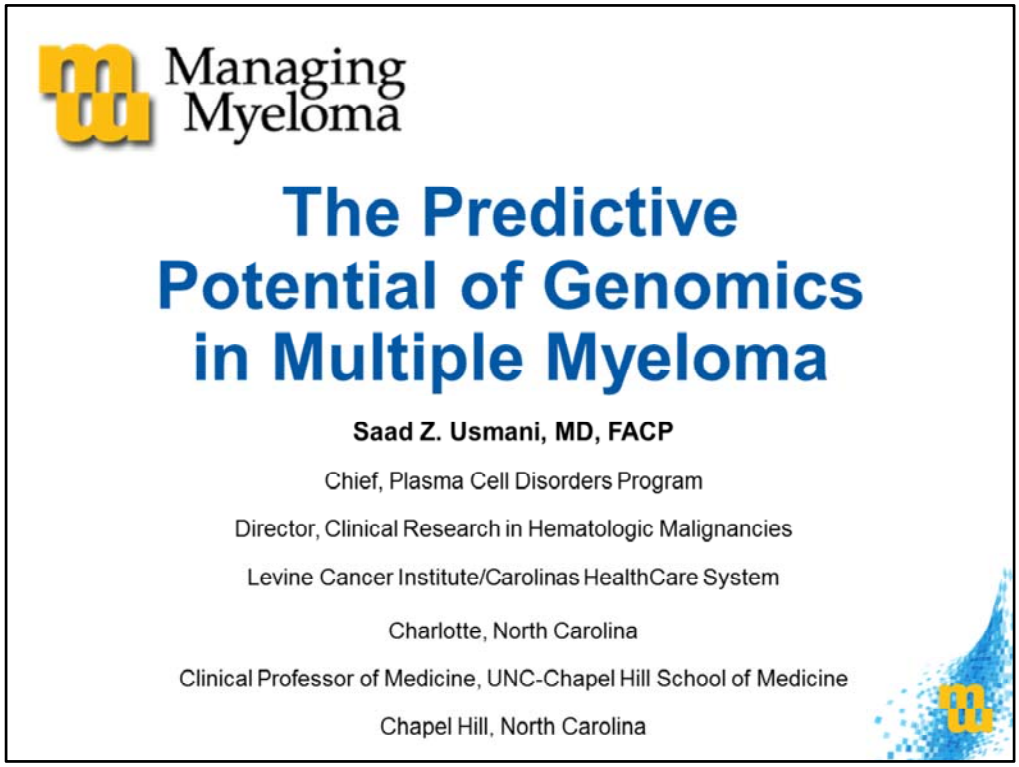
The Predictive Potential of Genomics in Multiple Myeloma



Welcome to *Managing Myeloma,* I am Dr. Saad Usmani. In today's presentation, I will be reviewing the predictive potential of genomics. Gene profiling studies have been found to provide important information regarding multiple myeloma biology, and constitute a powerful tool to predict outcomes and guide therapy. In this video, I will provide you with the latest information related to disease biology, risk stratification focusing on high-risk multiple myeloma, and potential drug selection strategies based on high-risk cytogenetics. Finally, I will summarize future thinking and emerging approaches in gene expression profiling. Let us begin.

The Predictive Potential of Genomics in Multiple Myeloma

Focusing on disease biology, what we have come to know about myeloma is that it is not one disease.

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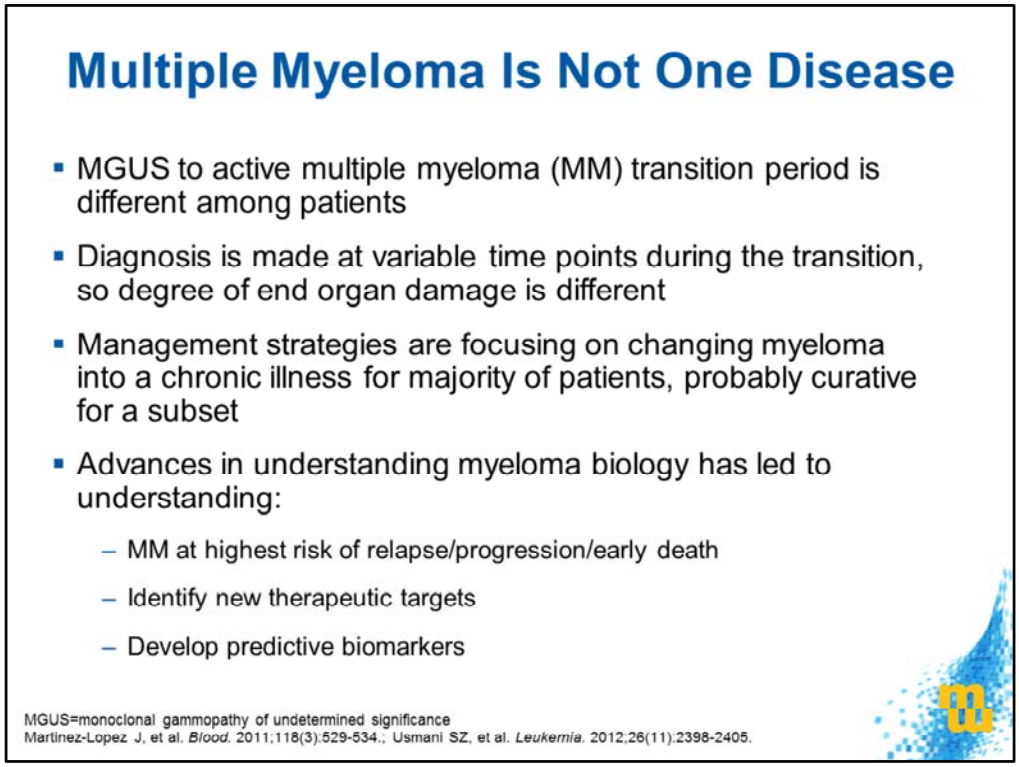

The MGUS to active myeloma transition period is different among different patients. The diagnosis is made at varying time points during that transition, so the degree of end-organ damage and the burden of disease is going to be different between patients. Managing myeloma with different strategies and now focusing on changing myeloma into chronic illness for the majority of patients and there is a potential of curability at least from a functional standpoint in a subset of myeloma patients. Advances in understanding biology of myeloma has led to understanding who are the patients at high risk of relapse, progression, and early death. We are able to identify new therapeutic targets, and we are in the process of developing predictive biomarkers that can help us identify which treatment strategies would be best for what kind of myeloma patients.

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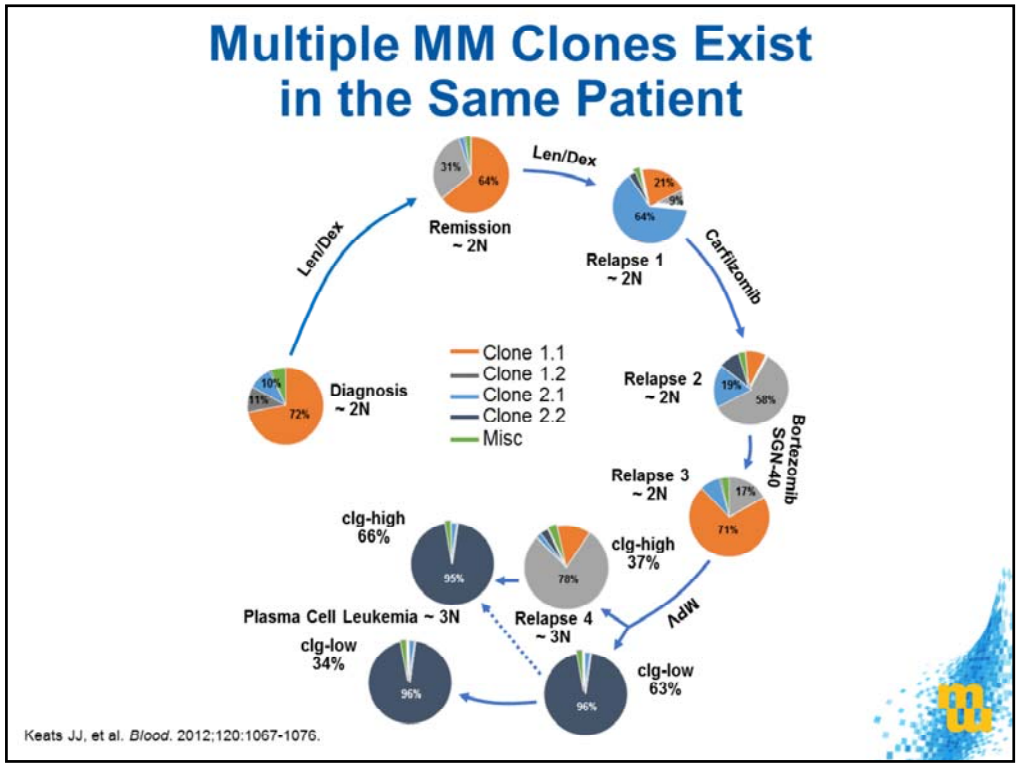

One of the things that we are recognizing in myeloma is that there are multiple myeloma clones that exist in the same patient. This figure shows a schema that was published a few years back where at baseline you can see that there are at least four different clones present in this given myeloma patient, but with each line of treatment, different clones appear to emerge at relapse, and they were dictated by the kind of therapies that were chosen for the myeloma patient. Eventually, that very tiny clone that was there from the very beginning and survived with subsequent relapses, emerged as the dominant clone and appeared to be resistant to all active myeloma treatments by that time, and resulted in that particular patient's demise. The main message from this slide is myeloma exists in a given patient in many different clones, and so there is evidence of clonal evolution as well as clonal tiding in each given myeloma patient that makes management of myeloma more complex.

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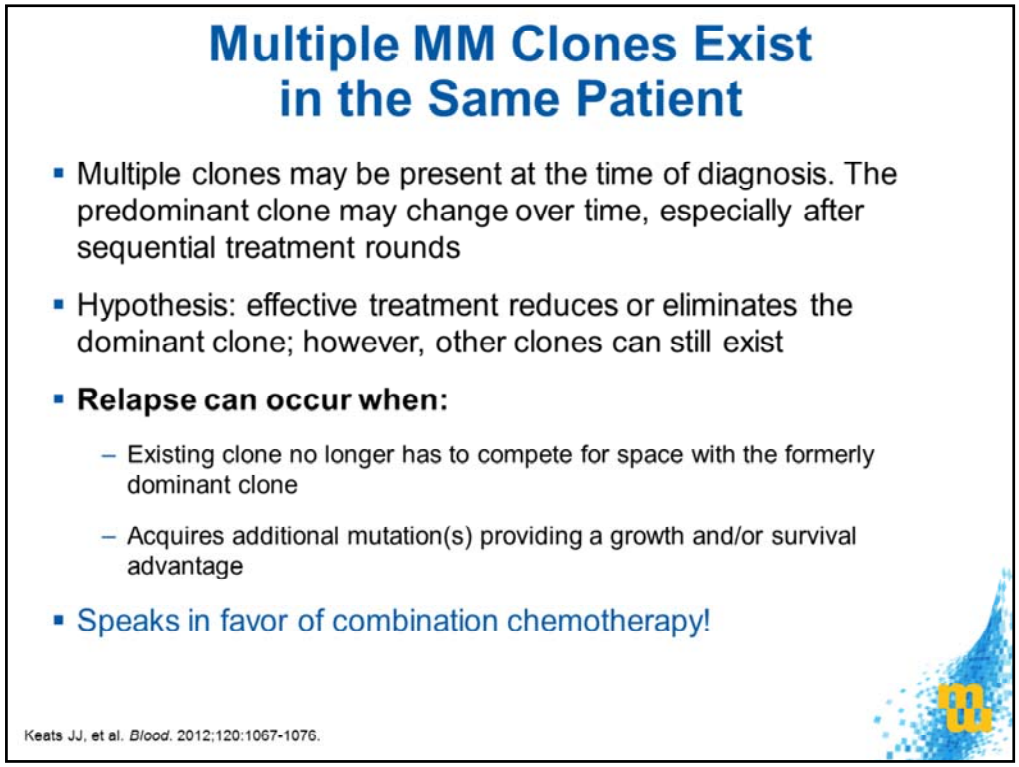

So having said that, it is extremely important to recognize that we have to develop tools to identify all the myeloma clones in a given patient, and based on the goals that we may have for that given patient, either disease eradication or control of disease, we have to develop combination chemotherapies that best suit a given myeloma patient. Right now what we are doing is treating the myeloma patients the same way and we do see the outcomes as being different.

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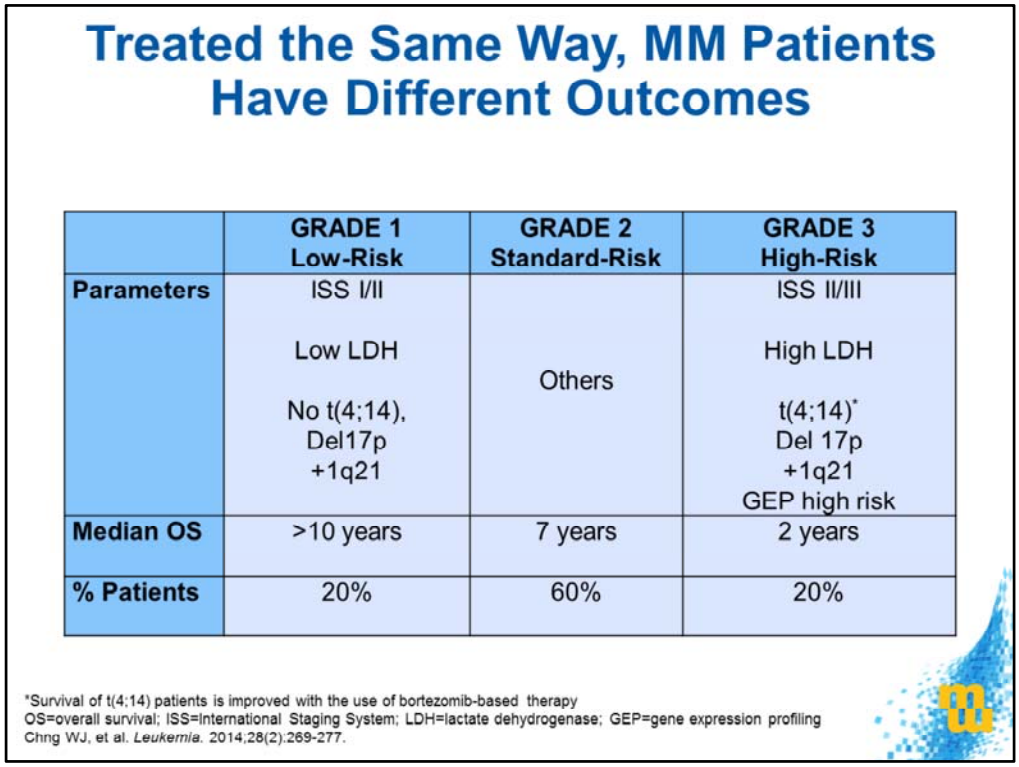

So, this was the original IMWG consensus on risk stratification that was published by Wee-Joo Chng and colleagues in 2013 where, if we start looking at myeloma from a low-burden perspective and picking certain karyotypic abnormalities and gene expression profiling features, we find that the outcome of myeloma patients is different when you have low-burden and low-risk disease compared to high-burden or high-risk disease features by various karyotypic abnormalities or gene expression profiling. However, it is not simply about disease biology.

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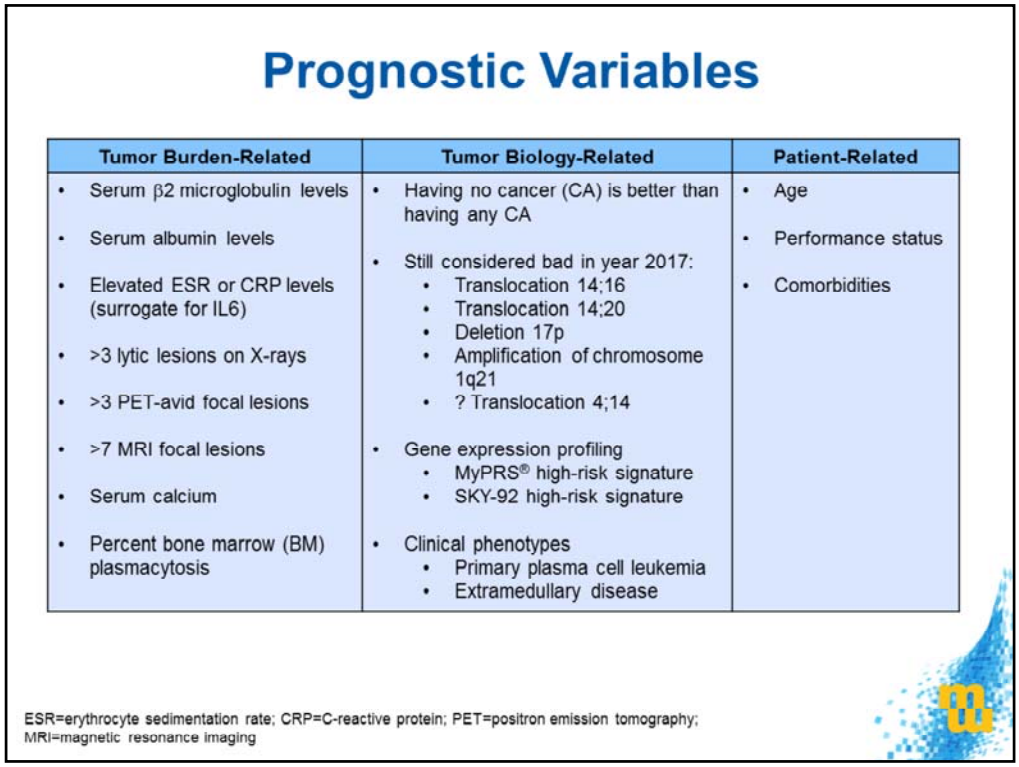

There are several ways in which we can measure the tumor burden and beta-2 microglobulin, serum albumin levels, elevated ESR or CRP levels (which tend to be the surrogate markers for IL-6 levels) and then either x-rays, PET scans, or MRIs can help determine the burden of bone involvement, and there are certain benchmarks that predict for higher burden of disease from that perspective. Then, elevated calcium levels and high percentage of bone marrow plasmacytosis are also tumor burden-related prognostic variables that we have to look at. From the tumor biology perspective, translocation 14;16, 14;20, deletion 17p, amplification of chromosome 1q2, especially four and more copies, appear to be poor-risk prognosticators. Translocation 4;14, I will share some data which shows that perhaps we have made some improvement in that particular subgroup of patients, and maybe that subgroup of patients with the use of proteasome inhibitors may be considered intermediate risk. There are two gene expression profiling models, MyPRS® high-risk signature which was developed by the University of Arkansas group and the SKY92 high-risk signature developed by the HOVON group that are emerging as commercially available tools that we can use. Then there are certain clinical phenotypes, like primary plasma cell leukemia and extramedullary disease, that on its own are poor prognostics from a tumor biology standpoint. Then, from a patient-related perspective, older age, frailty, poor performance status, and comorbidities have to play a big role in what kind of therapies patients may or may not be able to tolerate.

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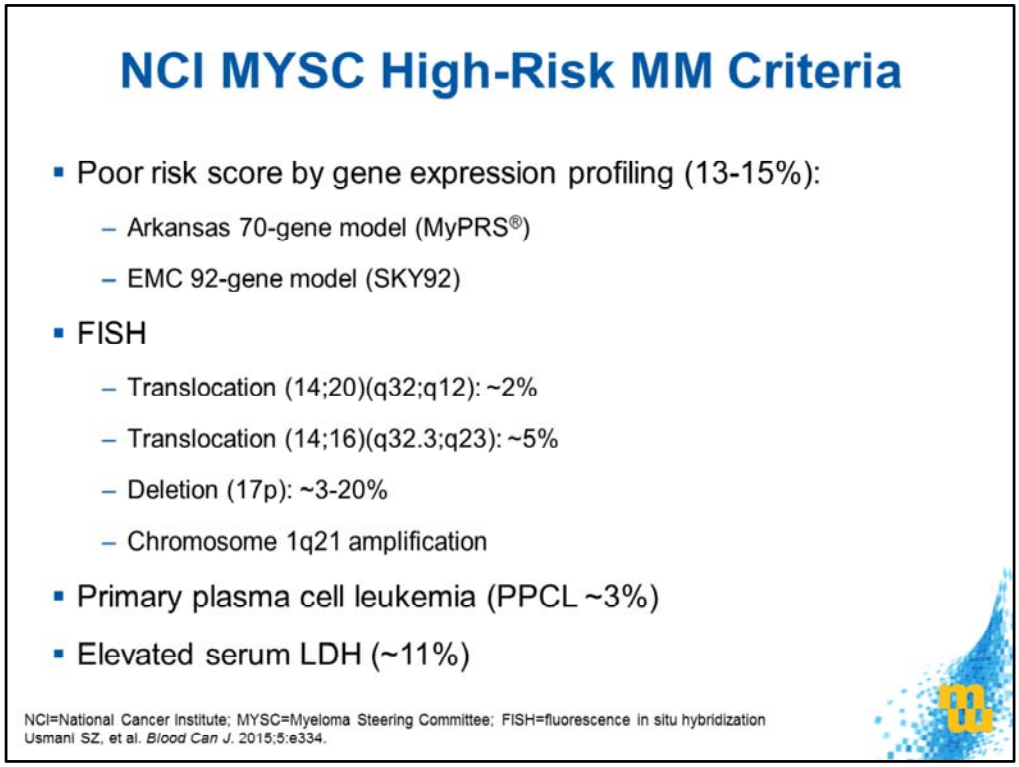

The National Cancer Institute in the US came up with the high-risk myeloma criteria under the purview of the Myeloma Steering Committee which includes poor-risk score by gene expression profiling, the Arkansas 70-gene model, certain FISH features such as translocation 14;20, 14;16, and deletion 17p, primary plasma cell leukemia, and elevated serum LDH twice above the normal limit as high-risk features. Then again most recently, the EMC/SKY92 gene model is something that is recognized as high risk, and then amplification of chromosome 1q21, especially four or more copies, appears to meet the high-risk criteria and is utilized for choosing clinical trial patients and putting them on high-risk clinical trials which I will be sharing a little later.

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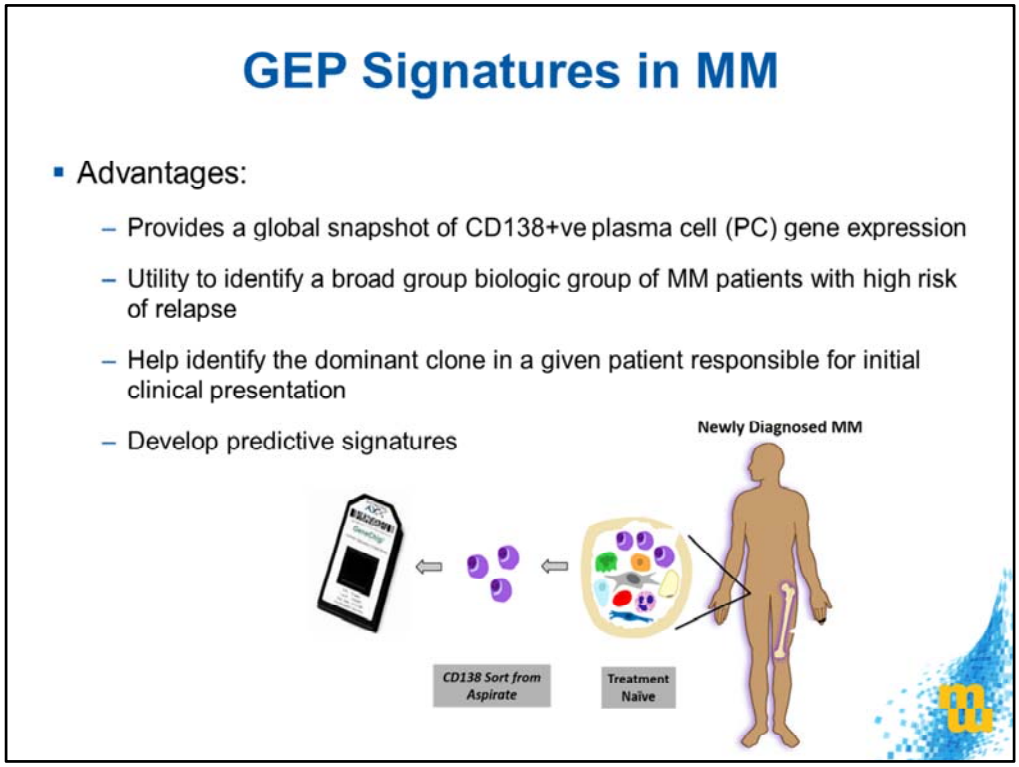

Gene expression profiling signatures in myeloma have several advantages.
They do provide a global snapshot of the gene expression in CD138 positive plasma cells. It can be utilized in a broader group of myeloma patients to identify high-risk patients. It can also identify the dominant clone in a given patient that is responsible for that clinical picture, and it can also help in developing predictive signatures.

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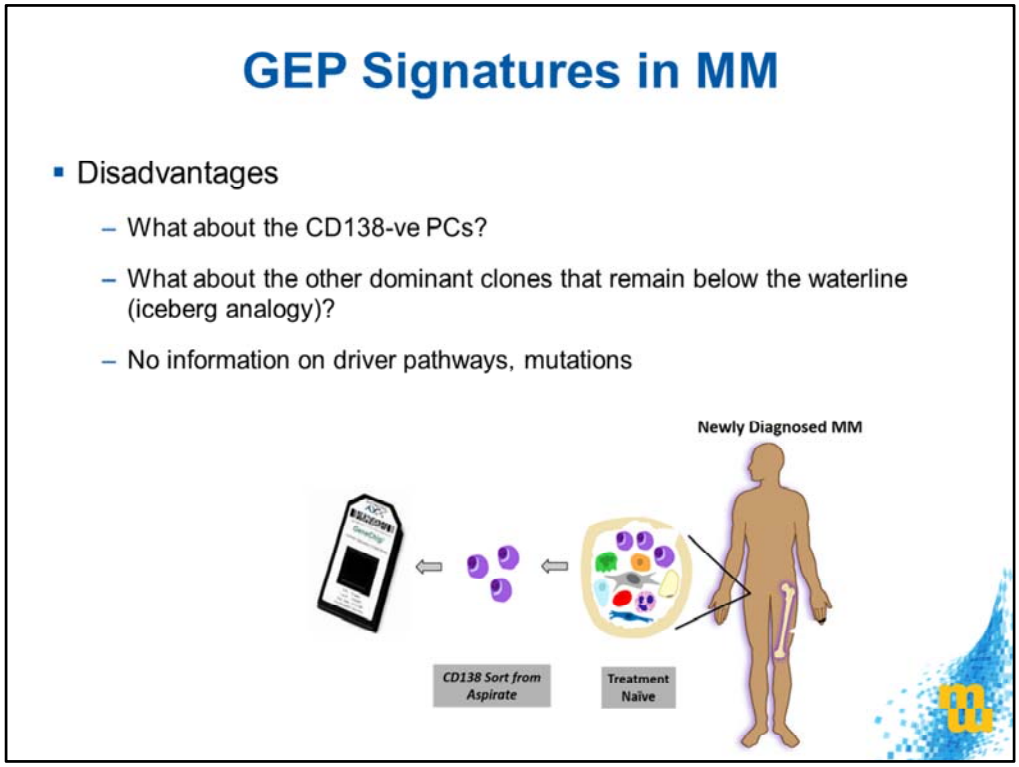

The disadvantages: the CD138 negative or low plasma cells tend to be excluded and then the gene expression profiling may not capture all the clones, just the dominant clones. It does not provide us with information about which pathways are most active; we do not get information about mutations either, but as a tool that can be widely utilized, it appears to be an effective tool.

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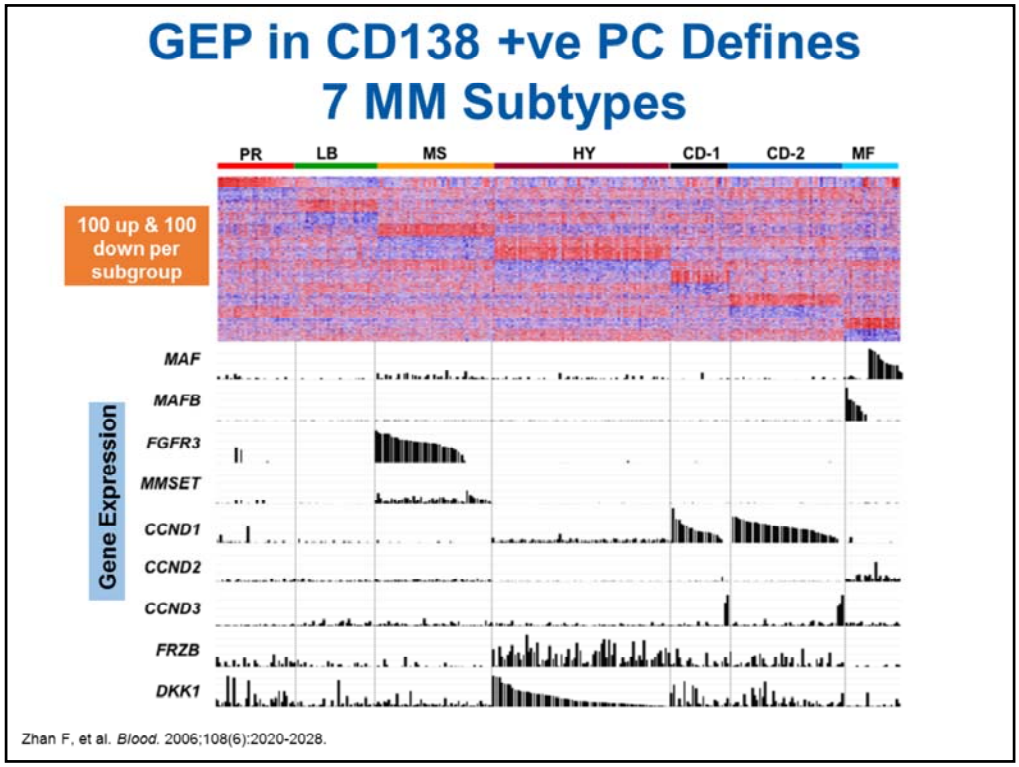

Gene expression profiling can help us identify different molecular subgroups of myeloma. So, this figure is taken from a publication almost 11 years ago in 2006, where seven different molecular subgroups of myeloma were identified based on their clinical risk of progression or relapse early when treated in a fairly uniform way in the total therapy clinical trial experience. As you can see, different genes were overexpressed or underexpressed highlighting the fact that the molecular biology does dictate clinical behavior in myeloma, and there was correlation of each of these subgroups to specific cytogenetic abnormalities.

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Molecular Subgroups and Cytogenetic Abnormalities

Molecular Subtype	% of Newly Diagnosed	Cytogenetics/FISH	Characteristic Genes Elevated in Class	Risk of Relapse
MS	17	t(4;14)	FGFR3, MMSET, CCND2, IL6R	Moderate
MF	6	t(14;16) or t(14;20)	MAF or MAFB, CCND2, IL6R	High
CD-1	6	t(11;14) or t(6;14)	CCND1 or CCND3	Low
CD-2	12	t(11;14) or t(6;14)	CCND1 or CCND3, CD20, VPREB3	Low
HY	31	Trisomies +3, +5, +7, +9, +11, +15, 19	GNG11, DKK1, FRZB	Moderate
LB	12	Typical HY trisomies; frequent del13, gain of 1q, rare gain of 11	CCND2, CST6, ARHE, IL6R	Low
PR	10	Made up of all subgroups	CCNB1, CCNB2, PCNA, MKI67, TOP2A, TYMS	High

Zahn F, et al. *Leukemia*. 2006;20(9):1484-1486.

So, this table shows you the different molecular subgroups of myeloma and which cytogenetic abnormalities appear to be more prevalent, and what kind of genes were correlated with those kinds of translocations within those molecular subgroups, and the kind of risk of relapse these patients have. So, making the point that myeloma is not one disease. It comes in at least seven different flavors and the risk of relapse is different for those subgroups of patients.

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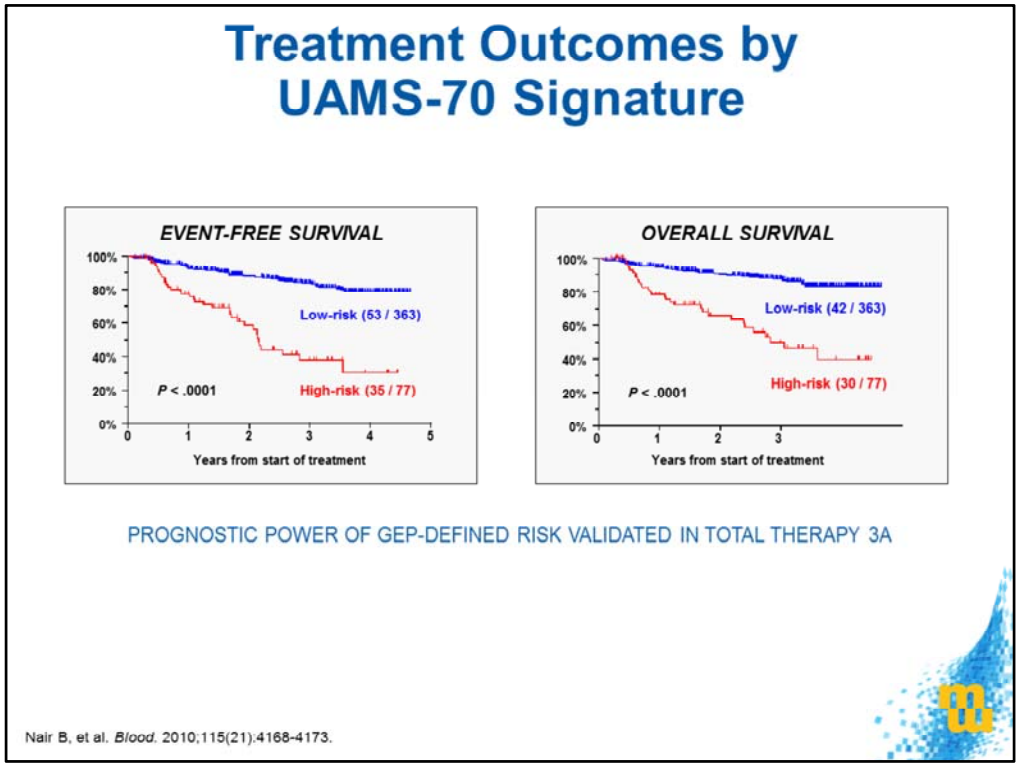

Then, the Arkansas group did develop the 70-gene signature where they reported differences in event-free survival as well as overall survival based on the 70-gene score, and as you can see from this figure, the dichotomy between those two groups was quite stark.

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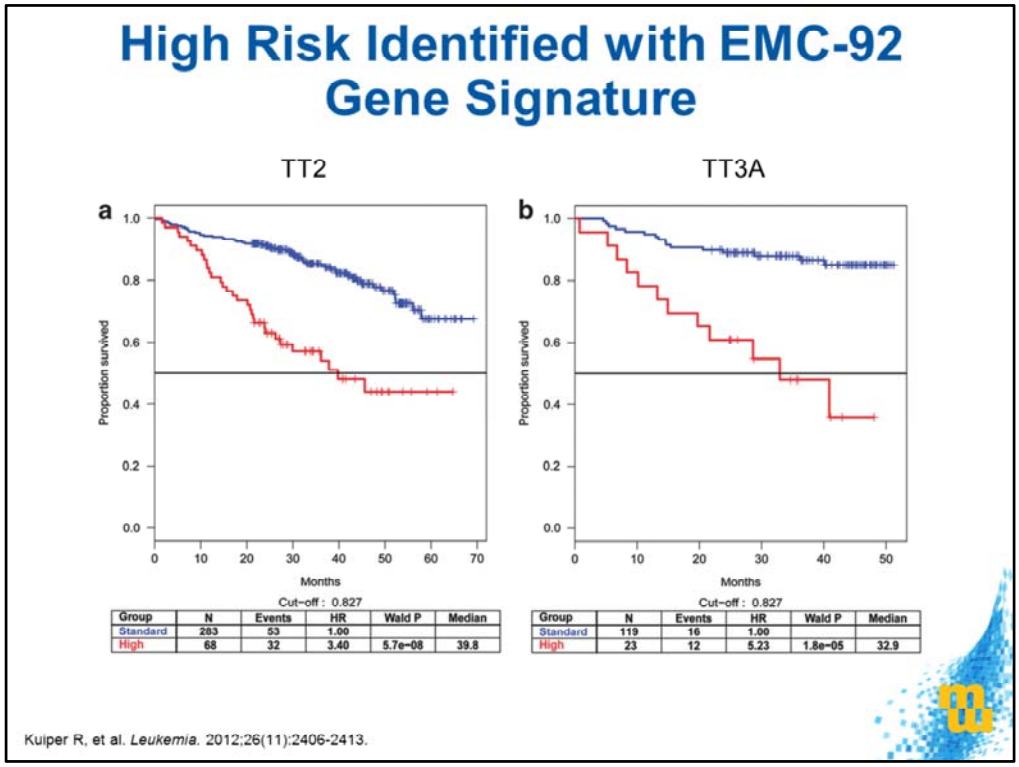

Similarly, the EMC92-gene signature which was developed by the HOVON group was published, and it showed the power of identification of patients at high risk of relapse using the 90-gene signature. Interestingly, the 70-gene signature developed by Arkansas and the 92-gene signature developed by HOVON had very few overlapping genes, nevertheless identified patients at high risk of relapse, showing you that there is more to disease biology in myeloma than meets the eye.

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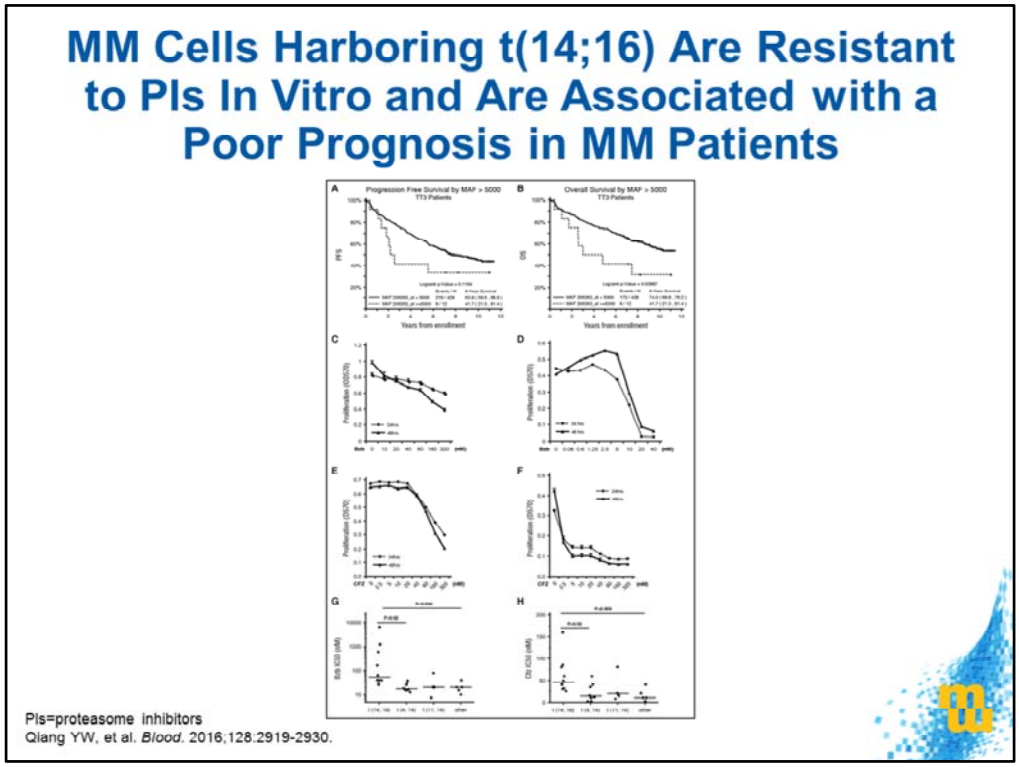

One very interesting study that was recently published by the Arkansas group focusing on the translocation 14;16 patients within the total therapy studies that the expression of MAF gene appears to be associated with poor prognosis in myeloma. When they compared patients who were on proteasome inhibitor based therapy versus those who were not, there appears to be a resistance to proteasome inhibitors in vitro in patients who have higher MAF gene expression, perhaps making the point that there might be a subset of patients who may not benefit from proteasome inhibitors as a class of drugs, making the point that perhaps we can have some predictive biomarkers that come out of that kind of experience where we can pick and choose therapies that may not be helping a certain subset of myeloma patients.

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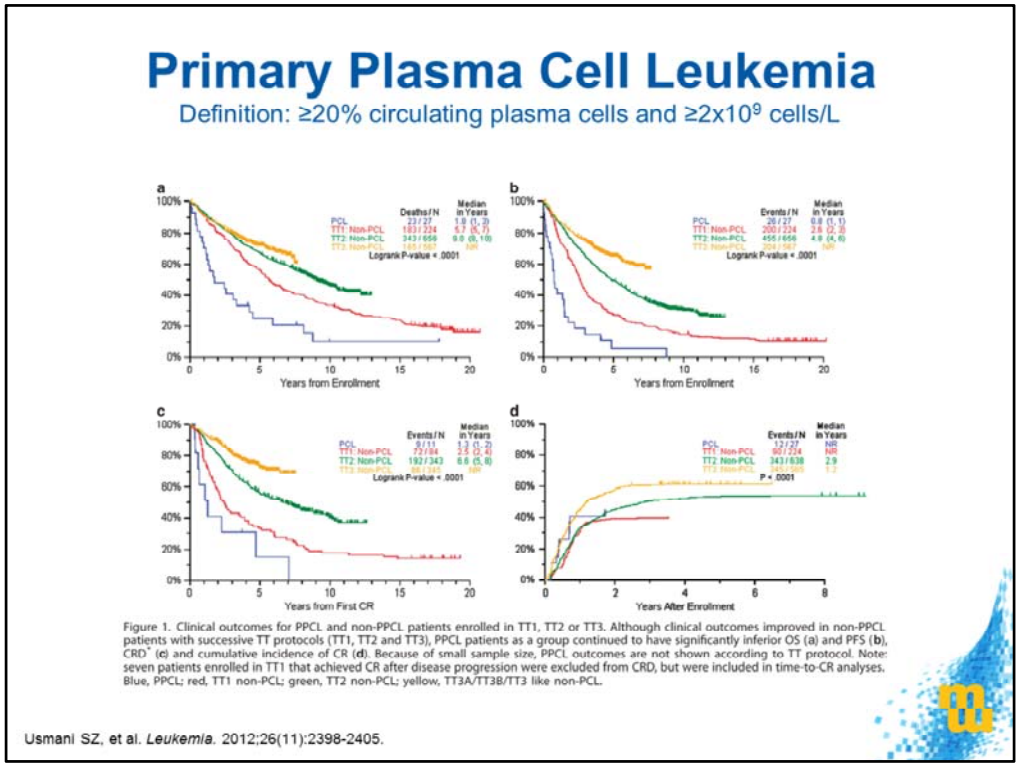

In the primary plasma cell leukemia patients, even with total therapy, three kinds of approaches appear to have extremely poor outcomes. So, this particular study was published about a little over 4 years back showing the fact that despite the use of proteasome inhibitors as well as IMiDs within the total therapy experience, the outcome of primary plasma cell leukemia patients was fairly dismal and has not changed over the span of 16 or 17 years of advances in the total therapy protocol schema.

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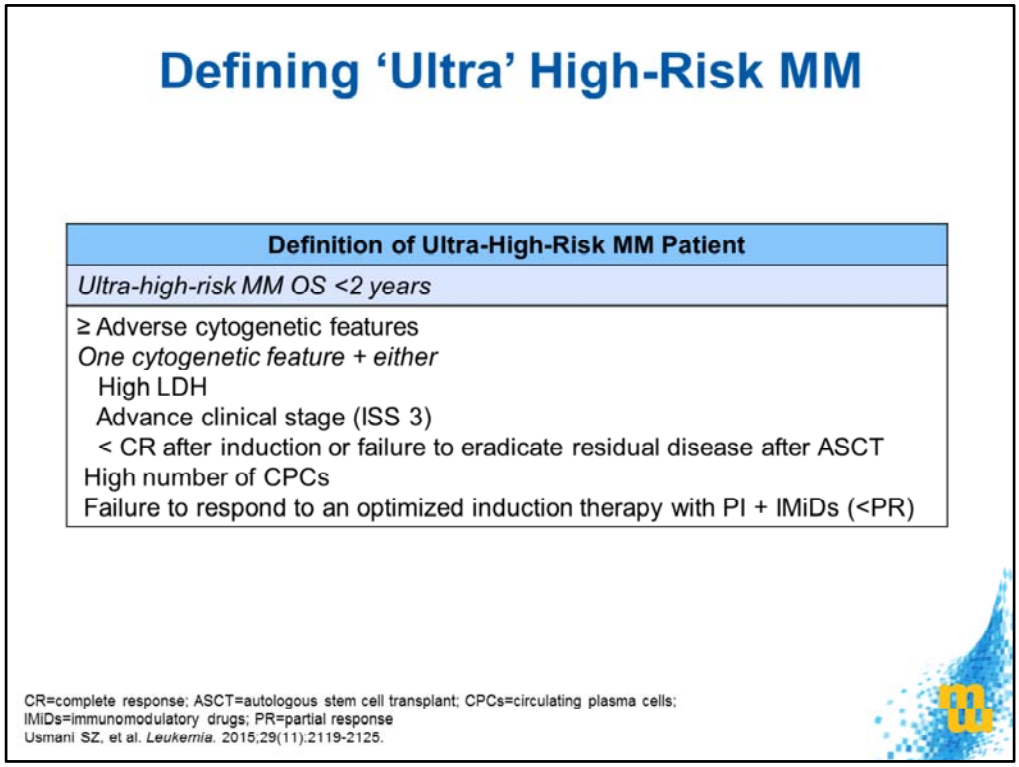

How do we define ultra-high-risk myeloma patients? The very simple definition is any myeloma patient who dies within 2 years of their diagnosis. What we can see with this particular table is patients who have more than two poor prognostic features, that include a poor cytogenetic feature along with high LDH or ISS stage 3, or patients who are unable to have a complete response or eradication of residual disease after induction of stem cell transplant, or patients who have a high number of circulating plasma cells despite optimal induction in transplantation, or failure to respond to optimized induction with PI IMiDs (so less than a PR). So, patients who are primary refractory, those are the patients who are at ultra-high-risk of dying from the disease, and that is a very clinically relevant definition that has been described for high-risk myeloma patients, picking out the really bad actors from within that high-risk subgroup.

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Survival of High-Risk Subgroup in Randomized, Controlled Newly Diagnosed Multiple Myeloma Trials

FISH	N1/N2	End point	Arm 1	Arm 2	Arm 1 (%)	Arm 2 (%)	Comment
t(4;14)	26/24	3-y OS	PAD/ASCT/ thalidomide*	VAD/ASCT/ bortezomib*	44	66	HOVON65/GMMG-HD4
	98/106	4-y OS	VAD	VD	32	63*	IFM-2005
	21/23	2-y OS	Thalidomide*	Placebo*	67	87	TT2
	21/29	2-y OS	Thalidomide-TT2	Bortezomib TT3	67	97*	TT2 vs TT3
Del(17p)	21/16	3-y OS	VAD/ASCT/ thalidomide	PAD/ASCT/ bortezomib*	17	69*	HOVON65/GMMG-HD4
	119/54	4-y OS	VAD	VD	36	50	IFM-2005
Non-hyperdiploid	92	3-y OS	VTD	VMP	53	72*	PETHEMA
Unfavorable FISH	152/141	3-y OS	CTD	VAD-cyclophosphamide	58	56	MRC IX intensive
	96/90	3-y OS	CTD	Placebo MP	34	26	MRC IX nonintensive
	99/98	3-y OS	Thalidomide	Placebo	45	69*	MRC IX maintenance

*Significant better survival outcome
Sonneveld P, et al. *Blood*. 2016;127(24):2955-2962.

If we start looking at the translocation 4;14 patients in the HOVON-65 trial experience looking at the arm that received bortezomib as part of the induction followed by maintenance with bortezomib, it appears that the arm that was getting bortezomib through-and-through may have equal survival benefit compared to standard-risk patients if they are receiving a proteasome inhibitor. Whereas, that was not clear for other groups including the deletion 17p group, where there may have been an improvement but not overcoming of the poor prognostic features when only bortezomib was utilized. One key element that we see in all these trials is the inclusion of a novel agent such as an IMiD and/or proteasome inhibitor for the broader unfavorable high-risk group appears to improve their PFS and survival outcome, but may not be able to overcome the poor prognostication that is confirmed by having that kind of FISH abnormality.

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RVD Consolidation and Maintenance in HRMM

Table 1. Patient characteristics

Patient characteristics (N = 45)	*At diagnosis N (%)*	*At ASCT N (%)*
Median age, years (range)	55 (33–75)	56 (33–76)
Sex		
Male	22 (49)	
Female	23 (51)	
Race		
Caucasian	24 (54)	
African-American	20 (44)	
Asian	1 (2)	
Isotype		
IgG	24 (54)	
IgA	10 (22)	
FLC	11 (24)	
High-risk features		
Del 17p	19 (42)	
Del 1p	9 (20)	
T (4;14)	2 (5)	
T (14;16)	5 (11)	
PCL	11 (24)	
Others (aggressive presentation)	7 (16)	
>1 Cytogenetic abnormalities	34 (75)	
ISS Stage		
Stage I	7 (16)	27 (60)
Stage II	13 (29)	13 (29)
Stage III	18 (40)	4 (9)
Unknown	7 (16)	1 (2)
Median hemoglobin (range)	9.8 (5.9–13.5)	10.20 (7.7–12.9)
Median creatinine (range)	1.55 (0.46–9.52)	0.86 (0.42–6.65)
Median calcium (range)	9.75 (8.2–15.5)	8.6 (7.7–10.2)
Median albumin (range)	3.6 (1.9–4.5)	3.6 (2.7–4.3)
Median β-2 microglobulin (range)	5.51 (1.67–30.68)	2.05 (0.89–22.05)
Median stem cells collected (range)		12.32 (6.09–25.70)

Abbreviations: ASCT, autologous stem cell transplant; FLC, free light chains; ISS, International Staging System; Ig, Immunoglobulin; PCL, plasma cell leukemia.

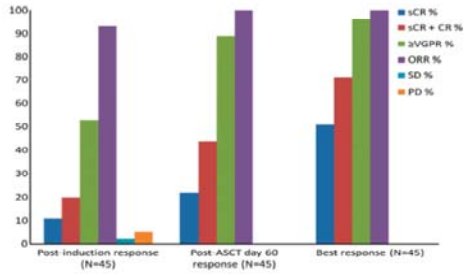

Figure 1. Response rates in patients with high-risk disease.

Nooka A, et al. *Leukemia*. 2014;28:690-693.

This is a curious study that was published by the Emory group that utilized RVD consolidation and then RVD maintenance in high-risk myeloma patients at their single center. They had reported on 45 patients. You can see the characteristics of patients, where most of the patients were ISS stage 2 or 3, and the high-risk features that they included in this particular study were deletion 17p, deletion 1p, translocation 4;14 and 14;16 as well as plasma cell leukemia. Seeing that post-induction, post-transplant, and then best response after having received RVD consolidation and maintenance was fairly impressive with an overall response rate of about 100% in the high-risk patients, and this kind of response was sustained, which is quite remarkable.

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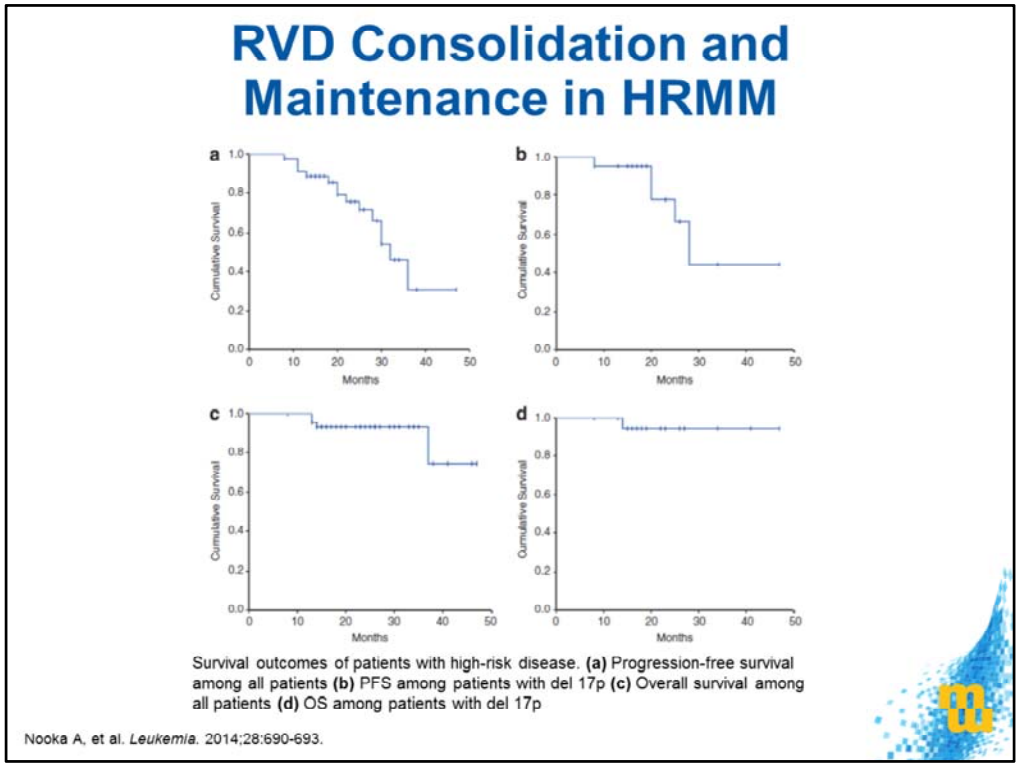

So, the progression-free survival as you can see in the figure B, going out at about 3 years was about 45% to 50% and the overall survival leading out to 3 or 3.5 years was well over 80%, which is again quite impressive. Looking at the overall survival among deletion 17p patients specifically appeared to be well over 90% at three years.

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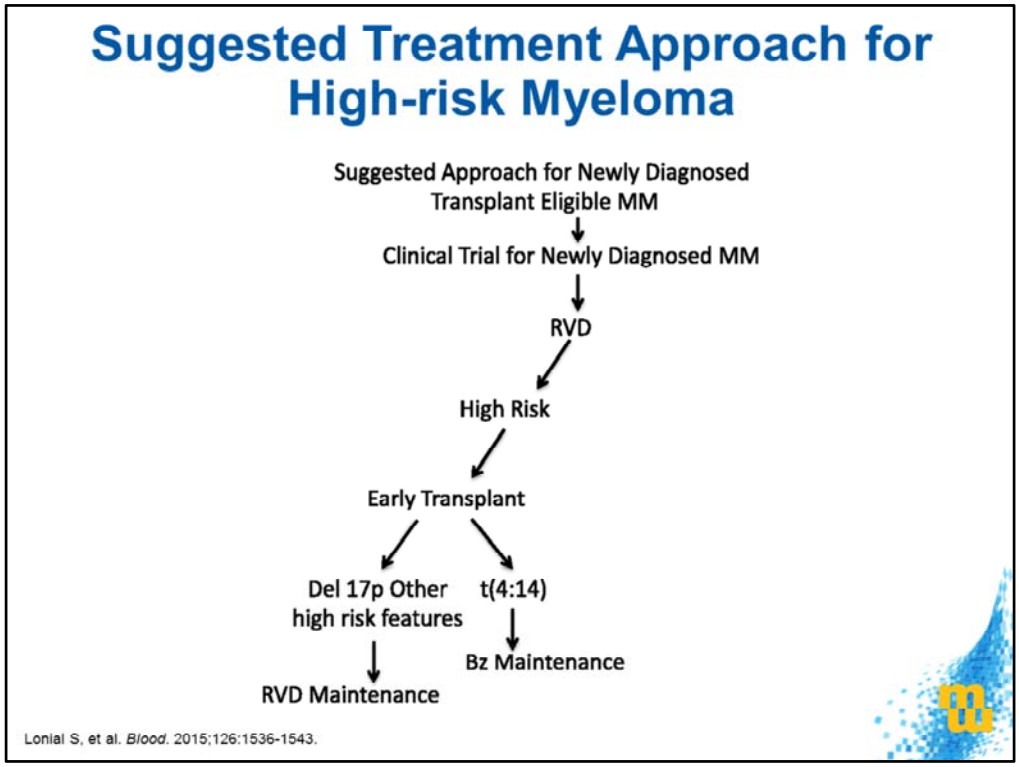

So, all of these observations lead us to believe that the optimal approach for newly diagnosed myeloma patients, after having received RVD induction, is to proceed with early transplantation. For deletion 17p patients and those with other high-risk features, a triplet maintenance may be most suitable; whereas, for translocation 4;14 patients, perhaps bortezomib maintenance would be fairly reasonable.

Having said that, there are emerging treatment strategies in the newly diagnosed setting.

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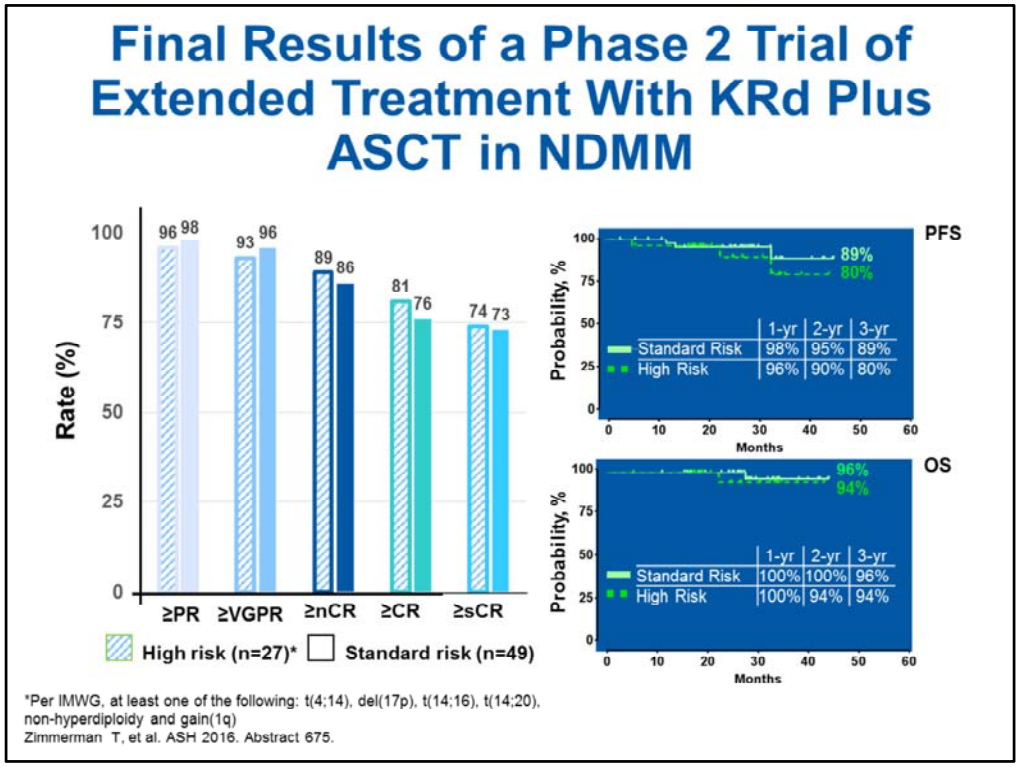

The MMRC clinical trial that looked at KRd along with autologous stem cell transplant and then KRd consolidation and maintenance. These were data presented by Dr. Zimmerman at ASH showing that high-risk patients, and you can see the criteria right there, appear to have similar depth of response as well as PFS and overall survival to standard-risk patients with this kind of an approach. So kind of building on the total therapy experience and the RVD consolidation and maintenance experience that the Emory group had, where you have a very effective induction regimen and you are consolidating patients with the three-drug combination followed by an extended maintenance strategy, thus improving the outcomes in high-risk patients.

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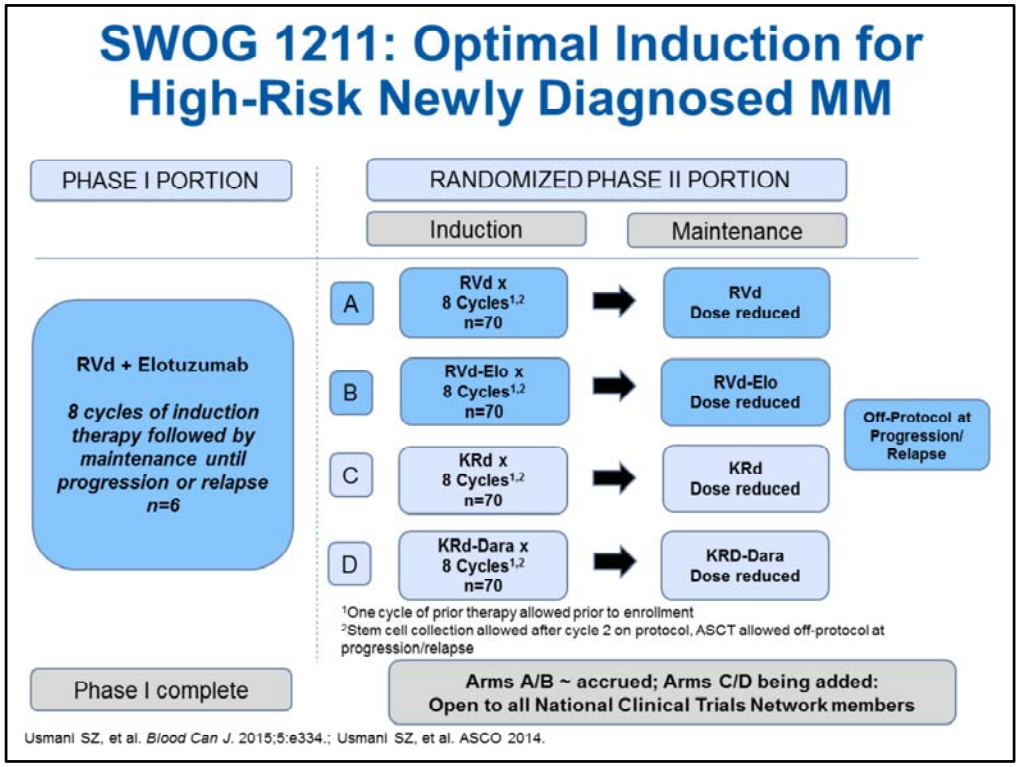

To add to that, there is a SWOG 1211 study trying to optimize induction therapy for high-risk myeloma patients for those patients who are transplant ineligible, or the patients who have deferred their stem cell transplant to first relapse. The two original arms on that study were RVD compared with RVD-elotuzumab. Induction was 8 cycles on each of the arms followed by a dose-attenuated maintenance with three or four drugs depending on which arm the patients were on. Later this year, two additional arms are being added to that particular trial, KRd and KRd-daratumumab, with a very similar schema, so 8 cycles of induction followed by three- or four-drug dose-attenuated maintenance. Patients who are stem cell transplant eligible do get their stem cell collection done after 2 cycles of induction, and then, if they have a relapse or progression, that is the time when they can get their stem cell transplant, but this particular trial includes patients who are transplant ineligible. So, the first two arms were accrued to middle of last year, and we should have a readout in the next 12 months or so and hopefully can figure out the optimal induction therapy for high-risk myeloma patients.

ASPIRE Trial: PFS by Risk Group

	KRd (n=396)		Rd (n=396)			
Risk Group by FISH	N	Median, months	N	Median, months	HR	*P*-value (one-sided)
High	48	23.1	52	13.9	0.70	0.083
Standard	147	29.6	170	19.5	0.66	0.004

PFS=progression-free survival
Dimopoulos M, et al. *J Clin Oncol*. 2015;33(suppl; abstr 8525).

Going to the early relapse setting, I am going to simply make the point with the next few slides that even though the three-drug combinations in the early relapse setting appear to trump two-drug combinations, if we start looking at risk categories by FISH, the high-risk patients, even though we have an improvement in their PFS, those patients do not truly have the same PFS benefit as standard-risk patients. Thereby making the point that even though the three-drug combinations appear to improve the outcomes of high-risk patients, they do not necessarily overcome the poor prognostic survival that is conferred by that particular FISH abnormality.

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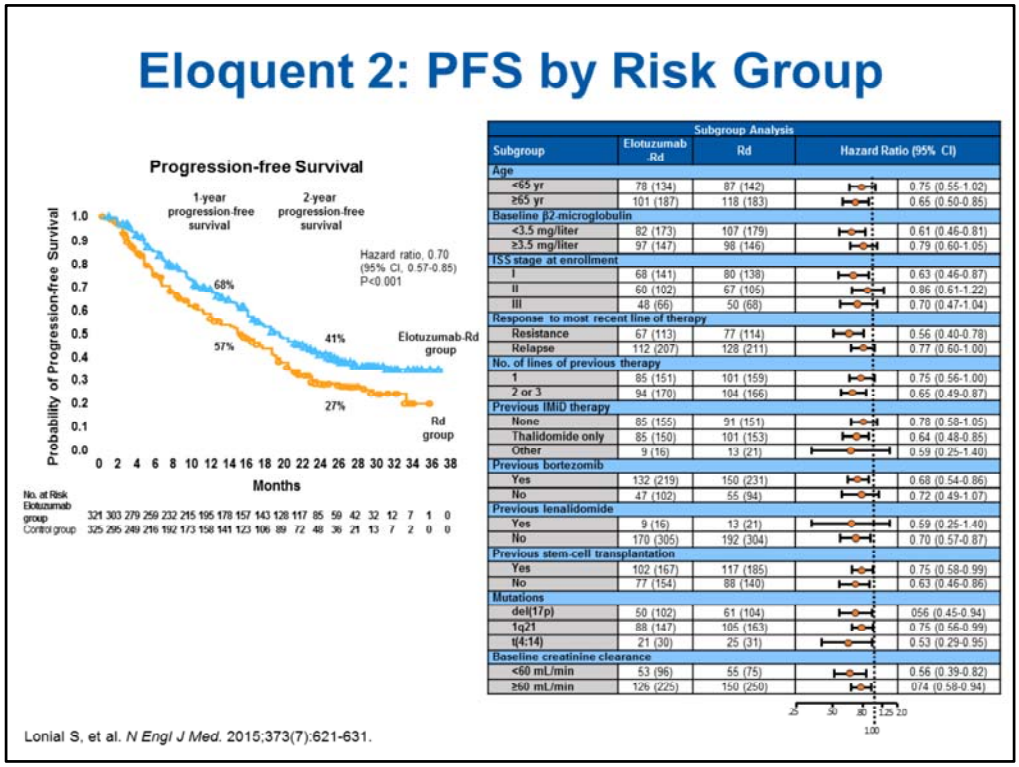
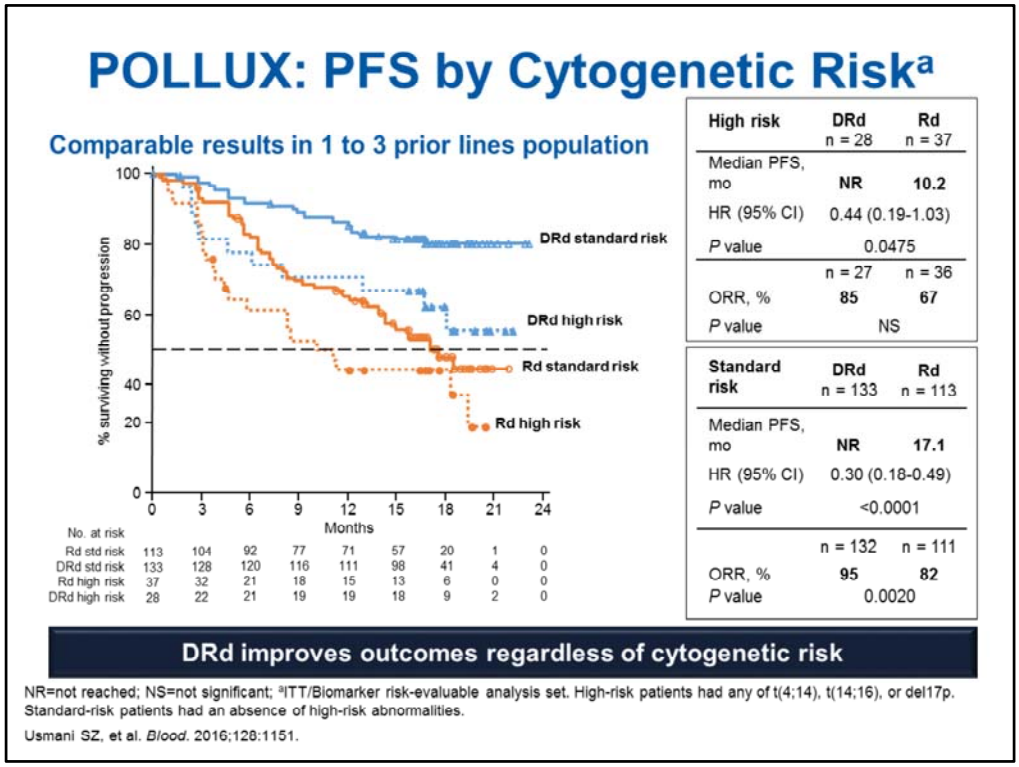


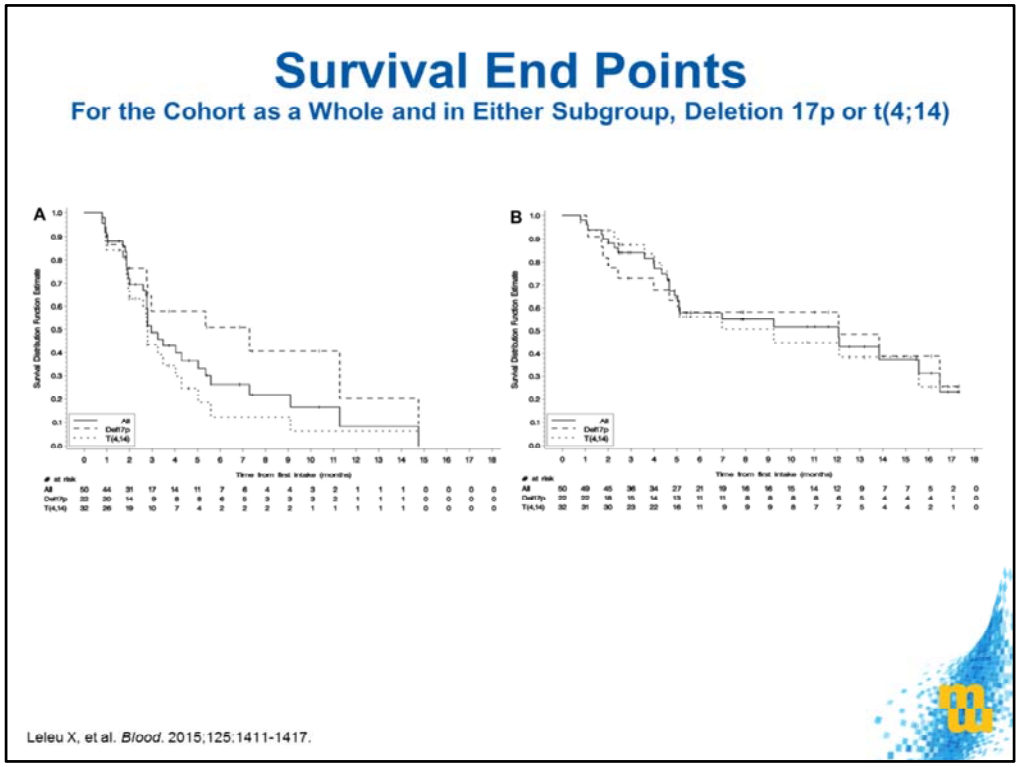
The same observation is true for the elotuzumab-lenalidomide-dexamethasone combination when compared to RD and the ELOQUENT-2 trial looking at the PFS benefit across risk stratification. There appears to be an improvement in the high-risk patients' PFS, but it is not the same as the standard-risk patients except for perhaps the deletion 17p group.

The Predictive Potential of Genomics in Multiple Myeloma



Looking at daratumumab-lenalidomide-dexamethasone (DRd) combination compared to lenalidomide-dexamethasone combination in the POLLUX study comparing results of one to three prior lines of treatments, we see that the DRd combination appears to improve the outcomes in high-risk patients, but as you can see that improvement does not appear to equal that of standard-risk patients. So, the point is even though the three-drug combination does improve the outcome it does not completely overcome the high-risk cytogenetic risk.

The Predictive Potential of Genomics in Multiple Myeloma



Another interesting observation with novel agents looking at pomalidomide and dexamethasone, Dr. Leleu presented a phase 2 study 2 years back which was focused on deletion 17p and translocation 4;14 patients showing, interestingly, that the deletion 17p patients appear to do much better in terms of progression-free survival, as well as response rates, compared to other high-risk features of patients that were included on that study, generating the hypothesis that perhaps pomalidomide does improve the poor prognostic implications of deletion 17p.

The Predictive Potential of Genomics in Multiple Myeloma

Venetoclax Monotherapy (N=66)

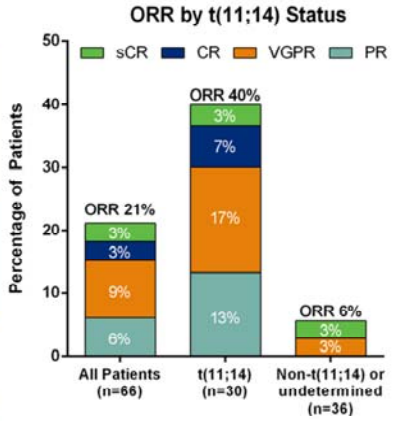
Design: Phase I, open-label, study of venetoclax monotherapy

Study Population: RRMM
- Median age: 63 years
- ISS stage II/III: 62%
- Median prior therapies: 5 (1-5)
- Prior BTZ: 94% (70% ref)
- Prior REV: 94% (77% ref)

Dosing and Schedule:
VEN: initial 2-week lead-in period with weekly dose escalation
- Final doses: daily at 300 mg, 600 mg, 900 mg, or 1200 mg
- Patients who progressed could receive VEN + dex and remain on study

- **Median time on VEN: 2.5 mo (0.2-23); 26% received VEN + dex for a median of 1.4 mo (0.1-11)**

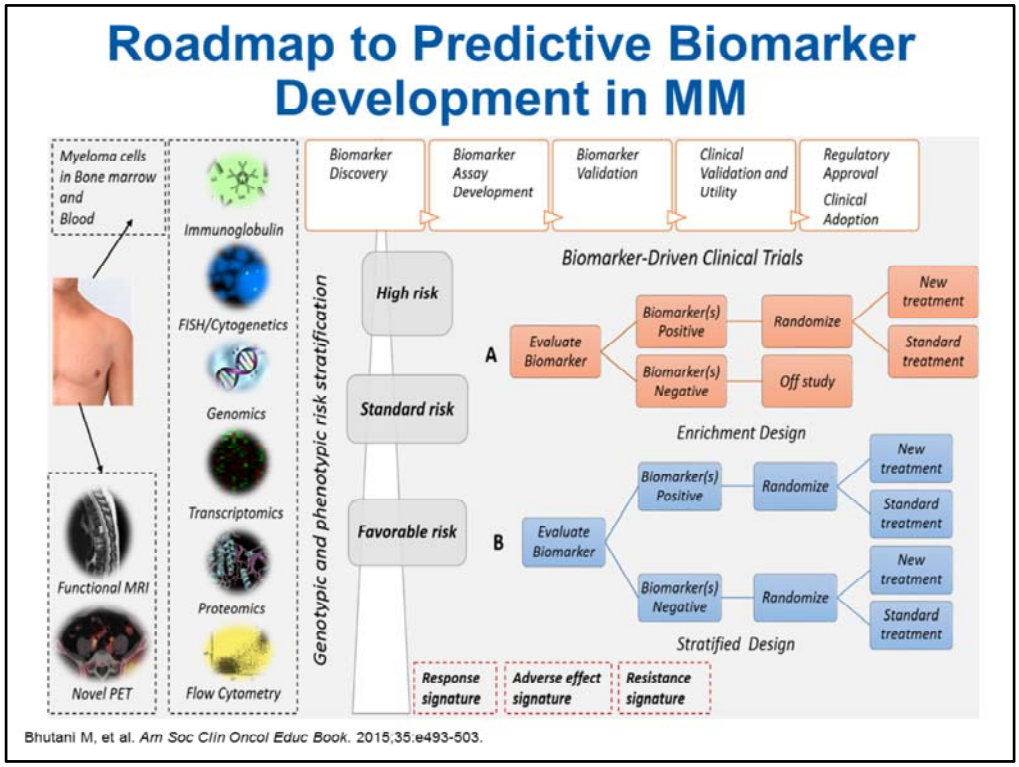
Safety, n (%)	Venetoclax
Gr 3/4 (≥10%)	Thrombocytopenia (26%), neutropenia (20%), lymphopenia (15%), anemia (14%), and decreased white blood cells (12%)
SAEs ≥2 patients	Pneumonia (n=5), sepsis (3), pain, pyrexia, cough, and hypotension (2 each)
Deaths	8 (all considered unrelated to VEN)



Kumar S, et al. ASH 2016. Abstract 488.

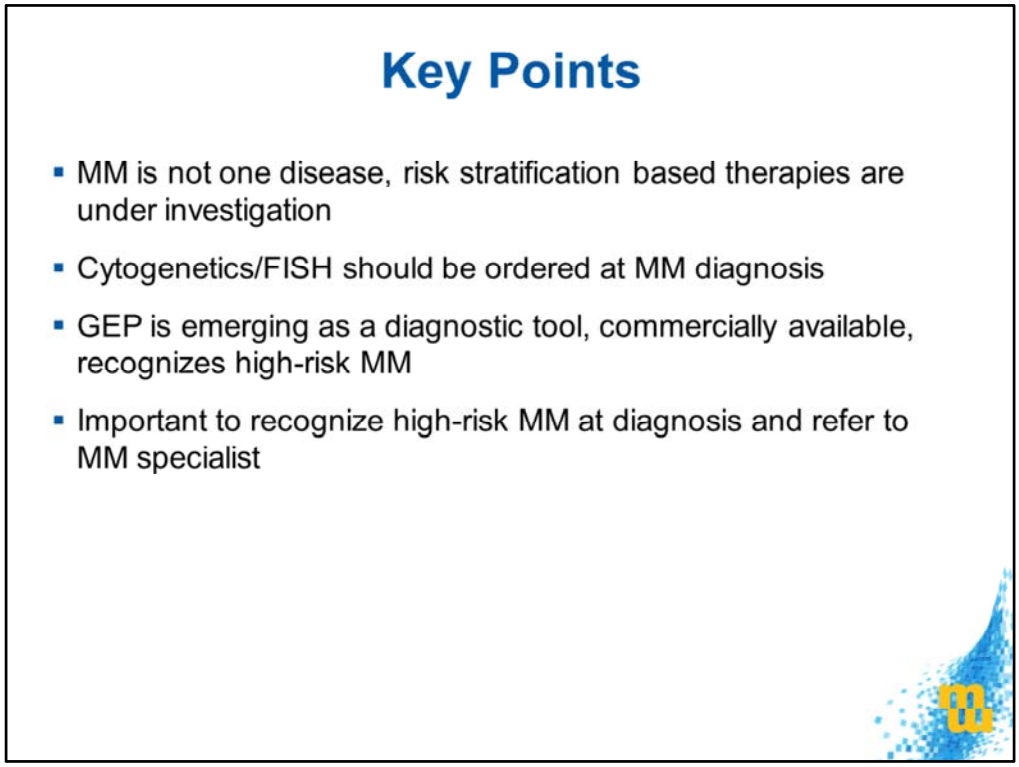
Venetoclax is a BCL-2 inhibitor which perhaps is the most exciting single agent that was presented at the ASH 2016 meeting. What was the most impressive thing about this particular study was the fact that the translocation 11;14 patients appeared to have very robust responses to the single agent where patients had median to five prior lines of therapy and for the most part were double refractory to both proteasome inhibitors, bortezomib, and lenalidomide, and this perhaps will be the first predictive biomarker-driven agent that gets approved for myeloma patients.

The Predictive Potential of Genomics in Multiple Myeloma



Bhutani M, et al. *Am Soc Clin Oncol Educ Book*. 2015;35:e493-503.

Now, this is a very busy slide but is a very important slide if you want to visualize how one would like to develop predictive biomarkers in myeloma. Ideally, one would like to look at the whole burden of disease by next-generation imaging, try to get a better sense of disease biology by looking at genomics, transcriptomics, and proteomics to tease out the multiple myeloma subclones and clones within any given patient. As you develop clinical trials, you want to have either an enrichment design where you are picking out the patients who are biomarker positive and then randomizing patients to new treatments and standard treatment, and this kind of design may have worked very well for translocation 11;14 patients where we are going to be looking at venetoclax. The second stratified design would be more relevant for the heterogenous high-risk group where we are evaluating biomarkers and randomizing patients regardless of whether they have the biomarker or not, and that is the design of the SWOG 1211 kind of study. Based on the translational signs that you are hooking up to these clinical trials, response signatures, adverse event signatures, and resistant signatures can be developed for any given patient.



Having said that, I would like to conclude and leave you with these key takeaway points. Myeloma as we recognize it, is not one disease. Risk-stratification-based therapies are under investigation. Cytogenetics and FISH should be ordered at diagnosis of myeloma in all patients, and very soon, GEP will be available to community oncologists and can be used as a diagnostic tool. It helps to recognize high-risk patients that can then go on high-risk myeloma studies. It is extremely important to recognize those high-risk patients and try to get them to a myeloma specialist sooner than later so that we can best advise you on the treatment strategy for those patients.

Thank you for viewing this activity.