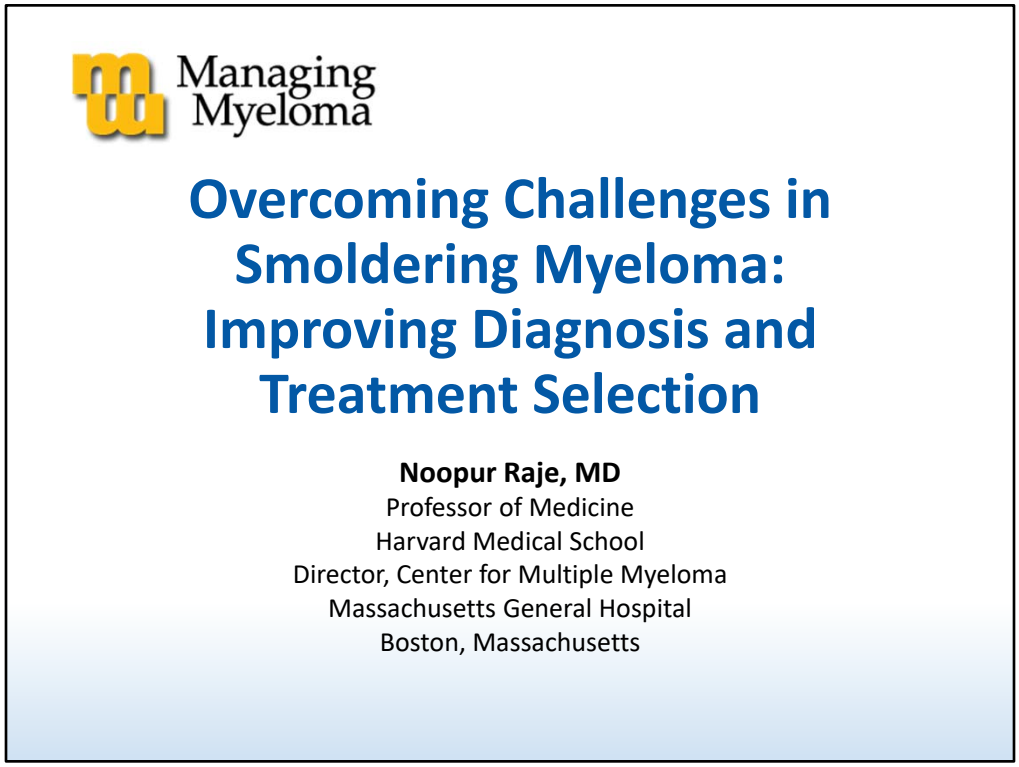
Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection



Hello and welcome to *Managing Myeloma.* My name is Noopur Raje and I'm going to discuss with you the current approaches to the diagnosis, risk stratification, and management of patients with smoldering multiple myeloma.

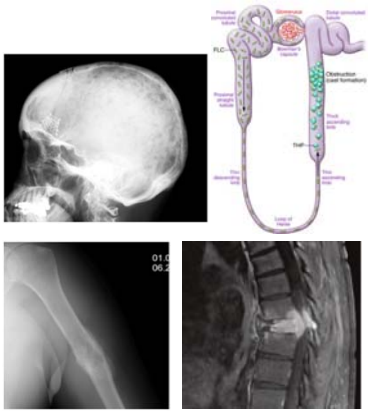
Disclosures

- Dr. Noopur Raje has received honoraria as a consultant from Amgen Inc., Bristol-Myers Squibb Company, bluebird bio, Inc., Celgene Corporation - A Bristol-Myers Squibb Company, Novartis AG, and Takeda Oncology.

Here are my disclosures.

When Is Myeloma Active (Symptomatic)?

- **CRAB** features
  - Hyper**C**alcemia
  - **R**enal Insufficiency
  - **A**nemia
  - **B**one Disease

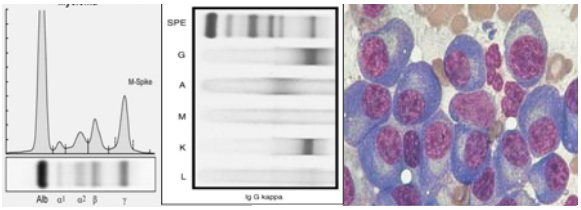


Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

Just as a way of background, when does myeloma actually become active or when is it symptomatic? I think all of you are familiar with the CRAB criteria which in essence, stands for hypercalcemia, renal insufficiency, anemia, and bone disease. Obviously, when a patient presents with any of these CRAB criteria, the diagnosis is quite straightforward and most of us, in fact, all of us, would actually treat these patients as if they had symptomatic active multiple myeloma.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection

But When it Is Not Active Myeloma…



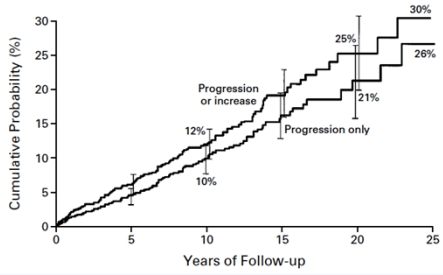
Monoclonal Gammopathy of Undetermined Significance

Natural History in 241 Cases

ROBERT A. KYLE, M.D.
Rochester, Minnesota

Two hundred forty-one patients with a monoclonal protein in the serum but initially no evidence of multiple myeloma, macroglobulinemia, amyloidosis or lymphoma were followed up for more than

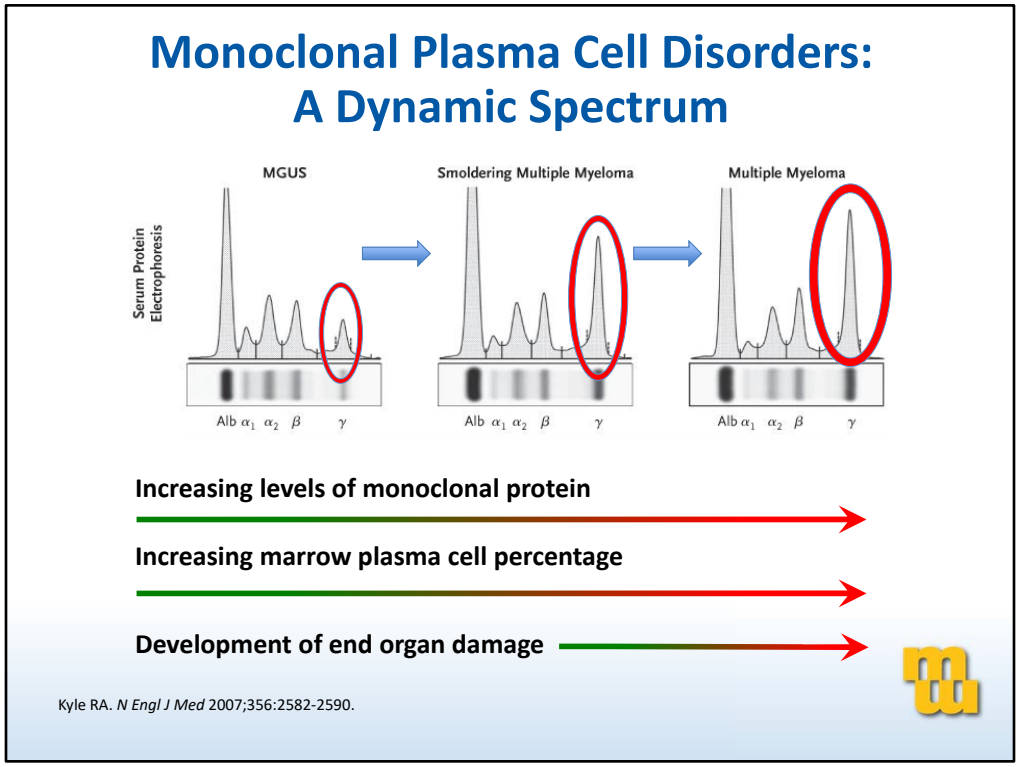
814 May 1978 The American Journal of Medicine Volume 64



Kyle RA. *Am J Med.* 1978;64(5):814-826.; Kyle RA, et al. *N Engl J Med.* 2002;346(8):564-549.

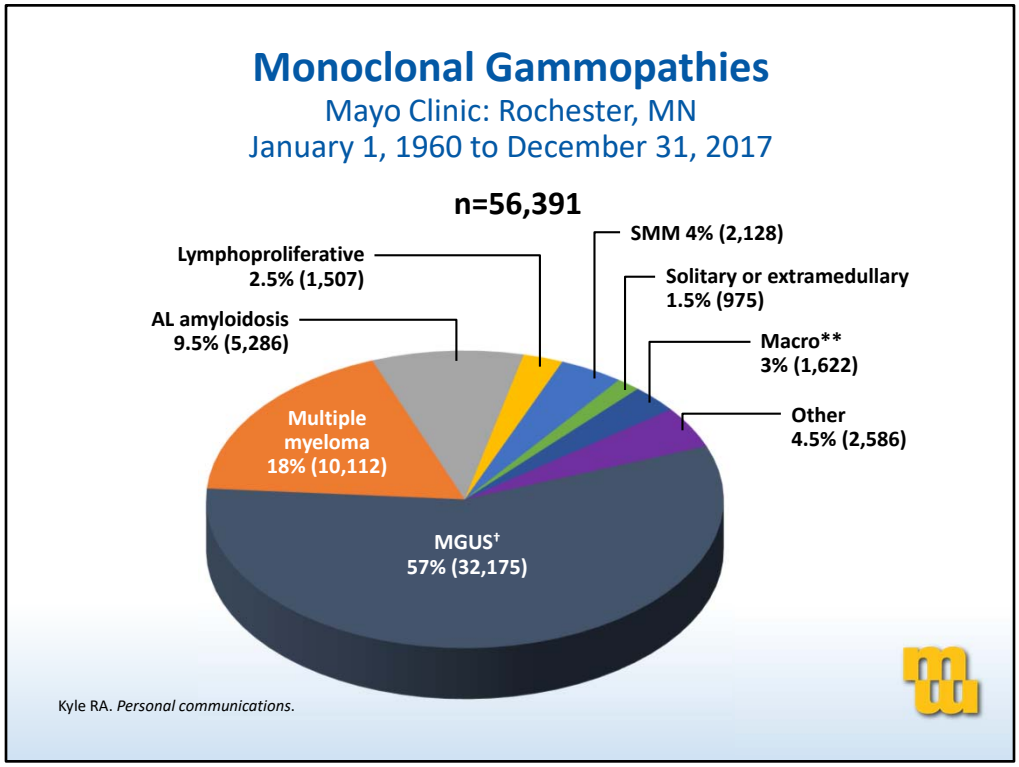
When the disease is not active, we do have in this state, a precursor disease state where you have the presence of a monoclonal protein and you do have increased plasmacytosis in patients, and this is referred to as monoclonal gammopathy of undetermined significance (MGUS). We do know that patients with MGUS have a risk of progression to active multiple myeloma. If you look at this curve here, you will see that over a 30-year period or over 25 years, the risk of progression to symptomatic active multiple myeloma is about 30% giving it about 1% per year risk of progression to active disease.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection

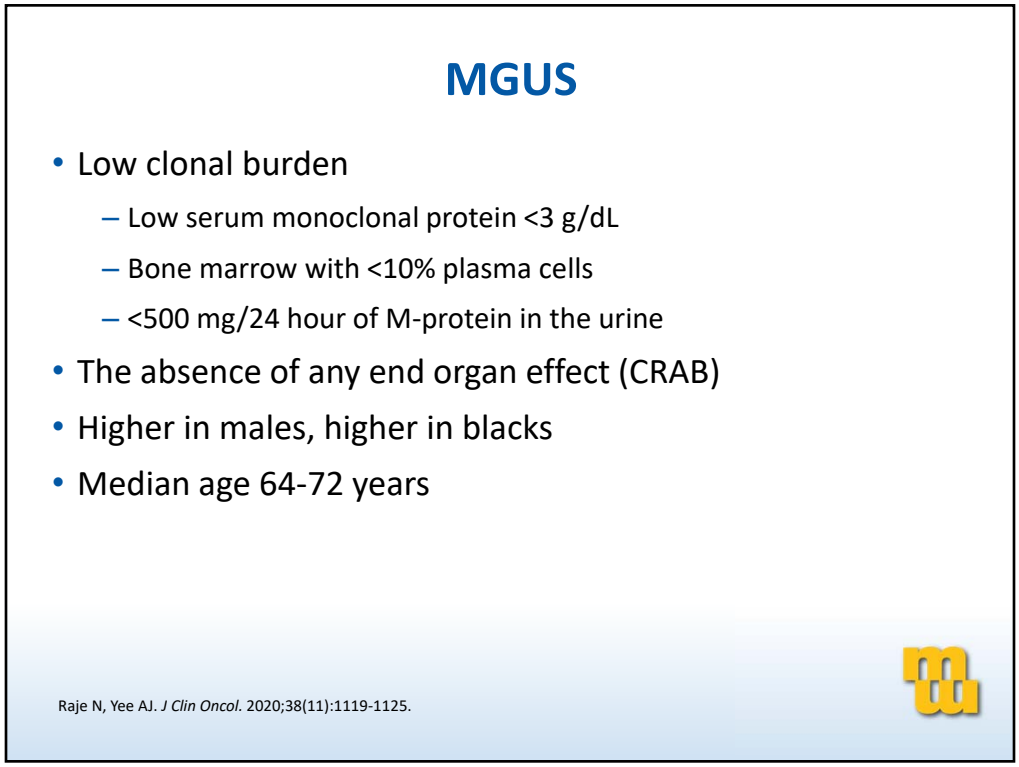


This is a spectrum of monitoring plasma cell disorders and, as you all know and are beginning to appreciate and recognize, this is a dynamic spectrum. At the stage of MGUS, you have the presence of the monoclonal protein and at the extreme other end is multiple myeloma where you have the monoclonal protein as well as the development of end organ damage. In between these two is the state of smoldering multiple myeloma, wherein patients have all the characteristics of myeloma without necessarily the end organ damage.

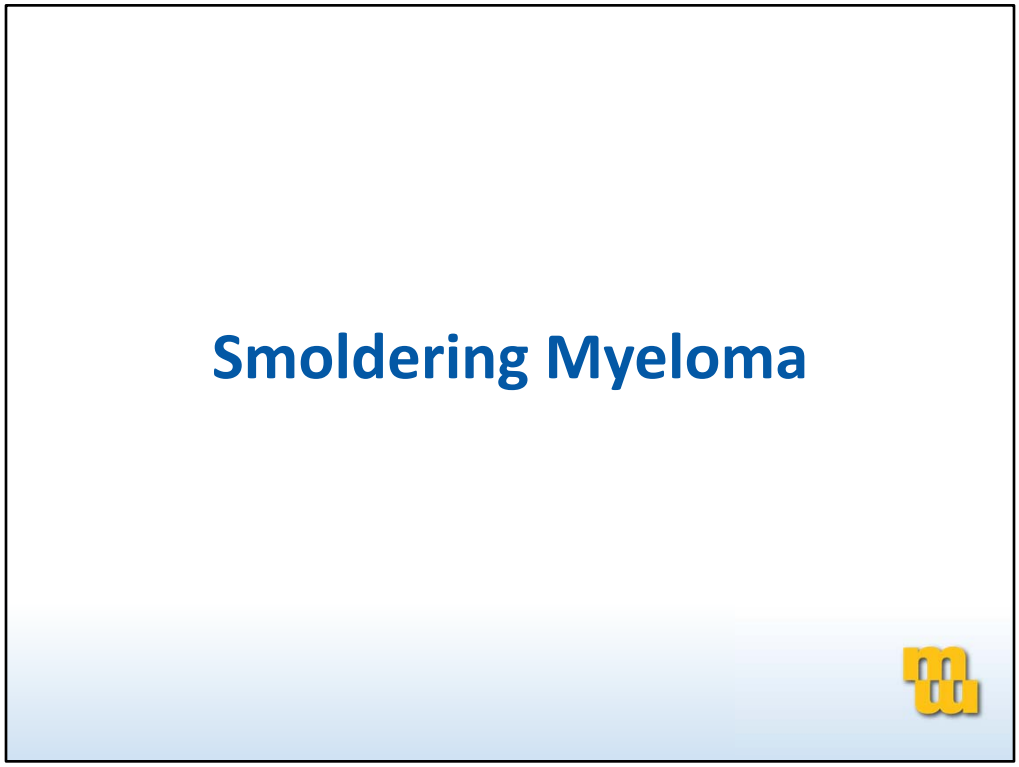
Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection



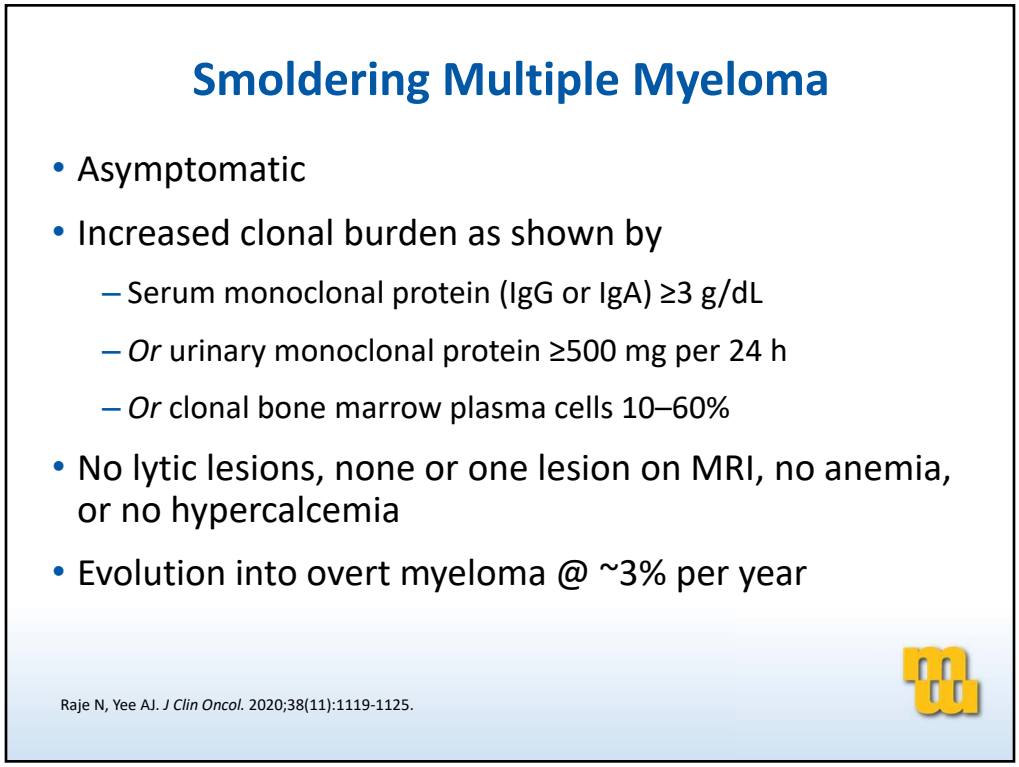
This is just an incidence of all of these monoclonal gammopathies and if you think about this, multiple myeloma accounts for about 18% and smoldering multiple myeloma, which is what we're going to be discussing today, accounts for about 4% of patients with a monoclonal gammopathy.



MGUS, as we've already discussed, is a low clonal burden. There is the presence of the monoclonal protein. There is bone marrow plasmacytosis, typically less than 10%, and none of these patients have any of the organ-defining symptoms or characteristics defined by CRAB as we've already discussed.

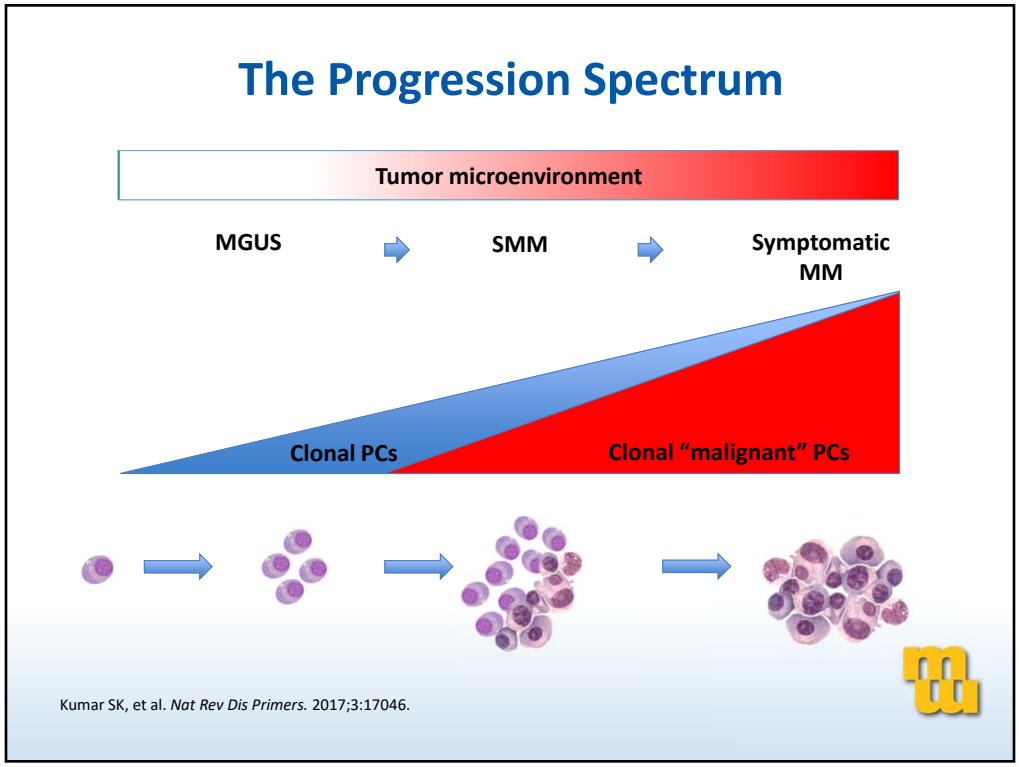


What about smoldering multiple myeloma?



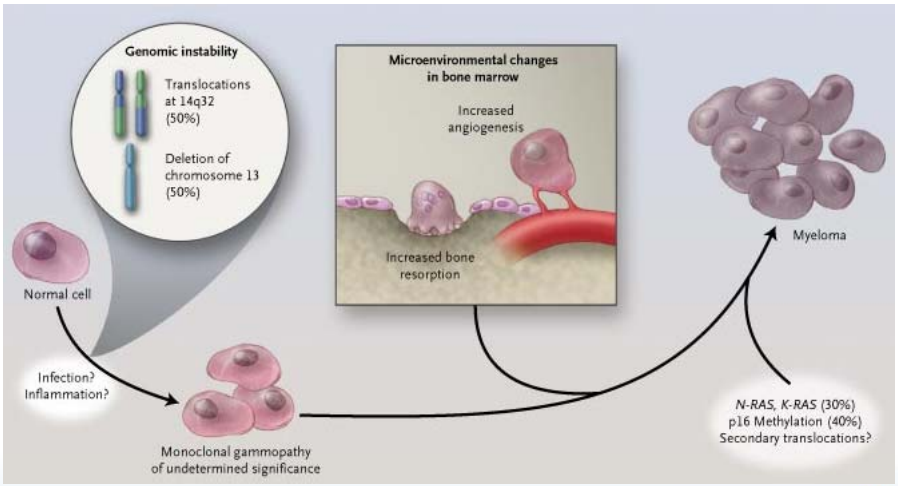
We talked about smoldering multiple myeloma being in between MGUS and multiple myeloma. It still remains an asymptomatic stage and it's associated with a slightly increased clonal disease burden with the presence of a monoclonal protein in the serum or the urine as well as an increase in bone marrow plasmacytosis. This has now been redefined. Anything more than 10% to up to 60% would fall into the category of smoldering myeloma. No end organ damage in the way of using an MRI or better imaging like PET scans without any evidence of focal disease and typically, the evolution as I've shown you with the MGUS is about at a rate of 3% per year or so.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection



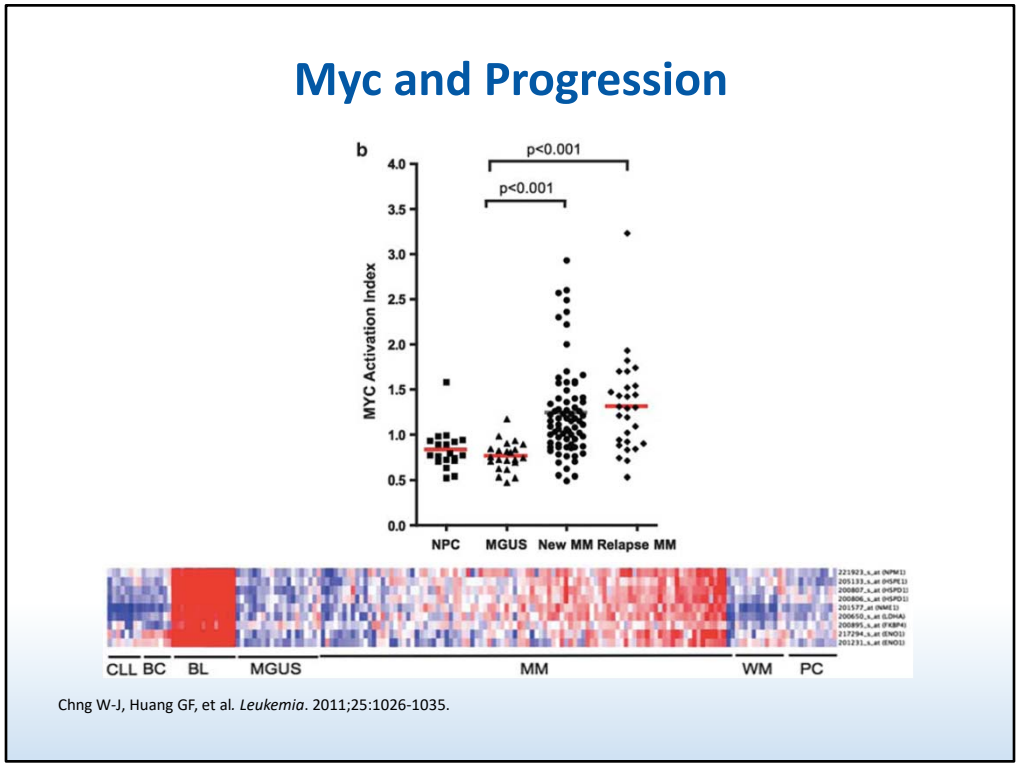
This is just explaining to you the progression spectrum of these plasma cell dycrasias where you have MGUS at one end and symptomatic multiple myeloma at the other end. As you progress through this, you will see that the clonal proliferation increases and with that, comes an increase in genetic instability as well.

Biology



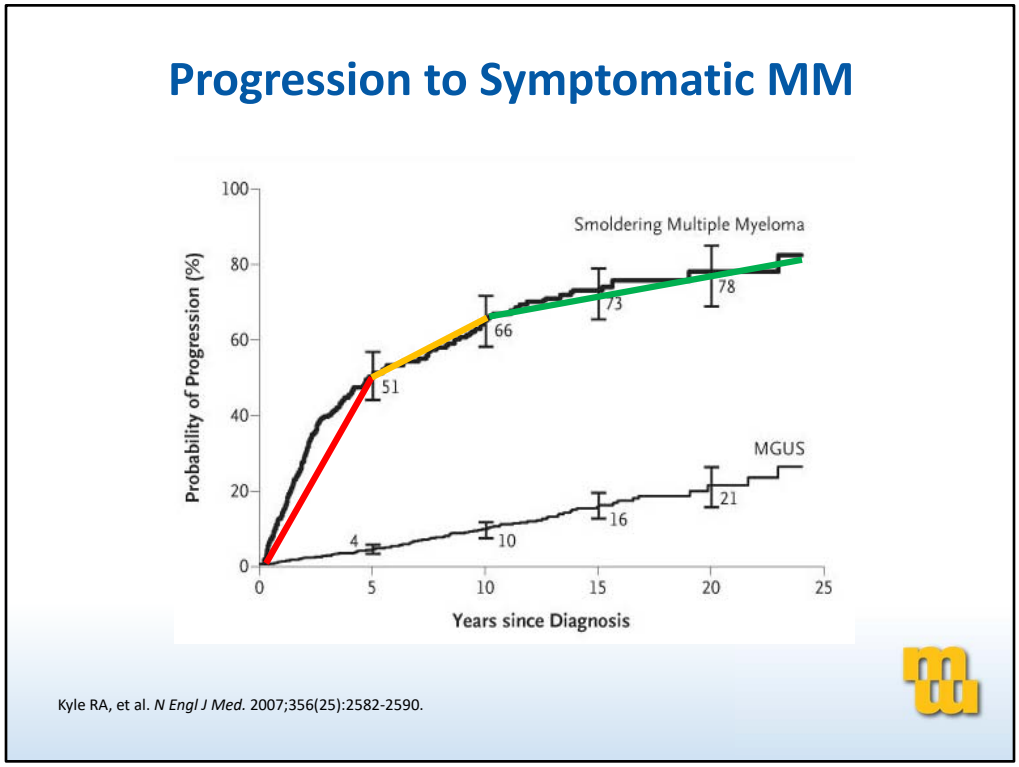
Kyle RA, Rajkumar SV. *N Engl J Med.* 2004;351(18):1860-1873.

This is depicted in this cartoon here where you start off with a normal plasma cell. The normal plasma cell, if it is exposed to antigen stimulation, either with an infection or any kind of inflammation, you can start having clonal proliferation. At this stage, it is the genetic instability which causes this clonal proliferation, which then allows the patient to transcend from the MGUS state to the multiple myeloma state.

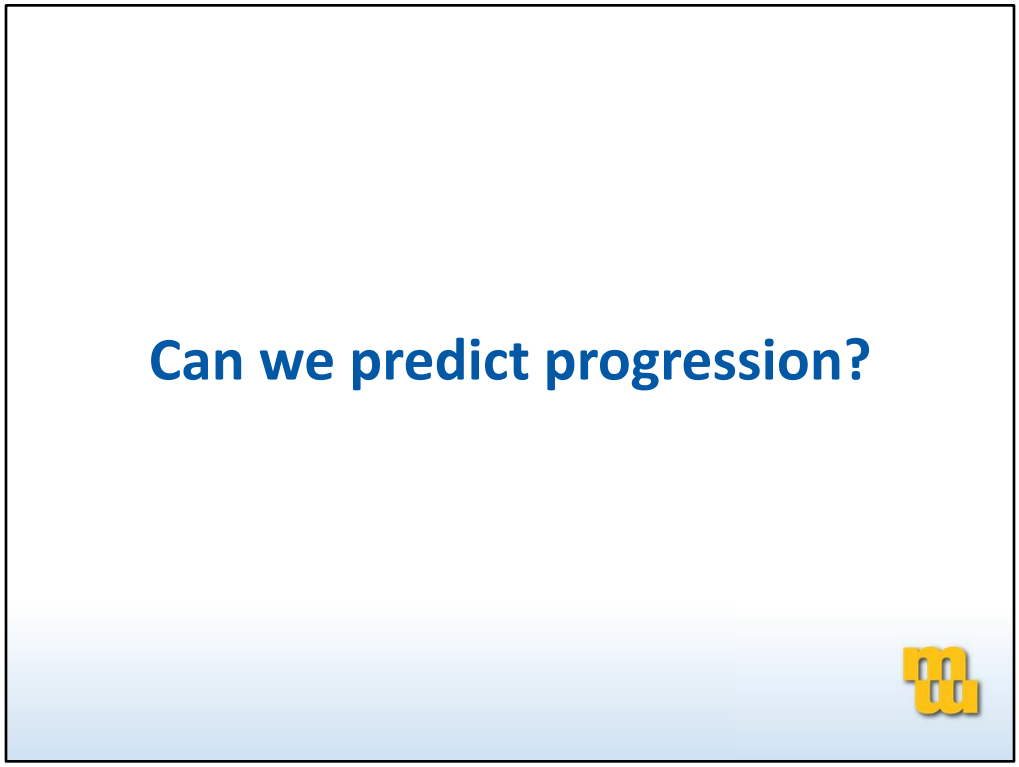


As you progress through these stages, what you also see is certain oncogenes, certain genetic transformation as well. Here I am describing to you the Myc or wake expression. Myc, as you all know, is an oncogene which is relevant to myeloma progression at the normal plasma cell of the MGUS level; Myc levels are very low. Once you have symptomatic multiple myeloma, even newly diagnosed or relapsed, you have an increase in Myc expression.

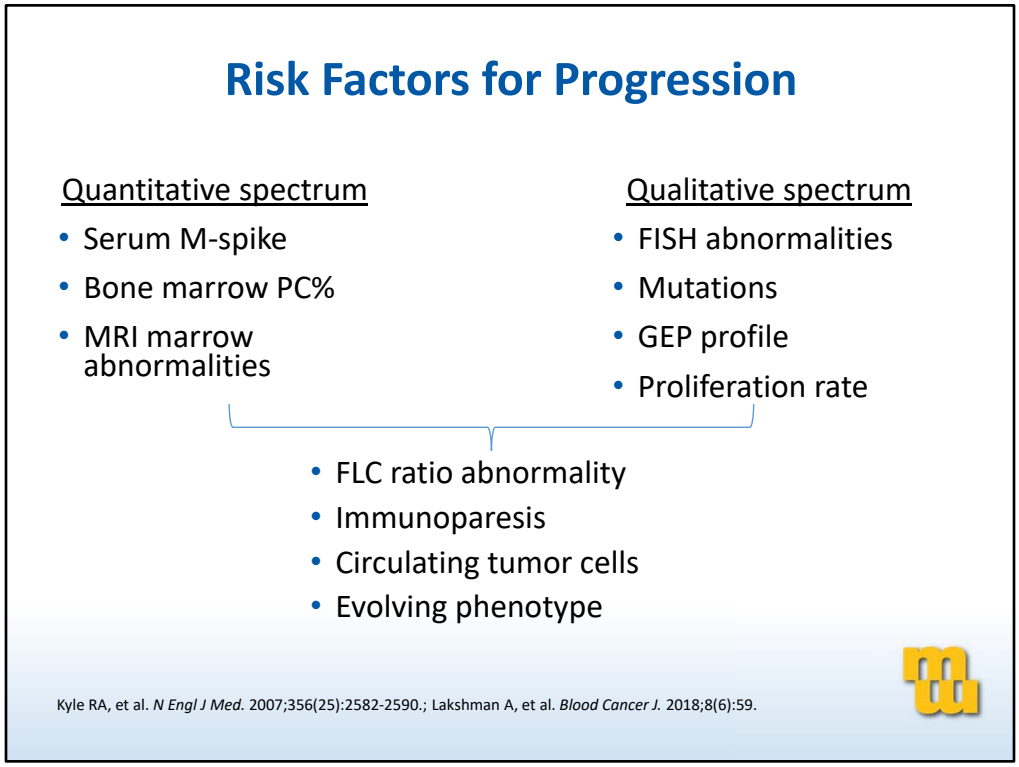
Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection



This is a graph just showing you the progression of smoldering multiple myeloma patients to symptomatic myeloma. At the bottom, you have the MGUS progression which we've already talked about. It's 1% per year, amounting to about 30% over 25 years. In contrast, if you look at patients with smoldering multiple myeloma, these patients, in the first five years have a 50% risk of progression. Then, as you follow them long enough, if they've not progressed in the first five years, the chances of them progressing drops down dramatically to about 10% or so and beyond this, it goes to about 5%. But the risk of progression from smoldering to multiple myeloma over the course of a patient's lifetime always does remain.

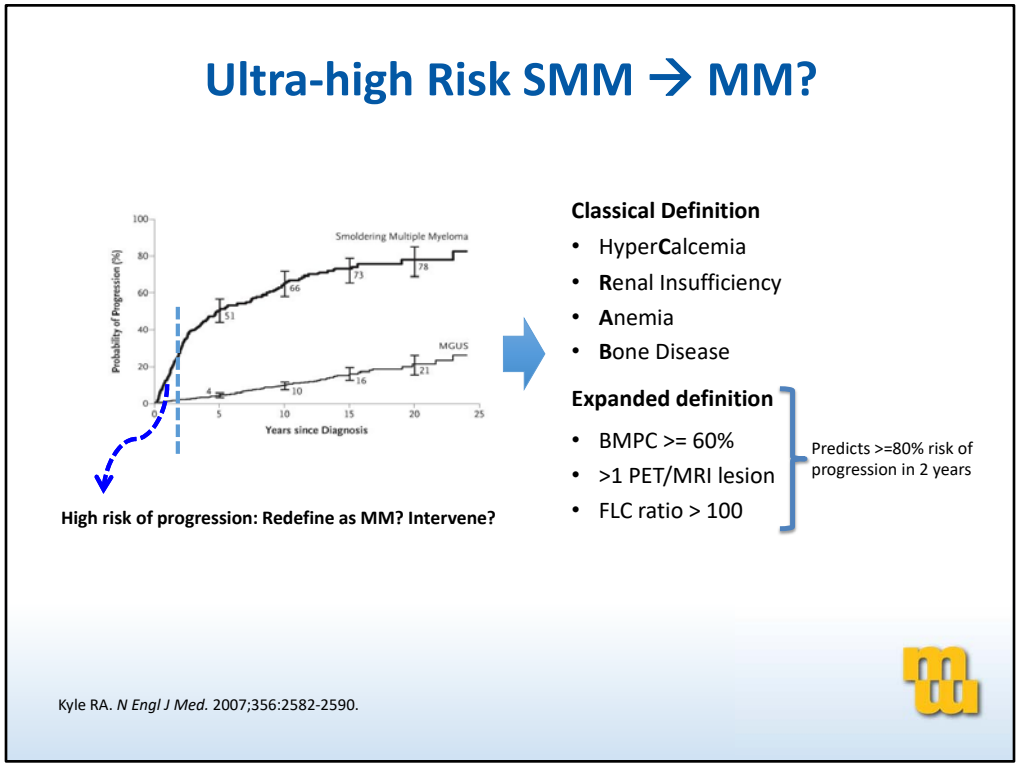


Then, the big question obviously is can we predict this progression?



We've done a lot of work around trying to identify risk factors for progression and those could be quantitative or qualitative; quantitative mostly by the number of plasma cells, the amount of M-protein, and bony abnormalities on advanced imaging, and qualitative is mostly what I talked to you about in terms of the genetic landscape and how these clonal plasma cells evolve genetically over time. With that, we've come up with a hybrid version for risk of progression where we looked at abnormalities of free light chain ratios, we look at immune paresis, we look at circulating tumor cells, and we look at the evolving phenotype of these patients.

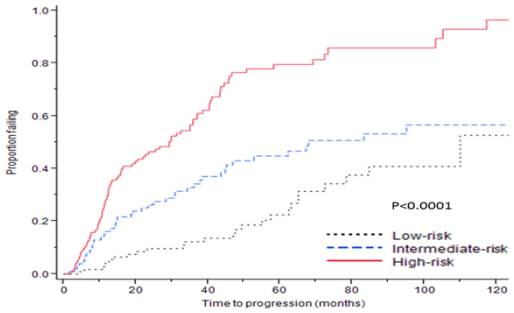
Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection



There is a subset of patients which we define as ultra-high risk smoldering multiple myeloma patients and these patients were the ones who had a very high propensity to progress within the first year of their diagnosis of smoldering myeloma. These then were defined as actually active myelomas, so we redefined what active symptomatic multiple myeloma should be. In the newest classification, in addition to the CRAB criteria, which I've already described, the expanded definition of active symptomatic myeloma, although some of these don't present with symptoms, when you would consider treating them because of that ultra–high-risk nature of these patients is where you have a bone marrow plasmacytosis of more than 60%, you have a better abnormality, even one lesion is enough and if you have a free light chain ratio of above 100. These patients, in the newer definition of symptomatic multiple myeloma, would be considered symptomatic and would be patients who you would consider treating as if they had active symptomatic multiple myeloma.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection

Revised Risk Stratification (20/2/20)



Factors

- BMPC >20%
- M Spike >20 g/L
- FLC ratio >20

Stratification

Low risk: 0
Intermediate risk: 1
High risk: ≥2

Time from diagnosis (years)	Low risk ($n = 143$)	Intermediate risk ($n = 121$)		High risk ($n = 153$)	
	Estimated rate of progression (%)	Rate of progression, % (CI)	OR for progression relative to low-risk group (CI)	Rate of progression, % (CI)	OR for progression relative to low-risk group (CI)
2	9.7 (5.3–17.1)	26.3 (18.4–36.2)	2.71 (1.08–6.83)	47.4 (38.6–56.4)	4.89 (2.25–10.69)
5	22.5 (14.2–33.6)	46.7 (35.8–57.9)	2.08 (1.07–4.08)	81.5 (71.3–88.6)	3.63 (2.12–6.22)
10	52.7 (30.1–74.2)	65.3 (45.5–80.9)	1.24 (0.61–2.69)	96.5 (80.9–99.4)	1.83 (1.09–3.30)

BMPC% bone marrow-plasma cell percentage, *CI* 95% confidence intervals, *FLCr* involved to uninvolved free light chain ratio, *OR* odds ratio

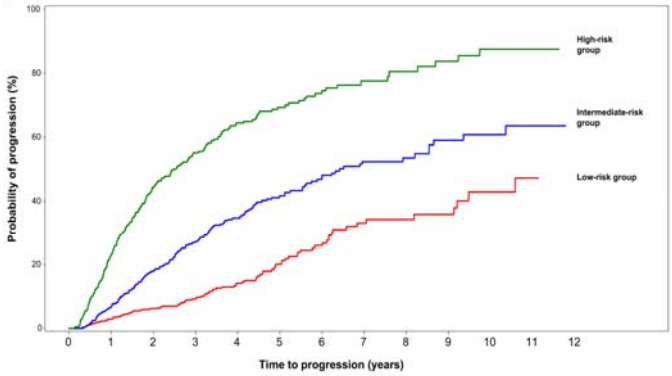
Lakshman A, et al. *Blood Cancer J.* 2018;8(6):59.

For smoldering multiple myeloma, we now have a revised risk stratification. This revised risk stratification is the 20/2/20 model where you're looking at bone marrow plasmacytosis of more than 20%, an M-spike of greater than 2 grams, and a free light chain ratio of more than 20. Now, depending on the number of risk factors, you can then classify them into high-risk, low-risk, and intermediate. I think this is really important because the high-risk patients have a 60% to 70% risk of progression to myeloma and if there is anything we need to be doing about this patient population, it's this patient population that we're trying to address in clinical trials to try and alter the natural history of smoldering multiple myeloma patients.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection

Progression by Risk Group

a



Characteristics included in the model

Serum M-spike: **>2 g/dL**
FLC Ratio: **>20**
BMPC: **>20%**

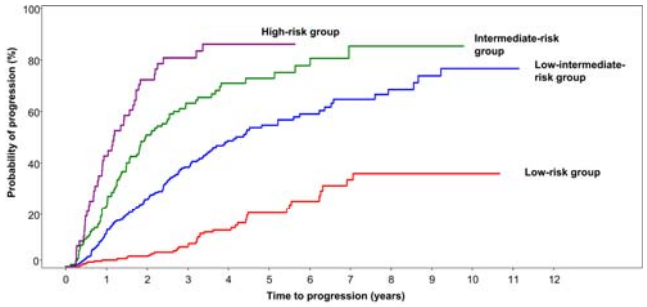
Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low-Risk	0	Reference	6.2%	522 (38.3%)
Intermediate	1	2.99 (1.97 – 4.54)	17.9%	445 (32.7%)
High	2-3	9.02 (6.15 – 13.2)	44.2%	396 (29.1%)

Mateos MV, et al. *Blood Cancer J.* 2020;10(10):102.

This is progression by risk. As you can see, the high-risk patients have nearly a 70% chance of progression, intermediate- and low-risk falls somewhere in between.

Risk Score to Predict Progression Risk at Two Years

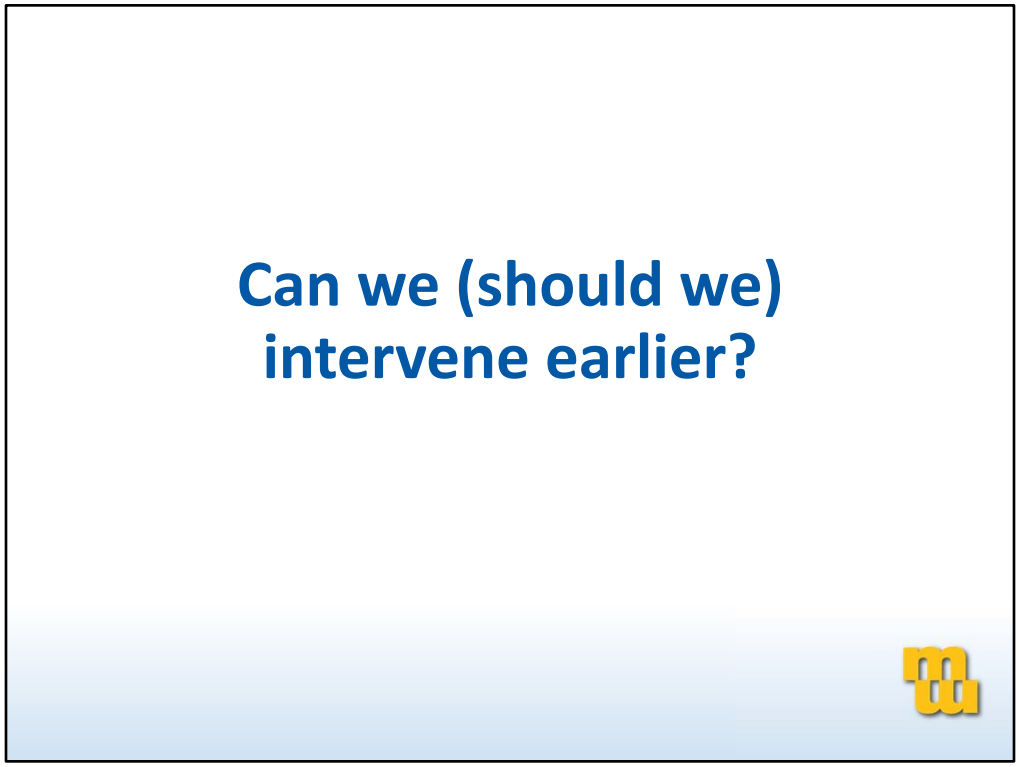
Risk Factor	Score
FLC Ratio	
0-10 (reference)	**0**
>10-25	**2**
>25-40	**3**
>40	**5**
M protein (g/dL)	
0-1.5 (reference)	**0**
>1.5-3	**3**
>3	**4**
BMPC%	
0-15 (reference)	**0**
>15-20	**2**
>20-30	**3**
>30-40	**5**
>40	**6**
FISH abnormality	**2**



Risk Stratification groups	Total risk score	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low	0-4	Reference	3.8%	241 (35.0%)
Low-intermediate	5-8	7.56 (3.77 – 15.2)	26.2%	264 (38.3%)
Intermediate	9-12	17.3 (8.63 – 34.8)	51.1%	133 (19.3%)
High	>12	31.9 (15.4 – 66.3)	72.5%	51 (7.4%)

Mateos MV, et al. *Blood Cancer J.* 2020;10(10):102.

This has also been adapted by the Spanish group. This is the data, which is presented by Maria Victoria Mateos wherein she's identified high-risk patients based on the scoring system wherein 70% to 80% of very high-risk patients can be identified by giving these patients these scores based on some of the parameters that we've already talked about.



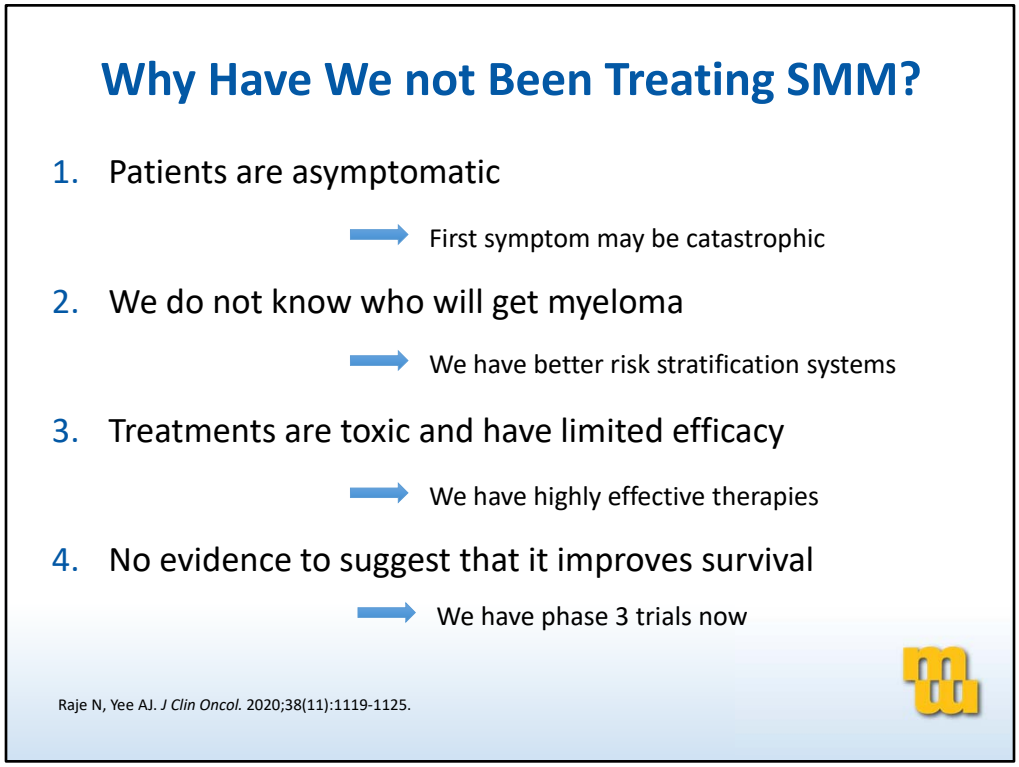
Once we know what the risk of progression is, the question obviously is can we and should we be intervening or should we be treating these patients any earlier?

SMM Is Not a Biological Entity

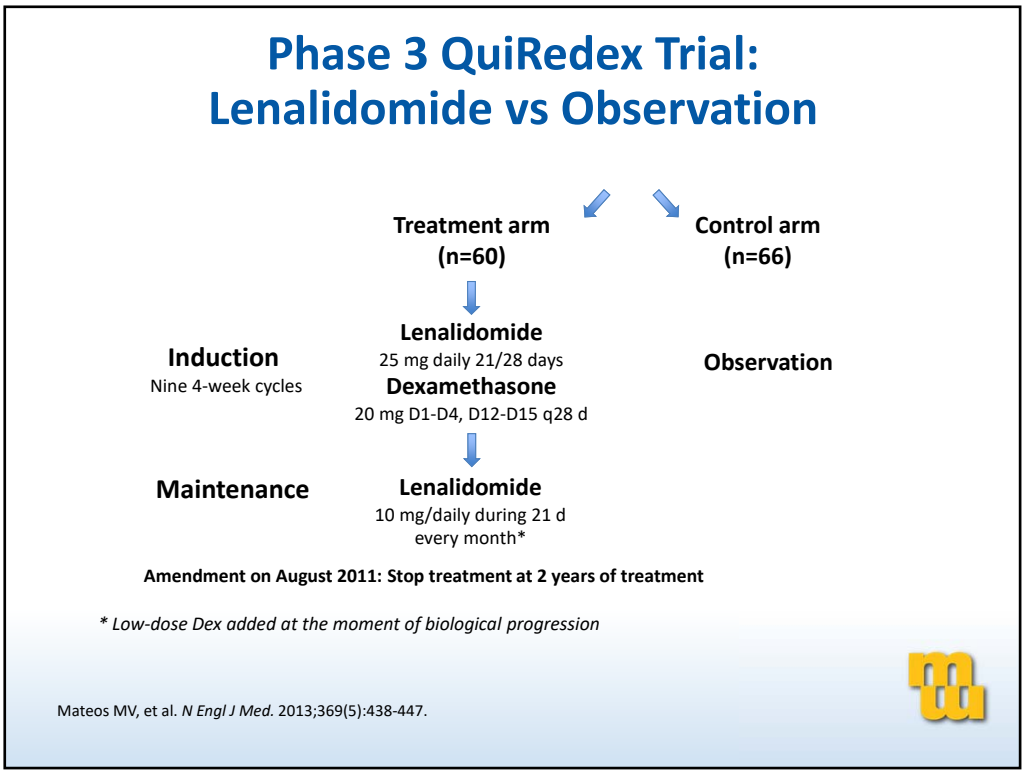
- Transitional stage
- Represent a mix of true MGUS with polyclonal but benign PCs and MM with “malignant” PCs
- No molecular marker available and morphological distinction not possible
- Situation akin to colon polyp

Raje N, Yee AJ. *J Clin Oncol.* 2020;38(11):1119-1125.

Now, this is still controversial, and this is still debatable and the reason why it still remains a debate is smoldering myeloma is not a real disease. It’s a transitional state somewhere between MGUS and multiple myeloma, and as I’ve already explained to you, these are asymptomatic patients. So to offer treatment completely to asymptomatic patients, we really need to understand the risk of their progression and only then, would we be subjecting them to treatment. That’s why, I think it’s so, so important to consider good risk-stratification in the smoldering multiple myeloma space.

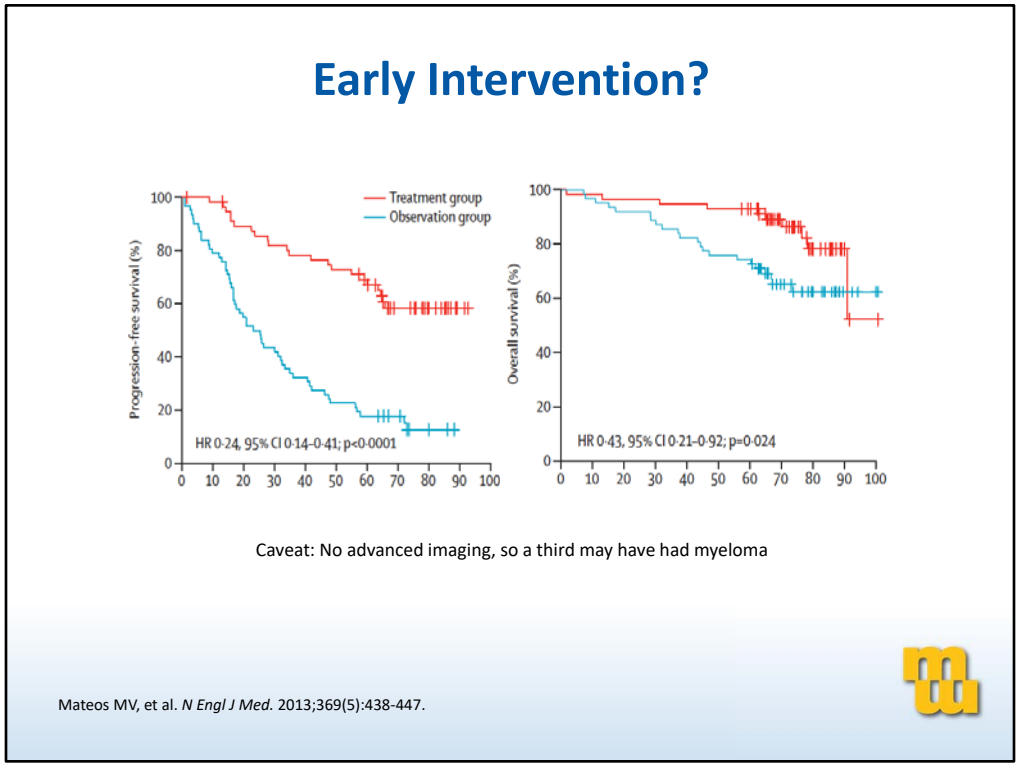


Again, the question here is why have we not been treating smoldering myeloma patients? Well, these patients, as I've already mentioned, are asymptomatic. The counter argument to that can in fact be that these are patients who even if they're asymptomatic, sometimes, symptoms can occur very rapidly. These symptoms are specifically bony problems and kidney-related problems that can be catastrophic. We do not know who will actually develop symptomatic myeloma because if you look the best risk stratification, we may be overtreating 30% or 40% of patients and therefore, better risk stratification needs to be accomplished and the other argument could be treatments are not without toxicities. Everybody has a toxicity. Having said that, we now have highly effective treatments which are less toxic as well, which again, makes the argument that maybe we should be considering treatment early. To date, we haven't seen any improvement in survival of these patients and we now have trials which we are doing. These are ongoing trials, and we will have data looking at overall survival as well. The trials are not yet mature when it comes to overall survival, but the hope is that we will be able to answer all of these questions in the very near future.

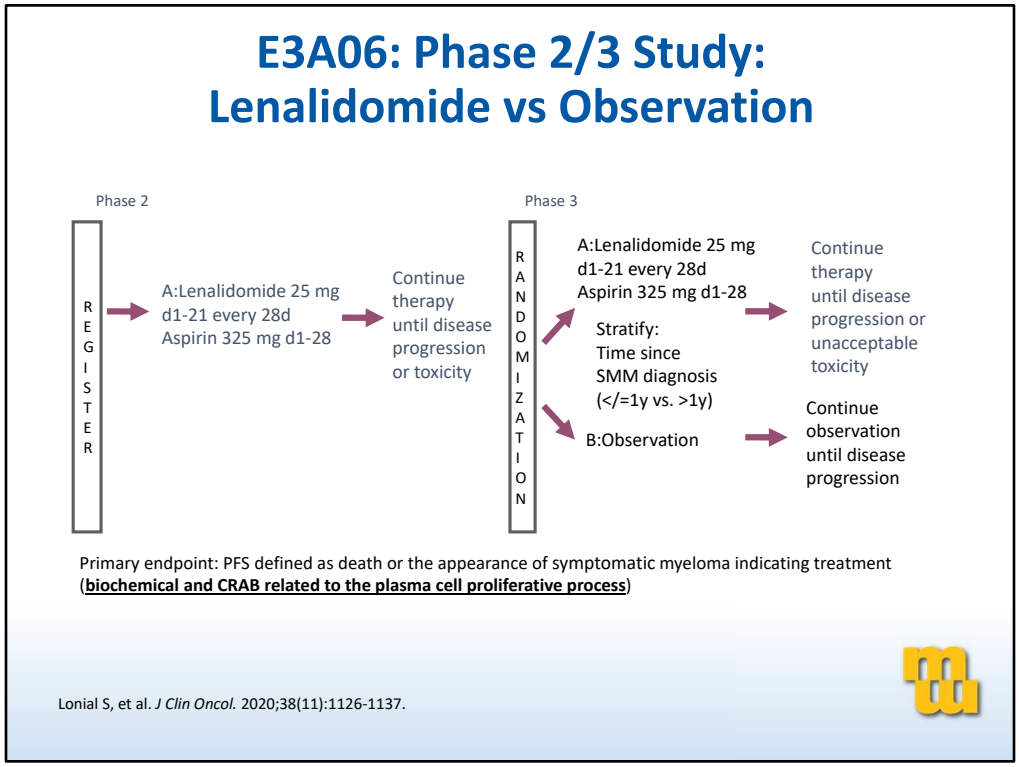


This is the data which sort of made us think about treating smoldering myeloma patients. This is the QuiRedex trial which has now been published in the *New England Journal of Medicine* more than seven or eight years back. These were patients with smoldering multiple myeloma who were treated with lenalidomide or who were observed.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection



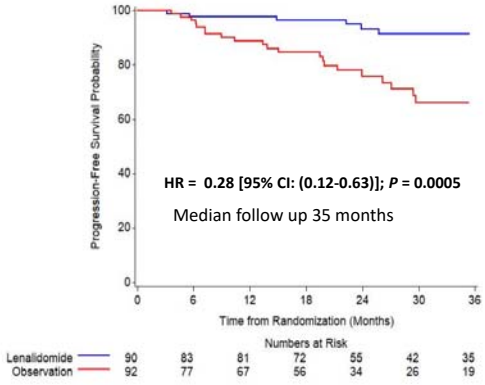
If you look at the data, these were patients who had obviously an improved progression free survival but most importantly, also had an overall survival. Looking at this data, it really made us think long and hard. Instead of adopting early intervention for all patients, we actually redefined what symptomatic multiple myeloma is because this was a trial which showed us that patients who are progressing, and the reason why we we're seeing a survival disadvantage in our smoldering multiple myeloma patients where a lot of patients were progressing with renal disease and bone disease, and therefore, the new definition of symptomatic multiple myeloma, we included free light chain ratio as well as better imaging technology to look for bone disease here.



This is the more recent study which was presented and published by Dr. Lonial. This is the ECOG trial E3A06. This was a phase 2/3 study wherein they took the QuiRedex study. They used high-risk smoldering multiple myeloma patients and then these were randomized to receive lenalidomide versus no treatment at all.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection

Response and PFS



HR = 0.28 [95% CI: (0.12-0.63)]; *P* = 0.0005

Median follow up 35 months

	Lenalidomide [n=44]	Lenalidomide [n=90]	Observation [n=92]
	Phase II	Phase III	
Category	N (%)	N (%)	N (%)
VGPR or Better	4 (9.1)	4 (4.4)	0 (0.0)
PR or Better	21 (47.7)	44 (48.9)	0 (0.0)
SD or Better	42 (95.5)	84 (93.3)	80 (87.0)

Phase 3 PFS	Len	Obs
1 year	0.98	0.89
2 year	0.93	0.76
3 year	0.91	0.66

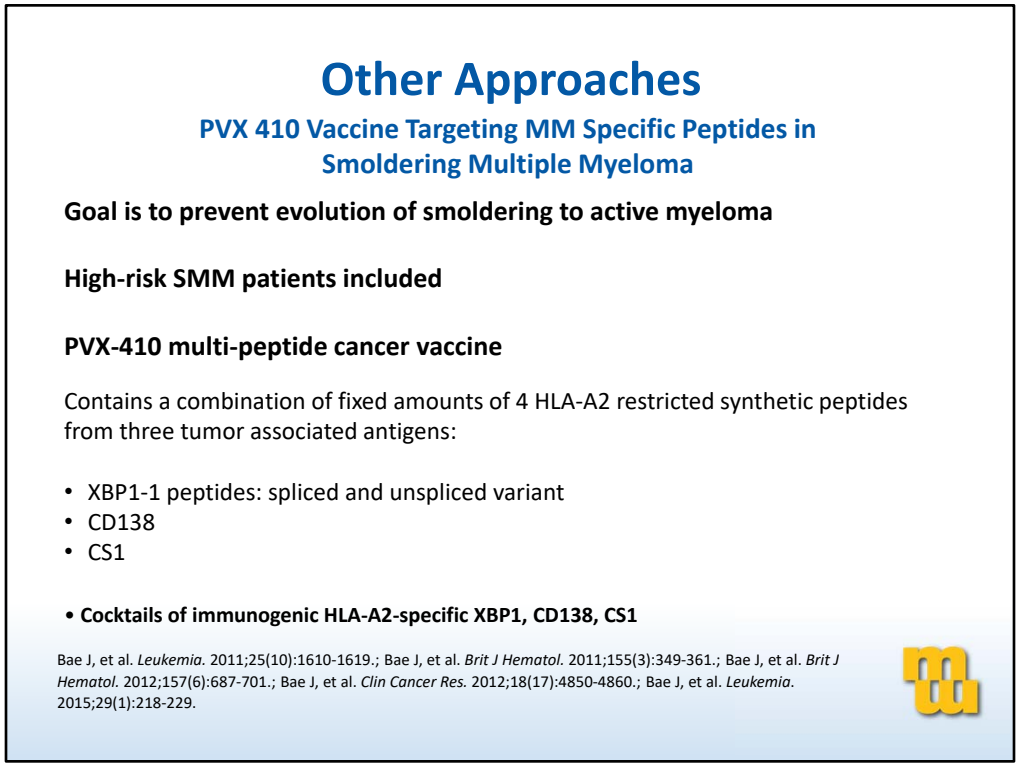
Lonial S, et al. *J Clin Oncol.* 2020;38(11):1126-1137.

As it is quite obvious, if you look at the patients who got lenalidomide, not surprisingly, the progression free survival was better for those patients who got lenalidomide. Response rates were better at a three-year follow up as well, suggesting that lenalidomide should be considered in the treatment of smoldering multiple myeloma patients.

More Questions than Answers

- If we treat, should we be treating like myeloma?
- Or should it be a low intensity to delay progression?
- Or should it be more aggressive to potentially cure the disease?
- What is a good surrogate for cure?
- When do we stop treatment?

Why have we all not adapted this as standard of care? There were lots of questions here because we still don't have a survival advantage. There is toxicity associated with lenalidomide and the big questions are if we treat, should we be treating with the curative intent like we treat myeloma or should we use a low intensity strategy as was shown in this ECOG trial with just lenalidomide alone? Obviously, these are unanswered questions. If cure is the goal, we need to be more aggressive and not just control the disease, and what would we be using as a good surrogate for cure? The other question is, these are asymptomatic patients, how long do we keep them on treatments which do impact patients' quality of life? So, lots of questions in the space and that's why we still don't have a clear-cut answer as to who needs to be treated for smoldering multiple myeloma.



There are other approaches being used and I'm just going to mention one of them which is the vaccine approach which we're using at our center at Mass General. What we've identified is a peptide-based vaccine after looking at a whole bunch of clonal plasma cells.

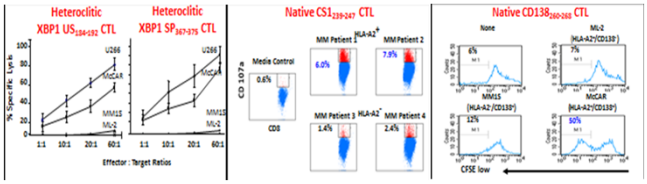
Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection

Myeloma Age Specific Peptide-based Vaccination

- **Single Antigen Targeting Peptides**

  -Polyfunctional responses: IFN-γ, cytotoxicity, proliferation, CD107a degranulation to patient MM cells and MM cell lines

  Bae J, et al. *Blood*. 2006.; Bae J, et al. *Blood*. 2007.; Bae J, et al. *CCR*. 2010.



We identified several proteins which were antigenic and then,

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection

Myeloma Age Specific Peptide-based Vaccination

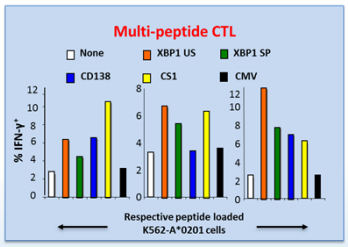
- **Single Antigen Targeting Peptides**

  -Polyfunctional responses: IFN-γ, cytotoxicity, proliferation, CD107a degranulation to patient MM cells and MM cell lines

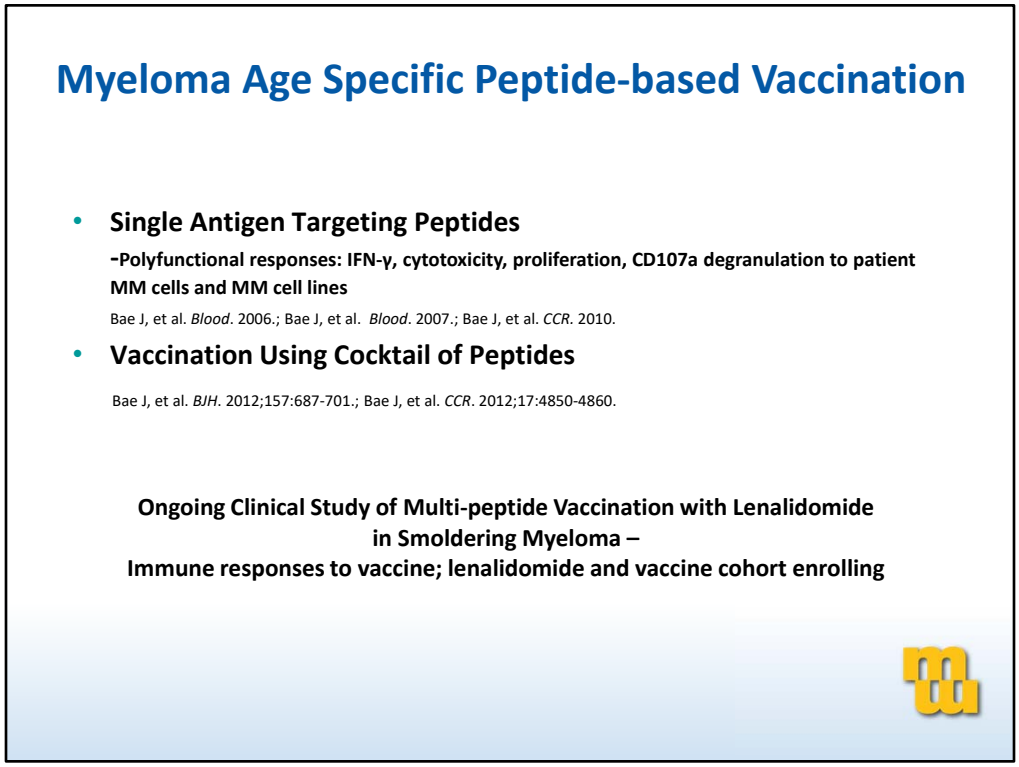
  Bae J, et al. *Blood*. 2006.; Bae J, et al. *Blood*. 2007.; Bae J, et al. *CCR*. 2010.

- **Vaccination Using Cocktail of Peptides**

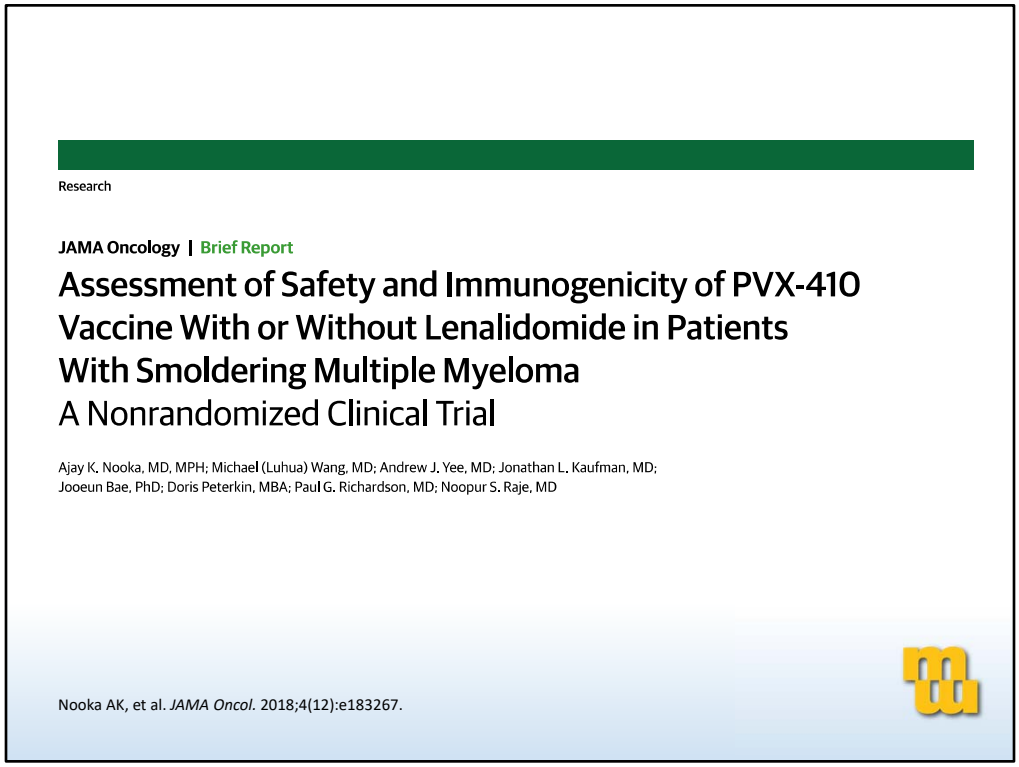
  Bae J, et al. *BJH*. 2012;157:687-701.; Bae J, et al. *CCR*. 2012;17:4850-4860.



we identified these peptides which we could put into a vaccination strategy.



What we were able to see quite nicely with this approach is that when we give the patient a vaccine



Research

JAMA Oncology | Brief Report

Assessment of Safety and Immunogenicity of PVX-410 Vaccine With or Without Lenalidomide in Patients With Smoldering Multiple Myeloma

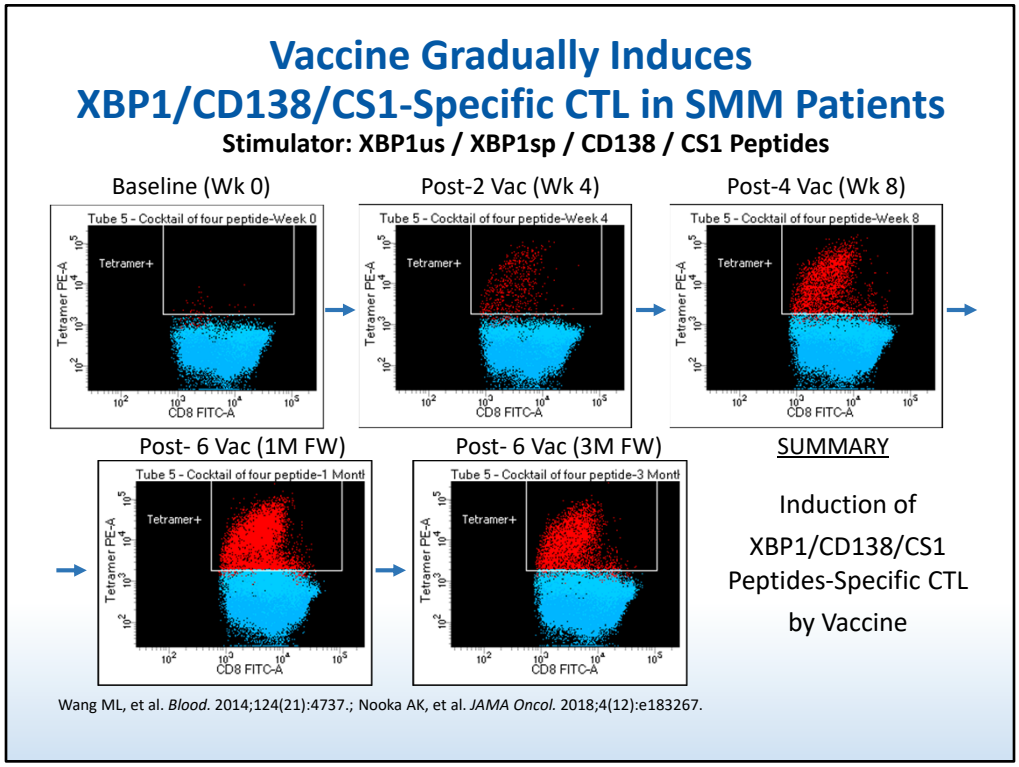
A Nonrandomized Clinical Trial

Ajay K. Nooka, MD, MPH; Michael (Luhua) Wang, MD; Andrew J. Yee, MD; Jonathan L. Kaufman, MD; Jooeun Bae, PhD; Doris Peterkin, MBA; Paul G. Richardson, MD; Noopur S. Raje, MD

Nooka AK, et al. *JAMA Oncol.* 2018;4(12):e183267.

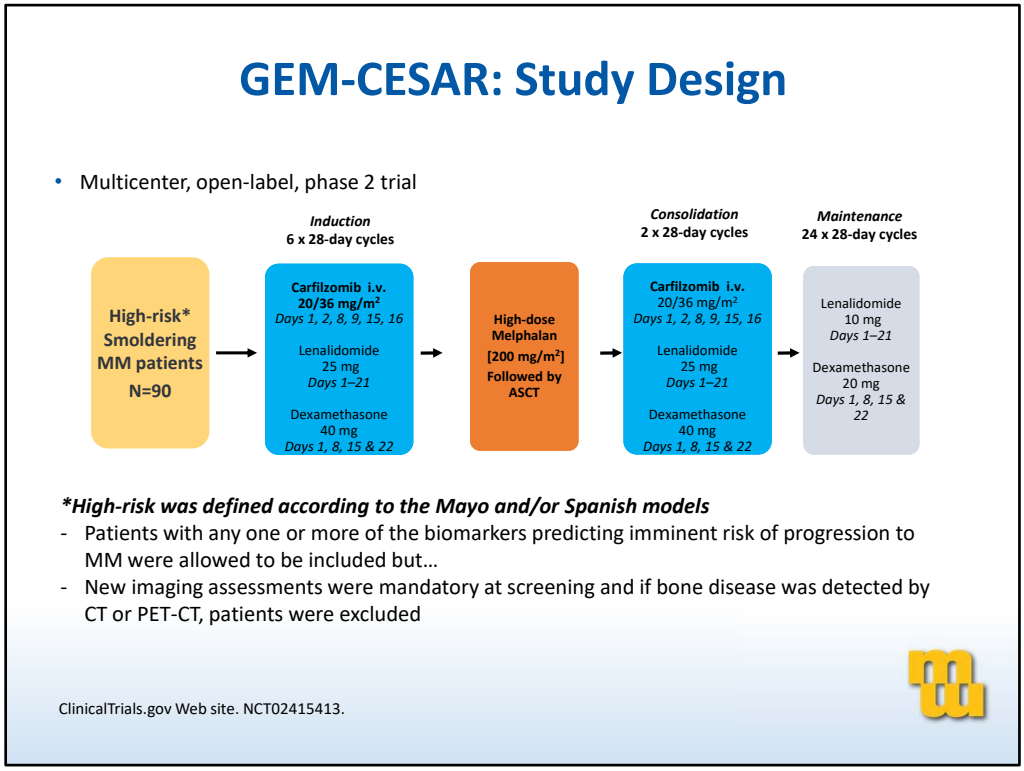
and you think about it as if you're getting the flu shot, you get the flu shot so that you prevent getting the flu. The idea behind PVX-410 is you get this vaccine, and you prevent the development of active symptomatic multiple myeloma.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection

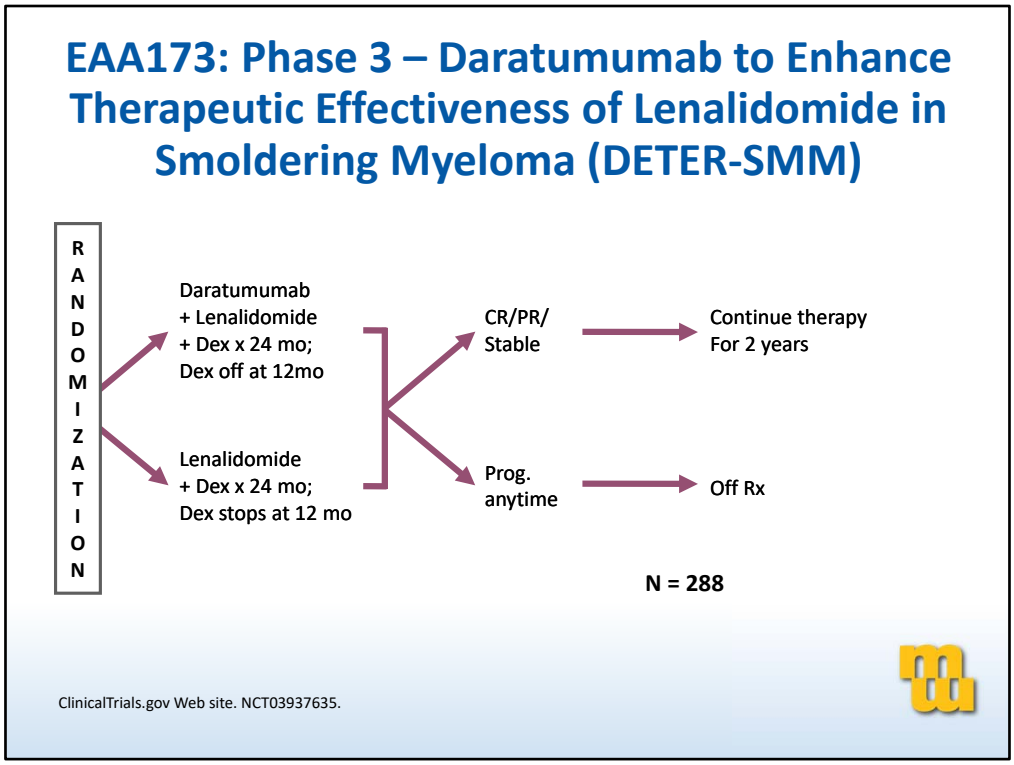


We have used this vaccination approach in smoldering multiple myeloma patients with the ideal of seeing an immune response in these patients, and when we use this tri-peptide vaccine, we were able to show an induction of peptide-specific CTLs, suggesting that patients are able to mount an immune response. Obviously, we need to look at long-term data and we need to see whether we can actually change the natural history of this disease and prevent the progression to multiple myeloma, so this is one end of the spectrum.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection

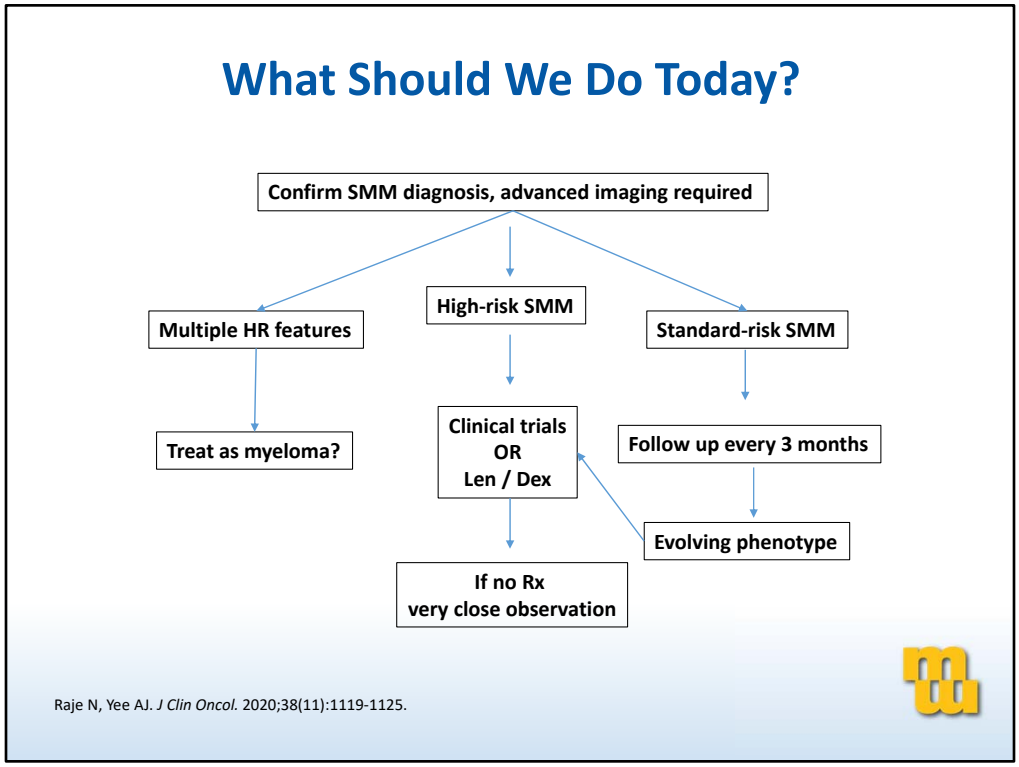


At the other end of the spectrum, we are treating smoldering myeloma patients as if they have active myeloma. This is the GEM-CESAR study; we're using a triplet combination, we're using an autologous transplant and we're using a curative approach with the intent that at the smoldering myeloma stage where there is not that much of genetic evolution, if you are going to be thinking about curing the disease, this is the platform to consider and therefore, use this approach so that you can get rid of this disease, so this is an ongoing trial as we speak, and we'll have to wait and see what the data unfolds.

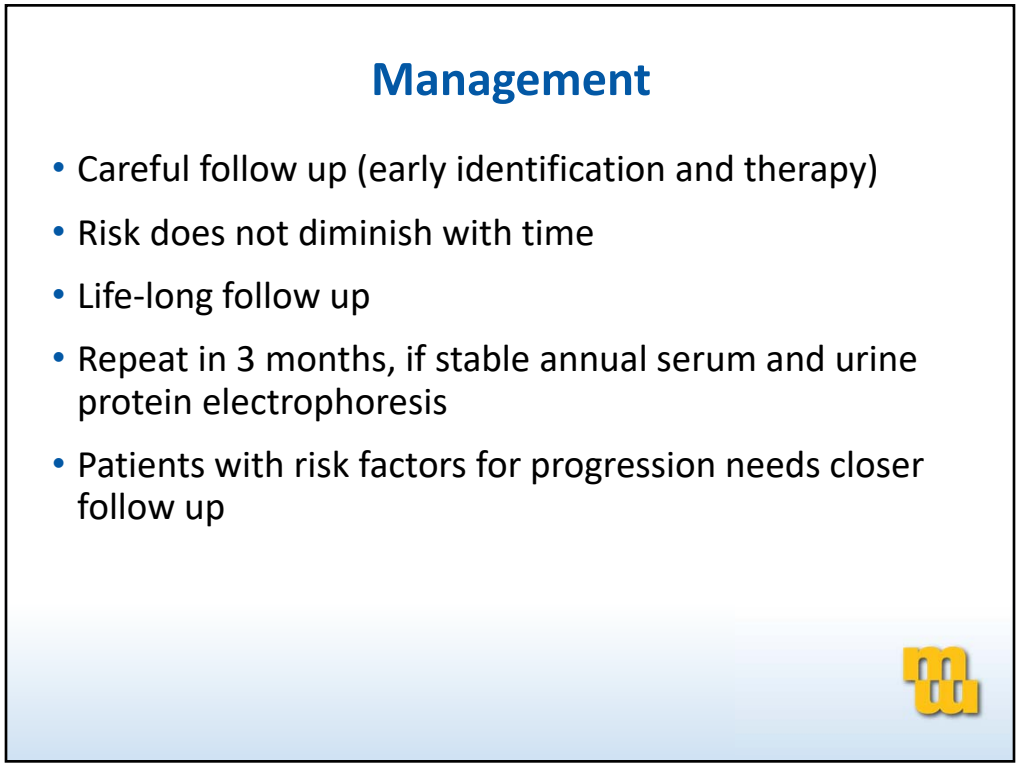


There are several other trials we're looking at as well wherein we are looking at overall survival as an outcome. This is an ECOG study looking at the use of daratumumab to enhance the effectiveness of lenalidomide, this is a follow-up study to the other ECOG trial that I've just mentioned. This is called the DETER smoldering myeloma trial and as the name suggest, we want to deter patients from progressing on to developing full-blown myeloma.

Overcoming Challenges in Smoldering Myeloma: Improving Diagnosis and Treatment Selection



With all of these, what should we be doing today? Obviously, we need to confirm the diagnosis and I've shown you how you can confirm the diagnosis. We need to try and identify who those ultra–high-risk patients are, and those ultra–high-risk patients certainly would be considered for active myeloma treatment. We should also be considering who the high-risk smoldering multiple myeloma patients are, and in my mind, even today in 2020, we should be considering using a clinical trial as the treatment. There is no real standard of care for the treatment of these patients. Standard-risk smoldering myeloma patients certainly need to be observed. They need to be followed and the recommendation is that they need to be followed every three months with all their parameters. If they have multiple high-risk features, I've already mentioned this, these would be somebody you would consider for extremely close follow up or almost consider treatment as if they had active multiple myeloma.



In general, I think once you've diagnosed smoldering myeloma, you have to have very careful follow up, you really have to identify risk factors in these patients because the risk of progression does not diminish overtime. These patients require life-long follow up and the least amount or the least amount of time between follow up in these patients is about three months or so. The other thing, which is really important to appreciate here, is risk can evolve overtime and the risk factors for progression need to be followed extremely closely in this patient population.

With that, I'd like to thank you all for your attention and thank you for tuning in to this presentation.