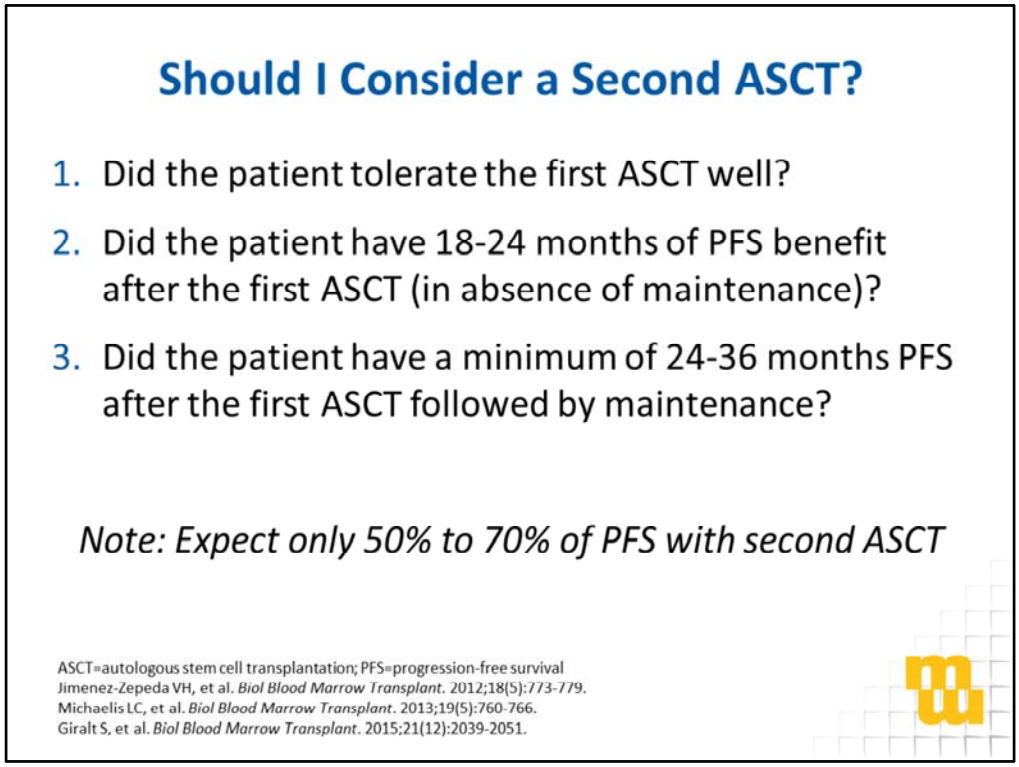
We are thinking about all of these factors as we go into our strategy toward the patient, but the overall approach is not regimented. It has to be evidence-based and rational, it has to be personalized for the patient. We are no longer thinking of this in terms of what to use in first relapse or second relapse, but basing our decision on several of these host and disease variables as we move along in managing these patients long-term.



When do I need to treat this patient? Immediate treatment is needed if a patient has a clinical relapse. When we talk about clinical relapse, this may not be proportionate to the rise in myeloma markers, and that is very important for us to understand. The M-spike may be 0.5 or 0.6 and it has been rising maybe over the last two or three months, but the patient is starting to have increasing bone pains or new bone lesions and presenting with hypercalcemia, even though the myeloma markers may not be very high. Next, significant biochemical relapse, a very quick doubling or tripling of myeloma markers over weeks or a few months, is going to be a very important landmark where you are seeing a highly proliferative kind of a relapse. In this relapse, myeloma needs to be cyto-reduced quickly, so the patient can have an improvement in their quality of life and disease burden. Serum M-protein of 10 g/L or more is high burden of disease that needs to be controlled fairly quickly. There are going to be patients who may not meet these criteria and if you choose to monitor them closely with monthly labs as well as clinic follow-ups, that would be reasonable, but maintain a low threshold on pulling the trigger on treatment for those patients.



Can I use the previous regimen again as salvage? When we think about that question, we have to think about the kind of depth of response the patient had with that regimen. How rapid was that regimen in reducing or cyto-reducing that patient, whether the patient had a very good partial response or better. How long did that response last? The duration of treatment is important. If depth and duration are reasonable, then you may consider retreatment with the same regimen. You have to know that the kind of mileage you can get out of that regimen is not going to be the same as it was the first time you used it. When we are talking about duration of response, we want to consider at least six months or more of durability of response in the relapsed/refractory setting. That threshold is continually improving, especially in the first relapse setting, with some of the newer treatment regimens which I will highlight a little later in this presentation.



Should I be considering a second autologous stem cell transplant? Well to answer that question, we will have to ask how did the patients do with their first autologous stem cell transplant? Did they tolerate it well, did they have any life-threatening complications with infections, and how good was their count recovery and physical recovery from autologous stem cell transplant in the first case? In today's day and age, a vast majority of patients actually do not have major complications from autologous stem cell transplant. Did the patients have a good benefit from the progression-free survival (PFS) perspective? If they did not have any maintenance, we consider at least 18-24 months of PFS benefit as a reasonable PFS benefit to start considering a second autologous stem cell transplant. In regards to maintenance treatment, we are talking about 24-36 months of PFS benefit from the first autologous stem cell transplant. If that is the case, then yes, you need to have a discussion about a second autologous stem cell transplant in a younger patient. The caveat is that the PFS benefit is probably not going to be the same duration, but perhaps may be 50-70% of the PFS they got from their first autologous stem cell transplant.

Let us dive into some of the new data in relapsed myeloma.

Immunomodulator-based Studies

	POLLUX DRd vs Rd[1]	ASPIRE KRd vs Rd[2]	ELOQUENT-2 ERd vs Rd[3]	TOURMALINE-MM1 IRd vs Rd[4]
≥VGPR	76%	70%	33%	48%
≥CR	43%	32%	4%	14%
Response duration, mo	NE	28.6	20.7	20.5
PFS HR (95% CI)	0.37 (0.27-0.52)	0.69 (0.57-0.83)	0.73 (0.60-0.89)	0.74 (0.59-0.94)
OS HR (95% CI)	0.64 (0.4-1.01)	0.79 (0.63-0.99)	0.77 (0.61-0.97)	NE

D=daratumumab; K=carfilzomib; R=lenalidomide; d=dexamethasone; E=elotuzumab; I=ixazomib; NE=not estimable

[1]Dimopolous MA, et al. *N Engl J Med.* 2016;375(14):1319-1331.
[2]Stewart AK, et al. *N Engl J Med.* 2015;372(2):142-152.
[3]Lonial S, et al. *N Engl J Med.* 2015;373(7):621-631.
[4]Moreau P, et al. *N Engl J Med.* 2016;374(17):1621-1634.

I am going to talk about the immunomodulator-based studies. We have had four trials that have been published in the last two years that are influencing the treatment choices we make. In all of these studies, lenalidomide and dexamethasone were used as the control arm. In the first column there you see the depth of response, VGPR or better, CR or better, response duration, as well as PFS and overall survival hazard ratios that have been mentioned. For the first study, daratumumab was combined with Rd showing a very good partial response of 76% and a complete response or better rate of about 43%. The ASPIRE trial, which combined carfilzomib with Rd and compared that to Rd, we see a VGPR rate of about 70% and a CR rate of 32%. As we start moving toward the right, the combination of elotuzumab with lenalidomide and dexamethasone appears to give less of a depth of response compared to the other two trials on the left. Ixazomib, when combined with lenalidomide and dexamethasone, again gives a reasonable depth of response. The key thing that I want to highlight on this particular slide is that the depth of response appears to be correlating with the duration of response that you are getting with these triplet regimens. In terms of ease of administration, as well as the side effect profile, the two regimens on the right, the elotuzumab and ixazomib combinations, are perhaps better tolerated and easier to administer compared to KRd or DRd, but then you are compromising on the kind of depth of response you get, as well as the durability of response. Each of these would be reasonable options for a patient qualifying for an immunomodulatory-based treatment. Patients already on lenalidomide maintenance were excluded from each of these four studies, so we have to take that as a caveat.

DRd vs Rd in RRMM Based on Previous Treatment Exposure

Design: Subgroup analysis of a randomized phase III trial

Study Population: RRMM (≥1 prior therapy, not refractory to Len)

Dosing and Schedule:
Len: 25 mg PO on days 1-21 per 28-day cycle, Dex: 40 mg PO qw
+/- Dara: 16 mg/kg IV qw for 8 weeks, q2w for 16 weeks, then q4w

Median follow-up: 13.5 months

Efficacy	Len-naïve		Len-exposed		BOR-naïve		BOR-exposed		BOR-refractory	
	DRd (n=226)	Rd (n=219)	DRd (n=46)	Rd (n=45)	DRd (n=44)	Rd (n=45)	DRd (n=228)	Rd (n=219)	DRd (n=54)	Rd (n=49)
Median PFS, months	NR	18.4	NR	NR	NR	15.8	NR	18.4	NR	10.3
HR		0.36		0.45		0.34		0.35		0.46
95% CI		0.25-0.52		0.22-1.12		0.13-0.86		0.24-0.50		0.25-0.85
P		<0.0001		0.0826		0.0170		<0.0001		0.0117
Est. 12 month PFS, %	83.0	59.9	84.1	63.1	85.4	69.2	82.8	58.7	70.8	44.4
ORR, %	96	79	87	71	98	82	93	77	92	68
P		<0.001		0.0729		0.0158		<0.0001		0.0024
≥ VGPR, %	79	47	78	38	74	55	77	43	75	36
P		<0.001		0.0001		0.0544		<0.0001		0.0001
≥ CR, %	44	21	44	12	42	23	44	19	46	13
P		<0.001		0.0011		0.0576		<0.0001		0.0003

Moreau P, et al. ASH 2016. Abstract 489.

In terms of the depth of response, the reason I want to mention the daratumumab combination is because it has been looked at more in-depth from a treatment exposure standpoint. When it comes to lenalidomide-naïve or lenalidomide-exposed patients, the median PFS duration as well as depth of response appears to be better in the three-drug combination compared to the two-drug combination. It is not as good as patients who have been naive to a particular drug like lenalidomide, for example, as you can see in this table.

DRd vs Rd in RRMM With 1-3 Prior Lines of Therapy

Design: Subgroup analysis of a randomized phase III trial
Study Population: RRMM (≥1 prior therapy)
Dosing and Schedule:
Len: 25 mg PO on days 1-21 per 28-day cycle, Dex: 40 mg PO qw, +/- Dara: 16 mg/kg IV qw for 8 weeks, q2w for 16 weeks, then q4w

Efficacy	1-3 prior lines of therapy		1-3 prior lines of therapy with high-risk cytogenetics		1-3 prior lines of therapy with TFI >12 months		1-3 prior lines of therapy with TFI ≤12 months		1-3 prior lines of therapy, refractory to last line	
	DRd (n=273)	Rd (n=264)	DRd (n=33)	Rd (n=33)	DRd (n=138)	Rd (n=145)	DRd (n=134)	Rd (n=119)	DRd (n=73)	Rd (n=67)
Median PFS, months	NR	18.4	NR	8.3	NR	18.4	NR	10.3	NR	10.3
HR		0.36		0.30		0.42		0.32		0.42
95% CI		0.22-0.46		0.14-0.97		0.24-0.74		0.21-0.51		0.25-0.72
P		<0.0001		0.0019		0.0019		<0.0001		0.0010
Est. 12 month PFS, %	83.2	60.4	-	-	88.0	74.5	78.1	43.1	-	-
TTP, months	NR	18.4	-	-	-	-	-	-	-	-
HR		0.32								
95% CI		0.22-0.46								
P		<0.0001								
ORR, %	94	77	91	69	96	86	92	67	92	66
P		<0.0001		0.0267		0.0084		<0.0001		0.0002
≥ VGPR, %	76	45	73	28	77	56	76	32	72	34
P		<0.0001		0.0004		0.0008		<0.0001		<0.0001
≥ CR, %	44	20	36	9	43	27	44	10	47	14
P		<0.0001		0.0104		0.0083		<0.0001		<0.0001

Usmani S, et al. ASH 2016. Abstract 1151.

If we start looking at prior lines of treatment – one to three prior lines of treatment by way of higher cytogenetics or how quickly the patients were relapsing from their first-line treatment before going on study – we again find that the three-drug combination appears to have a better depth of response and PFS, but it is not the same compared to someone who had normal cytogenetics with the DRd combination.

Proteasome Inhibitor-based Studies

	CASTOR DVd vs Vd[1]	ENDEAVOR Kd vs Vd[2]	PANORAMA-1 PVd vs Vd[3,4]	EVd vs Vd[5]
≥VGPR	59%	54%	28%	36%
≥CR	19%	13%	11%	4%
Median PFS, mo	NE	18.7	12.0	9.7
PFS HR (95% CI)	0.39 (0.28-0.53)	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
OS HR (95% CI)	0.77 (0.47-1.26)	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

D=daratumumab; V=bortezomib; d=dexamethasone; K=carfilzomib; P=panobinostat; E=elotuzumab

[1]Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.
[2]Dimopolous MA, et al. *Lancet Oncol*. 2016;17(1):27-38.
[3]San-Miguel JF, et al. *Lancet Oncol*. 2014;15(11):1195-1206.
[4]San-Miguel JF, et al. *Blood*. 2015;126(23):Abstract 3026.
[5]Jakubowiak A, et al. *Blood*. 2016;127(23):2833-2840.

If we start looking now at proteasome inhibitor-based therapy, within that group of patients we have three phase 3 trials comparing the control arm of bortezomib-dexamethasone to three different combinations. The CASTOR study looked at the combination of daratumumab with bortezomib and dexamethasone. The ENDEAVOR trial looked at carfilzomib and dexamethasone compared to bortezomib and dexamethasone. PANORAMA 1 compared the HDAC inhibitor panobinostat, bortezomib and dexamethasone, with bortezomib and dexamethasone. For comparative analysis, I did add the phase 2 data with elotuzumab, bortezomib and dexamethasone compared to bortezomib and dexamethasone to give a better assessment of the kind of options one has. It is a randomized phase 2 trial, therefore, we have to take that into account. It does appear that the DVd regimen gives a good depth of response, so does the Kd regimen. Each of these regimens were shown to have a better depth of response than the standard of care arm. The median PFS benefit has not been reached in the DVd study for the three-drug combination. It is about 18.7 months with Kd. Panobinostat Vd did have a superior median PFS benefit; the tolerability was an issue with that regimen, however this was a positive study. From a clinical practice standpoint, it appears to be a more difficult regimen to give to patients. The Vd, even though there was better depth of response, the median PFS was not as impressive in that phase II study. I would be highly surprised if we see a phase 3 trial with that combination coming anytime soon.

DVd vs Vd in RRMM Based on Prior Therapy and High-Risk Cytogenetics

Design: Subgroup analysis of a randomized phase III trial
Study Population: RRMM (≥1 prior therapy)
Dosing and Schedule:
V: 1.3 mg/m², d 1,4,8,11; D: 20 mg PO, d 1,2,4,5,8,9,11,12 for 8 cycles +/- Dara 16 mg/kg IV qw for cycles 1-3, d1 for cycles 4-8, then q4w

Median follow-up: 7.4 months

Rate of minimal residual disease was significantly greater among all evaluated thresholds among the patients who received 1-3 prior lines of therapy

Efficacy	1-3 prior lines of therapy		1-3 prior lines of therapy with standard-risk cytogenetics		1-3 prior lines of therapy with high-risk cytogenetics		1 prior line of therapy	
	DVd (n=229)	Vd (n=219)	DVd (n=191)	Vd (n=183)	DVd (n=38)	Vd (n=36)	DVd (n=122)	Vd (n=113)
Median PFS, months	NR	7.3	-	-	-	-	NR	7.5
HR		0.39		0.38		0.46		0.31
95% CI		0.28-0.55		0.25-0.58		0.22-0.97		0.18-0.52
P		<0.0001		<0.0001		0.0367		<0.0001
Est. 12 month PFS, %	62.2	29.3	58.7	27.0	63.2	26.7	77.5	29.4
TTP, months	NR	7.4	-	-	-	-	NR	8.4
HR		0.29						0.28
95% CI		0.20-0.43						0.16-0.49
P		<0.0001						<0.0001
ORR, %	84	67	-	-	-	-	89	74
P		<0.0001						0.0029
≥ VGPR, %	62	32					71	42
P		<0.0001						<0.0001

Mateos MV, et al. ASH 2016. Abstract 1150.

With these studies in mind, similar to what we saw with daratumumab combination with Rd, similar analyses were done with DVd comparing them to Vd. The studies show that the three-drug combination appears to benefit all subgroups, including standard- risk and high-risk cytogenetic patients. However, perhaps the depth of response and duration of response is not as good as someone who would be getting the treatment with one prior line of treatment. We have to keep in mind that the high-risk cytogenetics group is a small subset in the study, and even though PFS benefit is about the same, we have to do what we can with the available data. This slide will become relevant to how we pick treatment for the case that we have discussed.

DVd vs Vd in RRMM Based on Prior Treatment Exposure

Design: Subgroup analysis of a randomized phase III trial
Study Population: RRMM (≥1 prior therapy, not refractory to BOR)
Dosing and Schedule:
V: 1.3 mg/m², d 1,4,8,11; D: 20 mg PO, d 1,2,4,5,8,9,11,12 for 8 cycles +/- Dara 16 mg/kg IV qw for cycles 1-3, d1 for cycles 4-8, then q4w

Median follow-up: 7.4 months

Efficacy	Bortezomib-naïve		Received prior bortezomib		Refractory to Len at last prior line of therapy	
	DVd (n=89)	Vd (n=83)	DVd (n=162)	Vd (n=164)	DVd (n=45)	Vd (n=60)
Median PFS, months	NR	7.5	12.3	6.7	10.3	4.4
HR		0.25		0.46		0.37
95% CI		0.13-0.47		0.32-0.66		0.21-0.64
P		<0.001		<0.0001		0.0004
Est. 12 month PFS, %	72	28	55	27	-	-
ORR, %	88	70	80	60	81	50
P		0.0040		0.0001		0.0021
≥ VGPR, %	72	42	55	22	54	12
P		<0.0001		<0.0001		<0.0001
≥ CR, %	30	20	13	3	20	5
P		0.1199		0.0019		0.0261

Chanan-Khan A, et al. ASH 2016. Abstract 3313.

If we start looking at prior treatment exposure, patients who were bortezomib-naïve appear to have better depth of response and PFS benefit compared to those who had prior bortezomib exposure. Whereas for those who had been lenalidomide-exposed or refractory, the overall response rate and depth of response appear to be better in the DVd arm compared to the Vd arm.

DRd vs Rd and DVd vs Vd in RRMM: Assessment of MRD

Design: Randomized, controlled, prospective analysis of MDR from two phase III trials (POLLUX and CASTOR)

Study Population: RRMM (≥1 prior therapy)

Dosing and Schedule:

POLLUX

Len: 25 mg PO on days 1-21 per 28-day cycle, Dex: 40 mg PO qw

+/- Dara: 16 mg/kg IV qw for 8 weeks, q2w for 16 weeks, then q4w

CASTOR

V: 1.3 mg/m^2, d 1,4,8,11; D: 20 mg PO, d 1,2,4,5,8,9,11,12 for 8 cycles +/- Dara: 16 mg/kg IV qw for cycles 1-3, d1 for cycles 4-8, then q4w

Median follow-up:
- POLLUX: 13.5 months
- CASTOR: 7.4 months

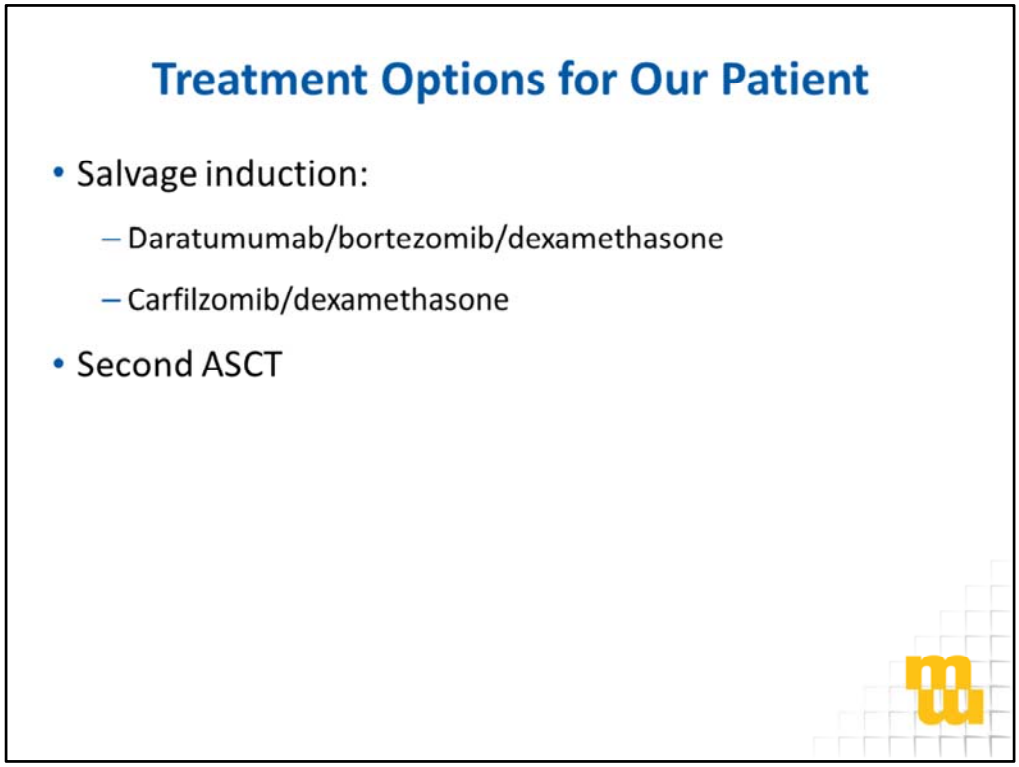
		POLLUX	CASTOR
Sensitivity threshold		**DRd vs Rd**	**DVd vs Vd**
10^{-4}			
	MRD, %	29.0 vs 7.8	13.5 vs 2.8
	Odds ratio	4.85	5.37
	95% CI	2.93-8.03	2.33-12.37
	P	<0.000001	0.000006
10^{-5}			
	MRD, %	22.4 vs 4.6	7.2 vs 1.6
	Odds ratio	5.99	4.69
	95% CI	3.21-11.15	1.57-14.07
	P	<0.000001	0.0017
10^{-6}			
	MRD, %	9.8 vs 2.1	3.6 vs 0.8
	Odds ratio	5.01	4.56
	95% CI	2.04-12.30	0.97-21.30
	P	0.000060	0.028

Patients who achieved MDR-negative status experienced fewer PFS events at threshold of 10^{-5}.

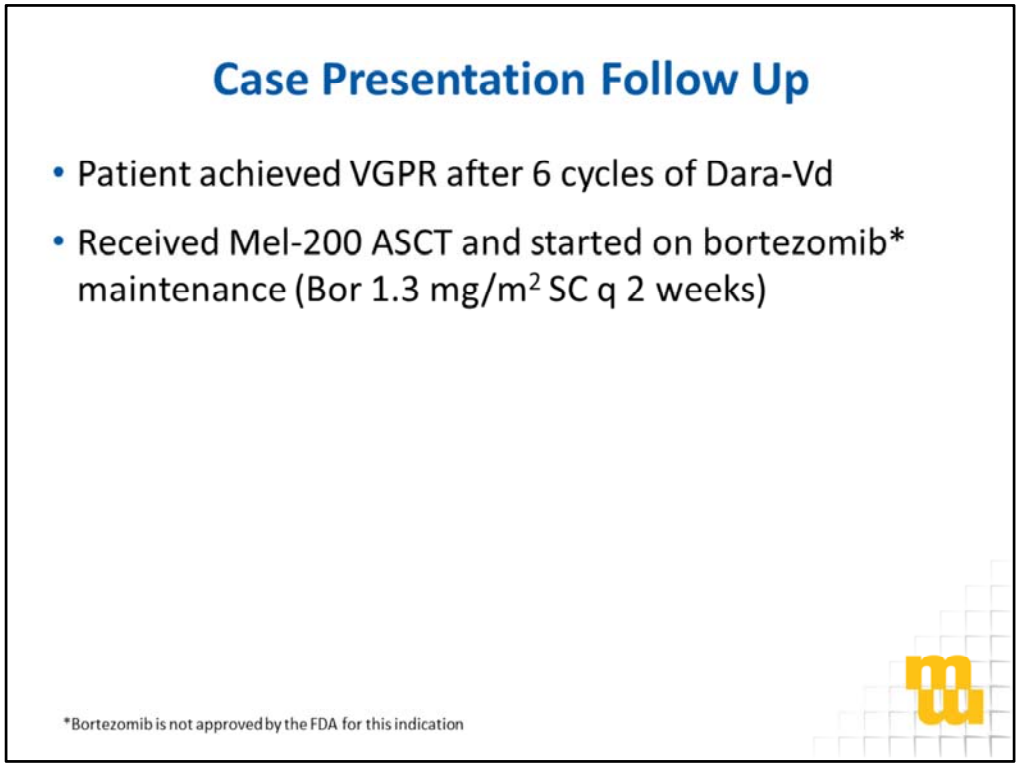
Among patients who achieved CR or better, MRD-negative rate was ≥3-fold higher across all thresholds in DARA groups.

Avet-Loiseau H, et al. ASH 2016. Abstract 246.

Looking at the depth of response from a minimal residual disease (MRD) status, we have had a lot of discussion about MRD as a new depth of response benchmark in studies. The CASTOR and POLLUX trials were the first ones to actually report this in a large randomized phase 3 fashion, demonstrating to us that the three-drug combinations did give better depth of response in terms of MRD negativity at the 10^{-4}, 10^{-5} as well as 10^{-6} thresholds. This would be an important thing to consider knowing that the patients who had MRD negativity actually did have the best PFS benefit on both the studies.



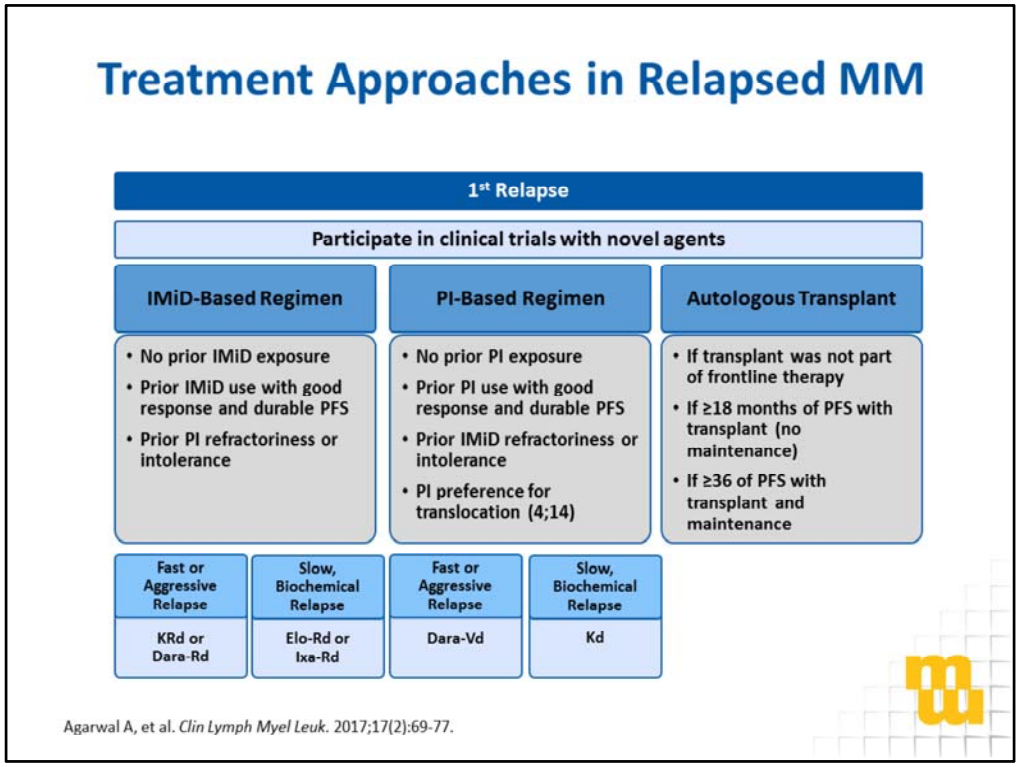
Now we are thinking about these treatment options. In my mind, for salvage induction treatment options, a proteasome inhibitor-based regimen would be something that I would consider for this patient (eg, daratumumab/bortezomib/dexamethasone, or carfilzomib/dexamethasone). The depth of response and the side effects that the patient may have had in response to prior treatments are coming into play. Then second autologous stem cell transplant comes into consideration knowing that our patient had an autologous stem cell transplant, was on maintenance for almost three years, so that would be a consideration for the patient.



Our patient did go on the daratumumab with Vd and achieved a very good partial response after 6 cycles. The patient then went on to receive Mel-200 and autologous stem cell transplant achieving a complete response, and then was started on bortezomib maintenance. I have to qualify the statement that bortezomib is not approved by the FDA for "maintenance," but this is the salvage setting and we are utilizing bortezomib to maintain the patient's response in the salvage relapsed setting.

Individualizing Patient Care:

Navigating Drug Sequencing Strategies in Relapsed/Refractory Multiple Myeloma



In terms of treatment approaches for relapsed myeloma, this algorithm walks you through the options one can offer to patients. If the patient is in first relapse, we do encourage the patient to participate in clinical trials with novel agents. IMiD-based regimens would be considered for someone who did not receive an IMiD in their first- line treatment, or if they had a fantastic response and duration of response to the IMiD-based treatment and have been off of IMiDs, or they had prior PI refractoriness of intolerance. If they are having a fast and aggressive relapse, KRd or DRd would be a good choice for those patients. If it is a slow biochemical relapse, Elo-Rd or Ixa-Rd may be a good option. PI-based regimens are recommended for patients with no prior PI exposure in first-line treatment, or who had PIs in the past with good response and durable PFS, who had prior IMiD refractoriness or intolerance, or who have translocation 4;14. If they are having a fast or aggressive relapse, the daratumumab with Vd would be a good option. If they are having a slow biochemical relapse, you may consider Kd as a regimen. Regarding autologous stem cell transplant, we did talk about the threshold we may have for patients who have not received a maintenance treatment or have received maintenance treatment, but that would be something one would consider in early relapse patients.

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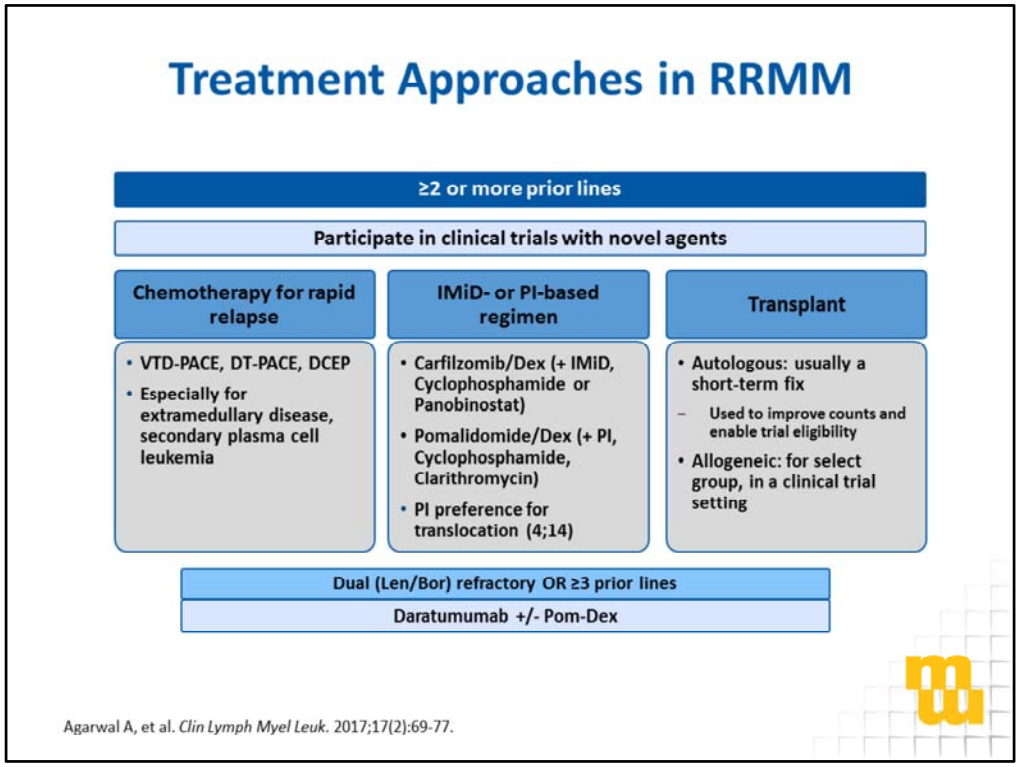
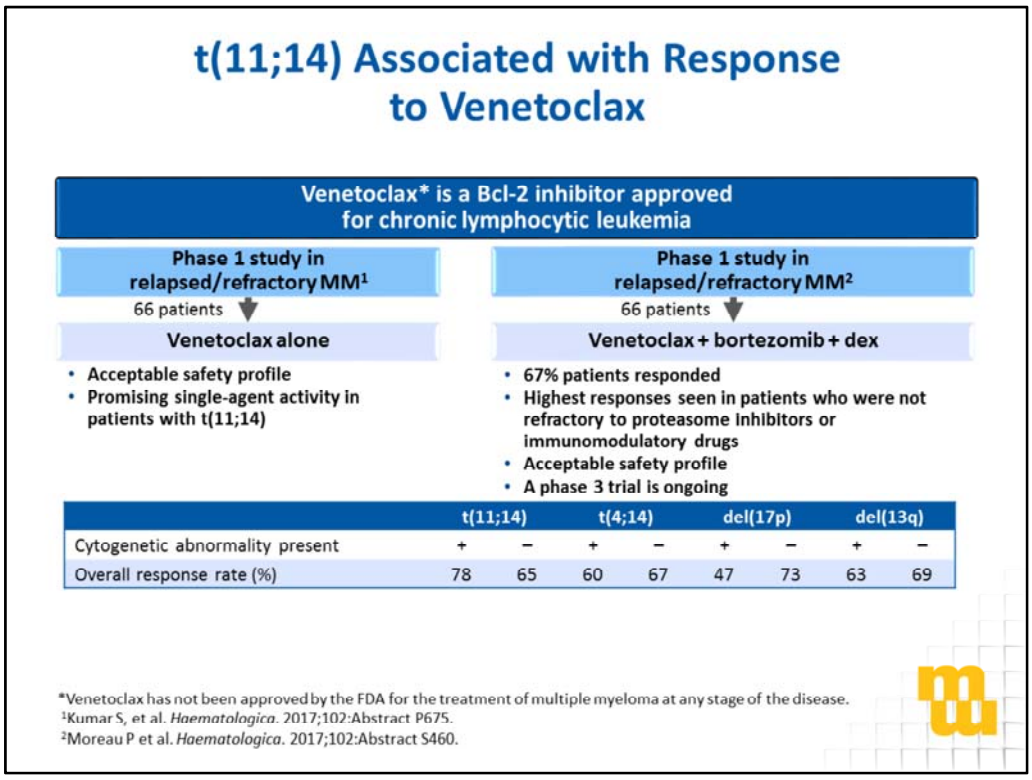


If we start talking about two or more prior lines of treatment, then we are talking about patients who may have had a rapid relapse and require a quick cytoreduction with a PACE-based or DCEP-based regimen. This is especially true for patients who have extramedullary disease or secondary plasma cell leukemia. Generally even if we employ that for a rapid or high-risk aggressive relapse, we then switch those patients over to a carfilzomib- or pomalidomide-based salvage regimen, with PIs being preferred for the patient who may have translocation 4;14. We do have daratumumab as an option for patients who are lenalidomide- or bortezomib-refractory or had more than three prior lines of treatment. Pomalidomide and dexamethasone can be added now to daratumumab as per the FDA label, and we use daratumumab-pomalidomide-dexamethasone quite commonly in our practice for patients who are beyond the two or more prior lines of treatment, especially if they have not had daratumumab as part of their first relapse treatment. Autologous stem cell transplants tend to be a very short-term fix. We use that modality more in patients who may have low marrow reserve, where we are trying to cyto-reduce them and give them autologous stem cells to improve their blood counts. Allogenic stem cell transplants are used in highly select relapsed/refractory myeloma patients, but the preference is to do that in a clinical trial like the BMT CTN 1302 study which is actively accruing patients.

Individualizing Patient Care:

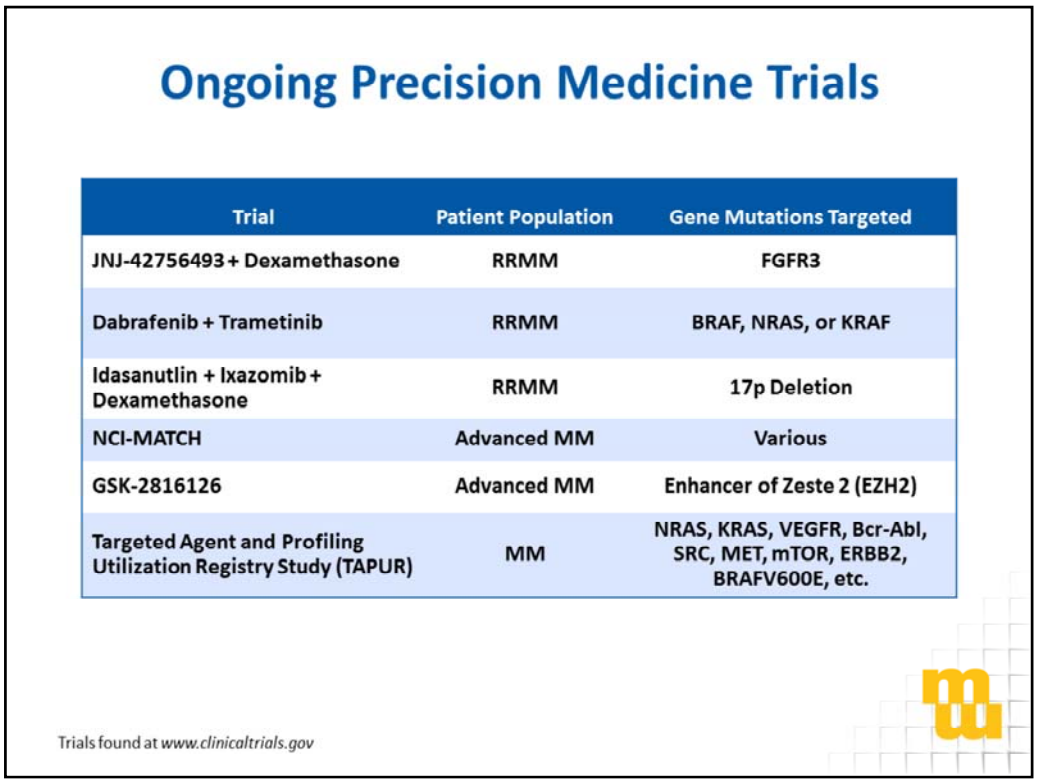
Navigating Drug Sequencing Strategies in Relapsed/Refractory Multiple Myeloma



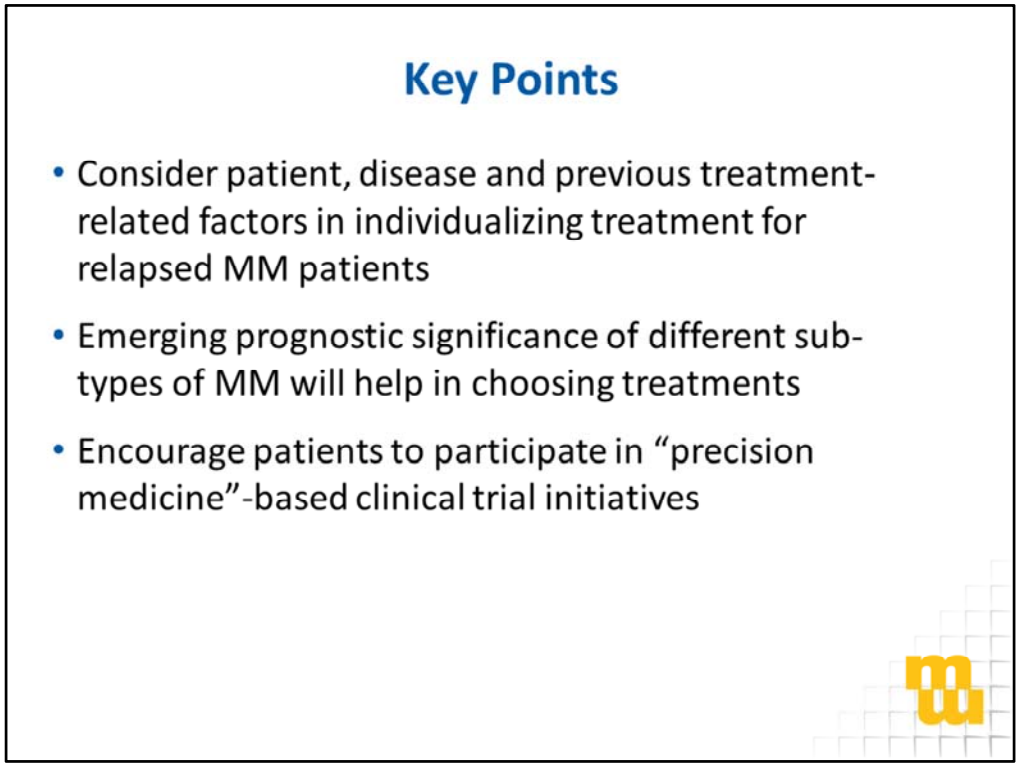
For translocation 11;14 patients, I want to mention that we do have a newer drug called venetoclax, which is an oral Bcl-2 inhibitor approved for CLL, and making its way through myeloma studies. What was very interesting with this particular strategy is the robust response seen in translocation 11;14 patients. Venetoclax as a single agent showed a 40% response rate in translocation 11;14 patients. For the phase 1 study that looked at the combination of venetoclax with bortezomib/dexamethasone for the translocation 11;14 patients, the overall response rate was 78%. There appears to be a better depth of response in patients who have translocation 11;14, or cyclin D1 overexpressed myeloma patients. It is very likely that venetoclax may become our first biomarker-driven treatment modality that becomes approved for myeloma patients.

Individualizing Patient Care:

Navigating Drug Sequencing Strategies in Relapsed/Refractory Multiple Myeloma



There are several ongoing precision medicine clinical trials which include relapsed/refractory or advanced myeloma patients. I have listed the FGFR3-targeted drug JNJ-42756493 with dexamethasone, then dabrafenib and trametinib are being combined for patients with relapsed/refractory myeloma who have BRAF, NRAS, or KRAS mutations. Then we do have idasanutlin with ixazomib and dexamethasone being examined for deletion 17p patients. The NCI-MATCH and TAPUR trials are looking at several different gene mutations being targeted, and myeloma is included in those studies as one of the eligible diseases. We will see if we see activity with those single agents in our myeloma patients. I imagine we would use those drugs in combination with the available platforms rather than as single agents, but these are very important single finding studies.



The key points to take away from this presentation are to consider patient-, disease- and previous treatment-related factors in individualizing treatment for relapsed/refractory myeloma patients. One also has to recognize the prognostic significance of different subtypes of myeloma while choosing treatment. One way in which I highlighted that is taking the translocation 11;14 patient who had an addition of deletion 17p at the time of relapse, perhaps signifying that the restaging bone marrow biopsies will start becoming important in myeloma. I do this frequently for my patients in clinical practice. The translocation 11;14 patients will have a biomarker-driven option that is coming down the pike. Venetoclax is already in clinical trials in phase 3 studies. They are going to start seeing more and more drugs that are more target-driven, and that is why it is important to encourage patients to participate in precision medicine-based clinical trial initiatives, like the NCI-MATCH or TAPUR. There are clinical trials that are being developed within the Multiple Myeloma Research Consortium, for example, where you will have patients receiving targeted therapies in addition to platform drugs. Having said that, I truly appreciate you joining us. Thank you for viewing this activity.