Is This a High-risk Multiple Myeloma Patient?
Diagnosis, Risk-stratification and Treatment Planning Considerations

Nikhil C. Munshi, MD
Professor of Medicine
Department of Medicine
Harvard Medical School
Boston, Massachusetts

We are talking today about a young patient with myeloma and his management, keeping in mind the issues regarding risk stratification and how it affects our treatment and how we analyze this patient and manage them from induction to maintenance. So, let's talk about a case.

Patient Presentation and Previous Medical History: This gentleman is a 48-year-old male patient who was in quite a good general health except a history of mild diabetes controlled through diet and oral therapy, but without any other complications, who had complaints of increasing fatigue over the last 2 to 3 months and had developed back pain which was initially treated with some analgesic, but eventually he was referred for further investigation.

Reminder Regarding the Initial Diagnostic Work-up for Multiple Myeloma (MM) [NCCN, Version 2.2014]:

Initial Diagnostic Work-up

- H&P
- CBC, differential, platelet count
- BUN/creatinine, electrolytes
- LDH
- Calcium/albumin
- Beta-2 microglobulin
- Serum free light chain (FLC) assay
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24-hour urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Cytogenetics
- FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q211 amplification]

The following are considered useful under some circumstances

- MRI
- CT scan (avoid contrast)
- PET/CT scan
- Tissue biopsy to diagnose a osseous or extraosseous plasmacytoma
- Bone densitometry

- Plasma cell labeling index
- Staining of marrow and fat pad for amyloid
- Serum viscosity
- HLA typing

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Oncology: Multiple Myeloma, Version 2.2014 (release date: 11/08/2013).

For a useful practice resource when assessing the diagnosis of a potential MM patient for the first time, see the *Managing Myeloma* MTR® under Patient Care Tools: Initial Diagnostic Workup Tool. The tool ensures that you do not miss any necessary tests as recommended by the NCCN for the initial workup of MM.

Investigation for risk stratification [Munshi, 2011; Chng, 2014]

Investigation recommended for risk stratification *It is recommended that the new combined ISS-genetic prognostic system be used as the new standard to define high-risk disease* (See Table 3) [Chng, 2014]
Serum albumin and β_2-microglobulin to determine ISS stage
Bone marrow examination for t(4;14), and del(17p) and 1q21 gain on identified PCs by FISH
LDH
Immunoglobulin type IgA
Histology: plasmablastic disease
Additional investigation for risk stratification
Cytogenetics
Gene expression profiling
Labeling index
MRI/PET scan
DNA copy number alteration by CGH/SNP array

PCs=plasma cells; FISH=fluorescence in situ hybridization; LDH=lactate dehydrogenase; MRI/PET=magnetic resonance imaging/positron emission tomography; CGH/SNP=comparative genomic hybridization/single nucleotide polymorphism.

Laboratory Findings: Initial investigation showed that his hemoglobin was 10.4 g/dL and his creatinine was 1.6 mg/dL [Table 1a]. This with mild anemia and borderline renal dysfunction led to further evaluation and he was detected to have IgG of 4300 mg/dL, lambda-free light chain of 1273 mg/dL, with a suppressed IgA and IgM as well as suppressed free kappa light chain [Table 1b]. He had bone marrow aspiration and biopsy done, which showed 40% monoclonal plasma cells all lambda staining, and that was followed by a skeletal survey which showed multiple lytic

lesions in the pelvic bone and femur [Table 1c]. This was followed by some additional investigation for risk stratification, which showed β-2 microglobulin of 5.2 mg/L and albumin 2.5 g/dL [Table 1a], and bone marrow cytogenetics and FISH analysis showed deletion 13q by cytogenetics and deletion 17p in 65% of the cells by FISH [Table 1c]. So, this is the presenting situation or condition for this patient.

Table 1a Work-up findings: Laboratory Values

Lab/Normal Reference Range	**Value**
WBC 3.0–11.0 k/µL	7,8 k/µL
Plt Ct 150–400 k/µL	170 k/µL
Hgb 13.0–17.0 g/dL	**10.4 g/dL** ↓
Hct 39.0–51.0%	45%
MCV 80–100 fL	86 fL
RDW-CV 11.5–15.0%	13.3%
Neut % 38.5–75.0%	59%
Abs Neut 0.9-4.2 k/µL	2.1 k/µL
LDH <618 U/L	180 U/L

Lab/Normal Reference Range	Value
BUN 8–25 mg/dL	24 mg/dL
Creatinine 0.7–1.4 mg/dL	**1.6 mg/dL** ↑
Calcium 8.5–10.5 mg/dL	9.7 mg/dL
Albumin 3.5–5.0 g/dL	**2.5 g/dL** ↓
Beta 2 microglobulin 1.21-2.70 mg/mL	**5.2 mg/mL** ↑
Alk Phos 40–150 U/L	98 U/L
24 hour total urine protein10-140 mg/24 hrs (Bence Jones)	**290 mg/24 hrs** ↑

(H)=high, (L)=low, WBC = white blood cell, Plt Ct = platelet count, Hgb = hemoglobin, Hct= hematocrit, MCV = mean corpuscular volume, RDW-CV = red cell distribution width–coefficient variation, Neut = neutrophils, Abs Neut = absolute neutrophils, BUN = blood urea nitrogen, Alk Phos = alkaline phosphatase, LDH= lactic acid dehydrogenase, ↑ = higher than normal reference range, ↓ lower than normal reference range. Values in bold depart from normal reference range. Reference Range for male African American. Tefferi A, et al. *Mayo Clin Proc.* 2005;80(7):923-936).

Table 1b. Work-up Findings: Laboratory Values (cont.)

SPEP:	**Value**
SIFE	IgG lambda monoclonal peak
M-Spike (g/dL)	**5.21 g/dL**

Lab/Normal Reference Range	**Value**
Serum IgG 717–1,411 mg/dL	**4,300mg/dl** ↑
Serum IgA 78–391 mg/dL	**48 mg/dl** ↓
Serum IgM 53–334 mg/dL	**33 mg/dl** ↓
Serum Kappa 534–1,267 mg/dL	**98 mg/dL**↓
Serum Lambda 253–653 mg/dL	**1,273 mg/dL** ↑
Kappa/Lambda	**0.07**

Gamma Glob = gamma globulin, SIFE= serum immun-fixation electrophoresis.

Table 1c. Work-up Findings: Bone Marrow Aspirate biopsy, Routine Cytogenetics, FISH, Skeletal Survey, and MRI

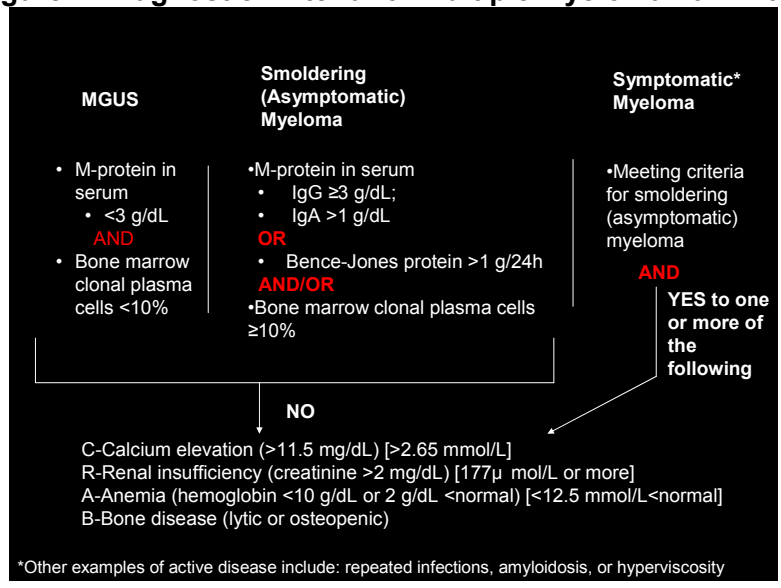
•BM Aspirate: 40% monoclonal plasma cells, all lambda staining	Routine Metaphase Cytogenetics: del 13q. *Fluorescence in situ hybridization (FISH)*: del17p (65% of cells) Skeletal Survey: Multiple lytic lesions of the pelvic bone and femur

Diagnoses, Staging, Risk-Stratification and Prognostic Assessment

Diagnosis

Now, if we look at any myeloma patient, in this one in particular, the first issue is does he have a symptomatic myeloma that requires therapeutic intervention? And that differentiates the patients who have MGUS and smoldering myeloma versus what one would call active myeloma. So for diagnosis of active myeloma, we need to have presence of monoclonal protein which this patient does have in the form of IgG lambda protein and also lambda-free light chain. Number two, you require 10% or more of clonal plasma cell which this patient does have, and finally a patient for active myeloma that requires therapeutic intervention should have one of the end-organs damaged. So, in his case, he has bone lesions and he has anemia, both considered end-organ damages. Serum creatinine is not high enough to be called by itself, but it is not entirely normal. So definitely, this patient has multiple myeloma [Figure 1]. [NCCN, 2014]

Figure 1. Diagnostic Criteria for Multiple Myeloma 2014-2015



Staging and Risk-stratification as Part of the Prognostic Assessment

International Staging System (ISS) Assessment

Then, the second aspect includes determining what his risk category is. He is an extremely young patient, and so what are the risks which are in this patient, low, intermediate, or high? There are two important risk categories that are looked upon at the present time. One is the International Staging System, and the ISS includes beta-2 microglobulin in serum and serum albumin. Now when both of them are in the normal range, serum beta-2 microglobulin less than 3.5 mg/L and serum albumin more than or equal to 3.5 at stage 1, if beta-2 microglobulin is more than 5.5 mg/L that becomes stage 3, and everything else becomes stage 2 [Table 1].

Table 1. International Staging System (ISS) [Greipp, 2005]

Stage	Criteria	Median survival (months)
I	Serum β2-microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL	62
II	Not stage I or stage III There are two possibilities for stage II: Serum β2-microglobulin <3.5 mg/L **But** **Serum albumin <3.5 g/dL** ***Or*** **Serum β2-microglobulin 3.5-5.5 mg/L** irrespective of the serum albumin level	44
III	Serum β2-microglobulin >5.5 mg/L	29

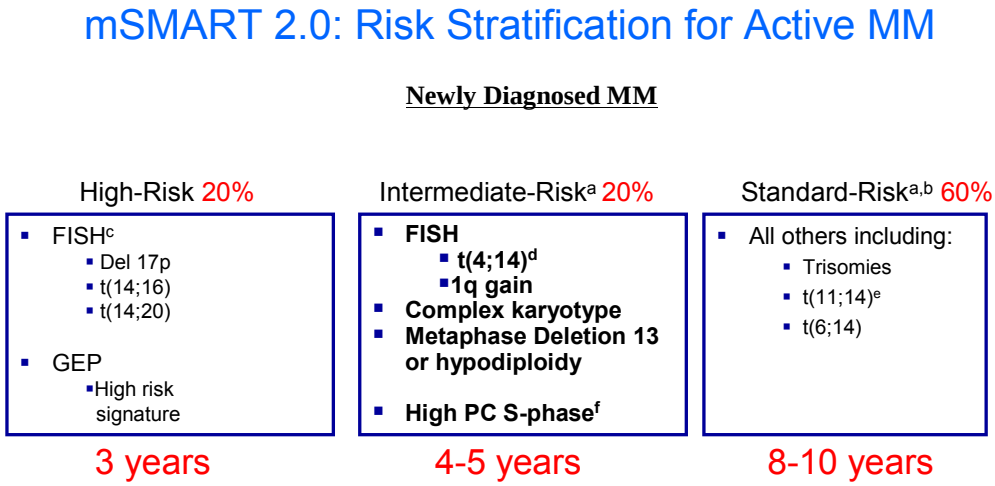
So, this gentleman is in stage 2 with high beta-2 microglobulin but not high enough to be in the stage 3 range and albumin of 2.5. So, that is one component, and stage 1 does better than stage 2 and 3, and stage 3 of course does worse than stage 2.

Genetic Abnormalities as Part of Risk-stratification

The second aspect that we can look at quite often and is quite an important aspect is to look for is genomic makeup of the patient, so by cytogenetic and FISH, if you identify abnormalities, that might determine patient's prognosis, and so any cytogenetic abnormality observed is considered a poor- or high-risk feature, and in this case, as cytogenetically or karyotypically identified deletion 13q which constitutes a high-risk feature. Now, if this was not observed and 13q was observed only by FISH, then currently, FISH-identified 13q abnormality is not

considered a high risk. So, when we do FISH, certain markers are routinely done and are connected with high-risk features, and the four of them which currently universally are deletion 17p, translocation 4;14, translocation 14;16, and more recently translocation 14;20. So, these are the translocations that are considered to be connected with higher risk and shorter survival [Figure 2]. [Avet-Loiseau, 2012]

Figure 2. Mayo Group mSMART Risk-stratification Criteria for Newly Diagnosed MM [mSMART v12, 2014; Mikhael, 2013; Kumar, 2009; Dispenzieri, 2007]



a Note that a subset of patients with these factors will be classified as high-risk by GEP
b LDH >ULN and beta-2 M > 5.5 may indicate worse prognosis;
cTrisomies may ameliorate
d Prognosis is worse when associated with high beta-2 M and anemia
e t(11;14) may be associated with plasma cell leukemia
f Cut-offs vary

Dispenzieri et al. *Mayo Clin Proc* 2007;82:323-341; Kumar et al. *Mayo Clin Proc* 2009 84:1095-1110; Mikhael et al. *Mayo Clin Proc* 2013;88:360-376. v12 //last reviewed March 2014

Now, as we will discuss very shortly, some of these can be overcome with some of the newer agents but not all of them, and especially deletion 17p is considered universally to be a high-risk feature. So, in this patient with deletion 17p, presence of it constitutes a high-risk disease. Now, this patient has 65% cells containing 17p deletion, and there was a publication by Avet-Loiseau several years ago that indicated for a 17p deletion to pose as a real high-risk prognostic indicator based on event-free and overall survival, it needs to be in more than 60% of the cells, which is the cut-off they determined from serial analysis. [Avet-Loiseau, 2007] If it is less, then the risk is not as high as it would be in those who have more than 60%. So, in this particular case, clearly, he has very predominant clones that expresses 17p deletion. It is worth noting that in a recent report at the ASH 2013 annual meeting, the Mayo group provided further supporting data regarding the prognostic value of the 17p deletion that indicates that if it is present at diagnosis or acquired at any time during the life cycle of the disease, it is associated with poor overall survival, and the proportion of PCs with del 17p appears to impact the prognostic value of this abnormality where patients with >80% involvement had particularly

inferior survival outcomes compared to the rest in their study. [Painuly, 2013] So, del 17p should always be considered a poor prognostic indicator and the proportion of cells that have this abnormality can further stratify the patient's prognosis from not as good as those without it to significantly poor. Now while we are talking about the clonal part, there has been emerging data that the myeloma clone evolves over time, and in fact, at the diagnosis, also the cells have multiple clones and then over time this clonal complexity or heterogeneity actually increases. [Brioli, 2014; Melchor, 2014] So, this patient could have fewer numbers of 17p-containing cells at one time point. Over time, it increases in number or in some cases it was not present before and it comes up later on, and the reason to mention this is that even though the patient in some cases may be low risk to start with at the time of diagnosis, over time he may acquire high-risk features and his risk stratification may change. [See Figure 3 A and B from Painuly, 2013]

Figure 3A and 3B. 17p deleted multiple myeloma: Clinical outcomes and predictive factors for acquisition of 17p deletion. [Painuly, 2013]

Figure 3A

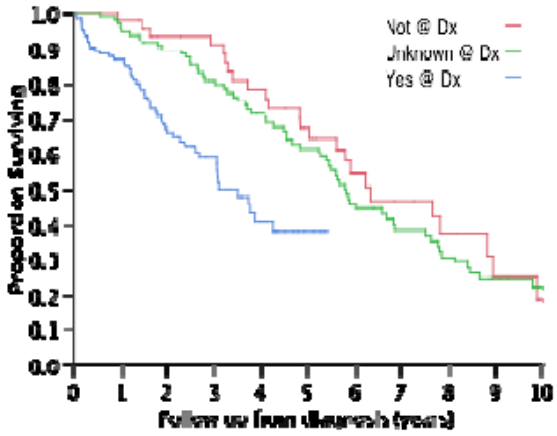


Figure 3B

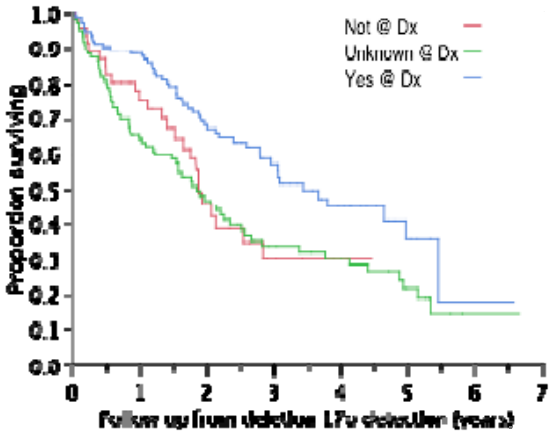


Figure Legend: 264 MM patients with del17p/monosomy 17 identified by FISH at some time during their disease course were studied. The median follow up from diagnosis was 5.4 years with 124 (47%) patients alive at last follow up; 123 (47%) had del 17p at diagnosis (Group Yes @ Dx), 95 had unknown 17p status at diagnosis (Group Unknown @ Dx), and 46 had no del 17p at diagnosis (Group Not @ Dx). The median overall survival (OS) from diagnosis for the entire cohort was 5.5 years; for the three groups the median survival was 3.1 (Yes @ Dx, 5.8 (Unknown @ Dx and 6.3 years (Not @ Dx), respectively [Figure 3A]. Similarly, the OS from the time of detection of del17p for the three groups were 3.4, 1.9, and 1.9 years respectively [Figure 3b].

So, one of the evolving concept that we have to keep in mind is that a patient who is at low risk today does not necessarily mean he is going to be low risk forever. He could at some point turn into higher risk disease with more significantly poor prognosis from that point onwards. So, some of the risk stratification especially in low-risk patients may need to be repeated periodically over the treatment span of the patient. Now, not necessarily in these patients but another higher risk feature which has been identified that we need to keep in mind are high plasma cell labeling index which is not very routinely done and so we do not mention it, but something that is important is patients with very high LDH disease, patients with extramedullary plasmacytoma,

patients presenting de novo with plasma cell leukemia at the time of diagnosis, and then there are some gene expression profile [GEP] features or signatures that have been recognized as indicating higher risk. [Patel, 2012; Gkotzamanidou, 2011; Oriol, 2011; Moreau, 2014; NCCN, 2014]

Genetic Expression Profile Signatures and Other Risk Indicators

There is a 70-gene signature, there is a 92-gene signature, and there is a 15-gene signature. [van Laar, 2014; Kuiper, 2012; Decaux, 2008; Kumar, 2011] Each one has around 15-20% of patients who will be categorized as high-risk disease, and they are being utilized although not universally applied yet because they are still cumbersome and quite often the higher risk is predicted by other features already so that gene expression profile may not contribute anything more, at least at the present time. [Chng, 2013] In some cases, IgA disease has been described as carrying higher or poorer risk; however, that is not used uniformly to differentiate patients from one versus another risk category. [Sirohi, 2001; Tricot, 1995; Pasqualetti, 1991; NCCN, 2014]

What Defines High-risk and Low-risk Patients?

IMWG High-risk, Standard-risk, and Low-risk 2014

In its most recent statement regarding risk stratification, the IMWG consensus panel agrees that a reasonable benchmark to define high-risk patients will be an overall survival of 2 years or less despite the use of novel agents. [Chng, 2014] Conversely, low-risk patients will be those that survive more than 10 years. Each of these two ends of the spectrum encompass about 20% of the population of newly diagnosed patients, respectively, with the remaining 60% falling into the IMWG risk-category of standard risk (Table 2). This schema also fits in with the mayo stratification of myeloma and risk-adapted therapy (mSMART) risk categories proposed by the Mayo Clinic. [Kumar, 2011; Mikhael, 2013; mSMART v12, 2014]

Table 2. Risk Stratification and Possible Therapeutic Questions Within Each Risk Category [Chng, 2014]

	High-risk	**Standard-risk**	**Low-risk**
Parameters	ISS II/III and t(4;14)[a] or 17p13 del	Others	ISS I/II and absence of t(4;14), 17p13 del and +1q21 and age <55 years
Median OS	2 years	7 years	> 10 years
% Patients	20%	60%	20%
Therapeutic Questions	There is a need for novel therapeutic approaches e.g. Allogeneic stem cell transplant or immunotherapy approaches		Do these patients benefit from maintenance therapy? Is VGPR a good enough response in these patients, as they may revert to a MGUS state

Abbreviations: ISS, International staging system; MGUS, monoclonal gammopathy of undetermined significance; OS, overall survival; VGPR, very good partial response.

[a]Survival of t(4;14) patients is improved with the use of bortezomib-based therapy.

Summary of Diagnosis, Staging, Risk-stratification and Prognosis for the Patient

So, at this stage, we have all the information on this patient. We need to categorize them as young, high-risk myeloma, newly diagnosed, who has borderline renal dysfunction but otherwise has rest of the features of what you would observe in classic myeloma. So, the treatment decision in this type of patient depends on a variety of factors as we pick the disease apart. So first thing, if we eliminate the smoldering myeloma possibility, we need treatment in this patient.

Treatment and Management Planning Considerations

Eligibility for Transplant and Consideration of Comorbidities and Sequelae

The second thing to consider is whether he is a transplant candidate, and obviously, he is a classic transplant candidate: young, good functional status and no contraindications. The people who are not transplant candidates are those who are older with multiple comorbidities including cardiorespiratory, with poor performance status or who are otherwise not willing. So, this gentleman at a young age is clearly a transplant candidate. And then, selection of primary therapy depends on other characteristics. It depends on patient's renal function, presence of neuropathy, bone disease, and other risk factors present as we discussed earlier such as genetic abnormalities, and then, if patients are old, we look at convenience and tolerability of treatment. [McCarthy, 2013; Rajkumar, 2014; Park, 2014; Moreau, 2014b; Cerrato, 2014] That is not a problem here. We need to give the best treatment that we can, and the most important thing, the bottom line for treating this patient is to get the best complete remission we can get, and there is an evolving concept of minimal residual disease (MRD), which is what we would want to attain, a molecular remission, and it is going to be an important endpoint in this patient to achieve the best outcome. [Lonial, 2014; Martinez-Lopez, 2014]

Tailoring Treatment to the Patient's Needs

So, keeping all these possibilities in mind in this patient, we have possible multiple options that we can consider or think about. Now, what are those option? And there is a very clear data that a three-drug regimen has superior responses and EFS compared to a two-drug regimen. [See the following supporting reviews: NCCN, 2014; Rajkumar, 2014] So, we would pick upfront, a three-drug regimen. The three-drug regimens that are available for this patient for utilization are first of all lenalidomide, bortezomib, and dexamethasone, the RVD combination. [NCCN, 2014; Roussel, 2014] Another combination possible is bortezomib, cyclophosphamide, and dexamethasone, the VCD or also known as CyBorD regimen. [NCCN, 2014; Reeder, 2014] These two are the predominant ones. On the European side, where lenalidomide is not commonly available, one can also use bortezomib, thalidomide, and dexamethasone, but it has quite high incidence of peripheral neuropathy as a problem, and I would not consider that as one of my leading candidates to treat this patient. [Engelhardt, 2014; Moreau, 2011] In the US, there is a movement toward thalidomide sparing regimens with the availability of lenalidomide. So then, we pick the treatment in this patient, and my choice in this patient would be the triplet combination of lenalidomide, bortezomib, and dexamethasone (RVD), which is consistent with mSMART recommendations for high-risk patients like this patient who has a deletion 17p, keeping in mind that lenalidomide is renally excreted and thus may require adjustment in accordance with the patient's creatinine clearance. [Palumbo, 2012a; Mikhael, 2013; NCCN, 2014] However, this patient's renal function is not significantly affected at his age, and creatinine his GFR is about 60, and that allows normal dose of lenalidomide in this patient.

If there was a concern, then using bortezomib, cyclophosphamide, and dexamethasone also is quite appropriate in this patient population. Subgroup analysis of the HOVON-65/GMMG-HD4 trial shows that bortezomib-based regimens both before and after ASCT overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma patients. [Scheid, 2014] Now, the second issue that comes up is, my decision involved taking into account he is at higher risk, and the answer is not direct. So, we have information on multiple publications that the patients who are at higher risk with 4;14 translocation for example, the higher risk can be overcome to some extent by bortezomib [San Miguel, 2008; Avet-Loiseau, 2010a; Barlogie, 2007; Chang, 2007; Pineda-Roman, 2007] and to a lesser extent also by lenalidomide. [Reece, 2009; but also see Avet-Loiseau, 2010b](Table 2). [Kalff, 2012]

Table 3. Outcomes of patients with t(4;14) MM across several clinical studies [Kalff, 2012]

Study	*t(4;14), % (N total patients)*	*Treatment*	*PFS t(4;14) patients, mo*	*PFS all patients, mo*	*OS t(4;14) patients, mo*	*OS all patients, mo*
Gertz et al.	26 (153)	HDT and ASCT	8.2[a]	17.8[a]	18.8[1]	43.9[a]
Chang et al.	15 (120)	HDT and ASCT	9.9[a]	25.8[a]	18.3[1]	48.1[a]
Reece et al.	28 (102)	Len/Dex	8.0[b]	7.1[b]	23.7	18.13
Avet-Loiseau et al.	14 (184)	Len/Dex	5.5[a]	10.6[a]	9.4[a]	15.4[a]
San Miguel et al	4[c] (682)	Bort/Mel/Pred	19.8	21.7	Not reached[d]	Not reached[d]
Chang et al.	6 (40)	Bort	10.4	6.8	15.1	12.3
Pineda-Roman et al.	10 (303)	Bort/Thal/Dex	Median data not presented			
Avet-Loiseau et al.	21 (507)	Bort/Dex	Median data not presented			

ASCT=allogeneic stem cell transplant; Bort=bortezomib; Dex=dexamethasone; HDT=high-dose therapy; Len=lenalidomide; Mel=melphalan; MM=multiple myeloma; mo=months; OS=overall survival; PFS=progression-free survival; Pred=prednisone; Thal=thalidomide.
[a]These differences were determined to be statistically significant.
[b]Reported as time to tumor progression.
[c]Patients had t(4;14) or t(14;16) translocation.
[d]OS measured for low-risk group; was not measured for entire population.

The 17p deletion very minimally is overcome by bortezomib, not much by lenalidomide. [Sonneveld, 2012; Neben, 2012; Knop, 2009] However, this combination is still going to be used in the patient whether he is at high risk, but this drug may have some benefit or low risk. So, in some ways, our induction regimen is not totally driven by specific risk feature in this patient population, and depending upon various protocols utilized, the patients get anywhere from 3 to 6 cycles of this regimen to get the patient into good remission status, hopefully in complete remission status, and there is data that almost 30-40% patients may end up eventually getting CR with lenalidomide, bortezomib, and dexamethasone. [Roussel, 2014] Indeed, an IFM phase II study has shown 58% achieved a CR and 68% achieved MRD (-) with RVD induction and consolidation and 1-year fixed duration lenalidomide maintenance in patients who have undergone transplant. [Roussel, 2014] This approach is being evaluated in the ongoing IFM/Dana-Farber Cancer Institute 2009 phase III study. At that point, the decision would be to consider transplant. Again in a young patient at his age, transplant is an important option. [NCCN, 2014] Especially, he has bone lesions, he has borderline renal dysfunction, I would not like to delay his transplant, which could be done in older patients with less of these other problems.

Now, the issue comes up is, does transplant help in the patients who have high-risk disease? And there has been some controversy generated saying transplant is not as beneficial in the patients who have high-risk disease, and that is not entirely accurate in the sense that it is true that the benefit of transplant in high-risk disease is less than the benefit of transplant in low-risk disease. However, if you compare transplant versus no transplant in higher risk disease, that is definitely a benefit that they do get, which is less than low risk but there is still a benefit. So, transplant is a good option for this patient for consolidation, and I would recommend that. Now if we do not get very good partial remission following transplant, then a tandem transplant could be indicated, but if the patients do get VGPR or better, then a single transplant is adequate in this patient, and then posttransplant, the main issue would be either consolidation and/or maintenance. As this patient has a high-risk disease, one should consider consolidation and a common consolidation in a situation like this could end up being either the patient is getting again the same three-drug induction regimen or use alternative VCD as a regimen to consolidate him further with 2 cycles. Following this, an important aspect is going to be maintenance treatment in this patient population. There are significant data about benefits of maintenance therapy. There are data about maintenance using lenalidomide, the three studies, two of which are done in younger patients following transplant, one is the CALGB Study which compared lenalidomide versus placebo maintenance and the French IFM 2005-02 Study which had lenalidomide versus placebo maintenance following 2 cycles of lenalidomide consolidation. [McCarthy, 2012; Attal, 2012] Both of these studies clearly show the benefit of lenalidomide maintenance as well as event-free survival is concerned. It is the survival that goes separate, remarkably, in both the studies. The CALGB study now already shows overall survival benefit that people who get lenalidomide have an improved overall survival. [McCarthy, 2012] The IFM Study as of a few months ago had not shown overall survival benefit. [Attal, 2013] So, we will have to wait over time to see if we do observe overall survival benefit or not. Similarly, there are studies done in older patient population with lenalidomide maintenance that are not directly applicable to our patient, but both the studies…there is an Italian study which compared MP versus MPR versus MPR with lenalidomide maintenance,[Palumbo, 2012b] which clearly showed MPR with maintenance do have superior outcome and very recently MM-20 study which compared lenalidomide-dex continuously with maintenance-type regimen versus

lenalidomide-dex versus MT and showed that patients who get RD plus continued maintenance do much better than the other group as far as PFS is concerned. [Facon, 2013]

So, getting lenalidomide maintenance is quite clear. However, the high-risk feature affects how we treat this patient. His utilization of an added agent for maintenance and one of the agents being used now in addition to lenalidomide is bortezomib in the maintenance. There is HOVON Study which has clearly demonstrated that patients can get bortezomib maintenance safely and effectively. The dosage for bortezomib in that case is standard 1.3 mg/m^2 but given every other week so every 2-week dosage. [Sonneveld, 2012] Where neuropathy is not observed, the patient can get it. So in this particular patient with high-risk disease, I would use bortezomib plus lenalidomide as maintenance. There is also emerging data that adding dexamethasone or prednisone could be beneficial. There is a recently presented Italian study where lenalidomide plus prednisone was compared with lenalidomide alone and showed a significant EFS benefit for lenalidomide-prednisone combination for maintenance. [Falco, 2013] An early report evaluating RVD consolidation followed by RVD maintenance in high-risk patients who have undergone transplant is tolerable with excellent response rates and promising PFS and OS. [Nooka, 2013] So, two- or even three-drug maintenance may be appropriate in this patient, and so this is the initial management of this patient.

What is going to make me do different in this patient moving forward just very briefly is going to be that because he has a high-risk disease and he is extremely young patient, he would be considered as a candidate for allogenic transplantation, probably at the first relapse, especially if the first relapse happens within 1 year, which quite often these high-risk patients do have. Then none of the other treatments are going to be curative or would provide a long-term remission-free survival and consideration for allogenic transplant would be an important option, but then, the rest of the management would depend on when the patient relapses and how he relapses and how he is managed. Allogeneic stem cell transplant should only be conducted in the setting of a clinical trial. [NCCN, 2014] This is one of the most important considerations. A young patient such as this with high-risk features may well benefit from clinical trial. Clinical trials should be discussed with the patient and strongly encouraged.