# Performance Status Adaptive Therapy in Multiple Myeloma


Hi, my name is Dr. Joshua Richter. I currently work at the Hackensack University Medical Center in the Division of Multiple Myeloma, and I am an Assistant Professor of Rutgers University. I am going to talk today about *Performance Status Adaptive Therapy in Multiple Myeloma.*

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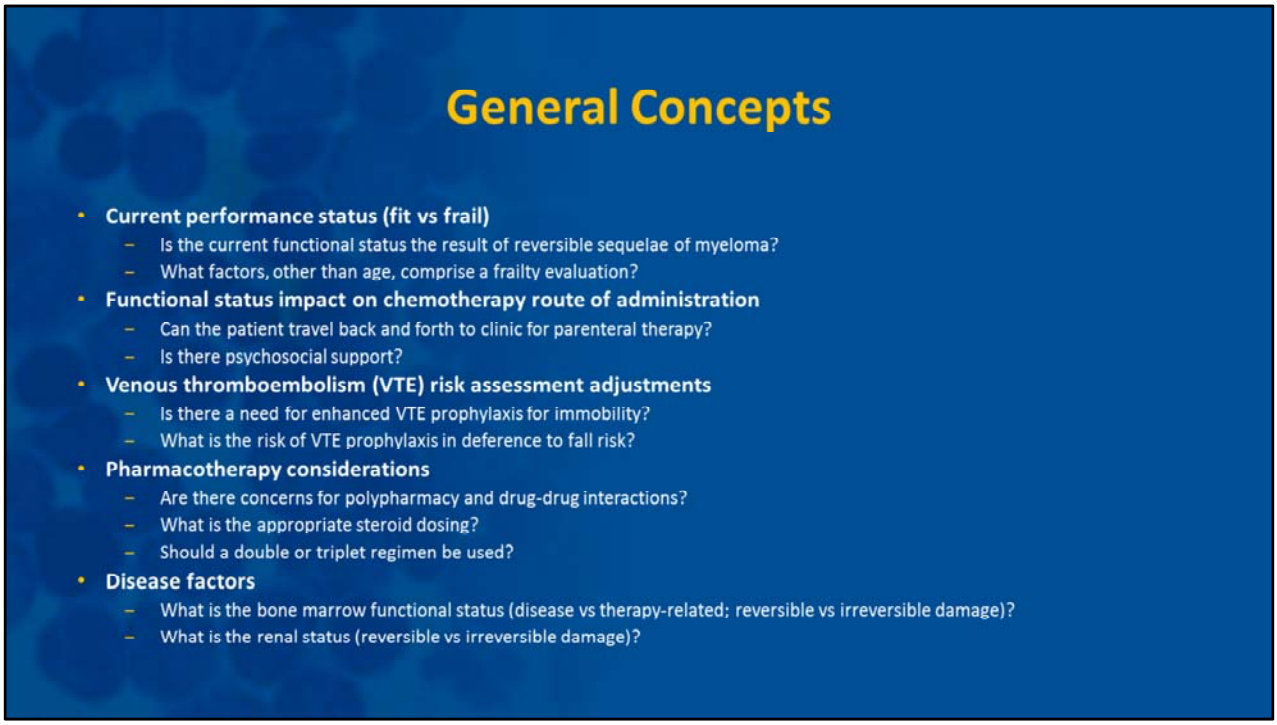


There are some general concepts that are worthwhile reviewing in this concept of how to treat patients based on their risks both from a disease standpoint and a patient standpoint. First off, what is their current performance status? Is the patient more fit or more frail? Now, this is a difficult concept because this may be due to general comorbidities such as heart disease, lung disease, or other cancers. However, this may be related to multiple myeloma itself, and if some of these factors which affect frailty are related directly to multiple myeloma, they may be reversible and may alter the way you approach treating your patient. Now, has does the functional status of your patient affected the route of chemotherapy? We have a lot of therapies nowadays in multiple myeloma. There were four therapies approved by the FDA in 2015, three in the month of November alone, and we have had 10 therapies approved in the last decade. Many of these therapies are parenteral, intravenous, and subcutaneous. However, some are now oral. So, one of the things that is worthwhile to take into account is what is the current performance status in relation to your patient's ability to come to clinic to receive parenteral chemotherapy or should we be thinking more of oral chemotherapy for ease of administration? Thromboembolic risk is another concern for patients with multiple myeloma. If you take age-matched correlates, patients with plasma cell dyscrasia, even MGUS, but more so with multiple myeloma, are at an inherently higher risk of developing a thromboembolic event simply from having the disorder. Once you start adding other therapies such as immunomodulatory agents and dexamethasone, this may further increase things. These things are worthwhile to take into account when thinking about the therapy for your patient, not only with regard to what therapy they are on but what supportive medications would be needed to support them.

For example, if someone is at higher risk for thromboembolic event, either due to immobility or other disorder, you may have to think about the administration of aspirin or full-dose anticoagulation for these patients. Now again, if someone is quite frail, this may be risky in so far they may have a risk for falling and in turn bleeding events. What about pharmacotherapy considerations? Many of the patients with multiple myeloma are older since myeloma in general is a disease of the elderly with the median age being around 70 years. Many of these patients have other comorbid conditions that require other therapies: heart disease, diabetes, and high cholesterol. So, it is worthwhile to consider these things when deciding which therapy you are going to employ for your patient who may or may not be fit or frail. And what about the disease factors? Things to think about our bone marrow function and renal status. Now again, bone marrow function is a fluid concept. Bone marrow function may be altered as a result of advanced disease or side effects from previous chemotherapy, so it is worthwhile to evaluate whether or not these changes in the bone marrow function are potentially reversible or not potentially reversible, and the same thing with renal status. Our patients often have advanced renal disease either from disease or from other comorbid conditions such as diabetes. Again, when choosing the dosing and type of chemotherapy for your patient, it is worthwhile to take this into consideration.

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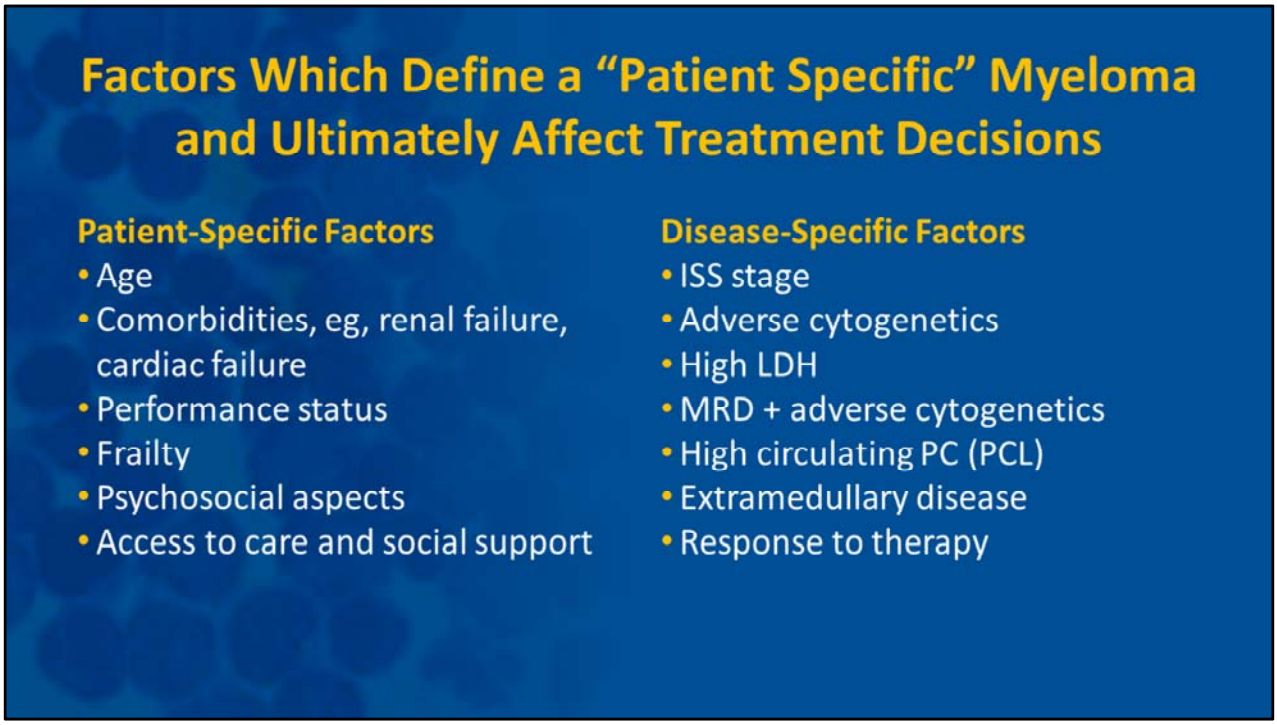


So, it is worthwhile to distinguish between patient-specific factors and disease-specific factors. Again, patient-specific factors, when evaluating their risk, fitness, or frailty are things such as age, comorbidities, general performance status, their overall frailty assessment, psychosocial aspects, and access to care and social support. On the disease side, we have to take into account other high-risk features such as ISS stage. In patients with more advanced disease, higher ISS stage may be at greater risk, adverse cytogenetic factors, and now that we have the Revised International Staging System, things such as LDH take into account, minimal residual disease status, high circulating plasma cells, extramedullary disease, and response to prior therapy. It is worthwhile to distinguish these things to better pinpoint what the appropriate therapy is for your patient, and in age of modern medicine with "personalized medicine," we need to be sure that we are not using a one-size-fits-all approach to our patients. Certain patients may need more aggressive or less aggressive therapy based on their disease status and their host status.

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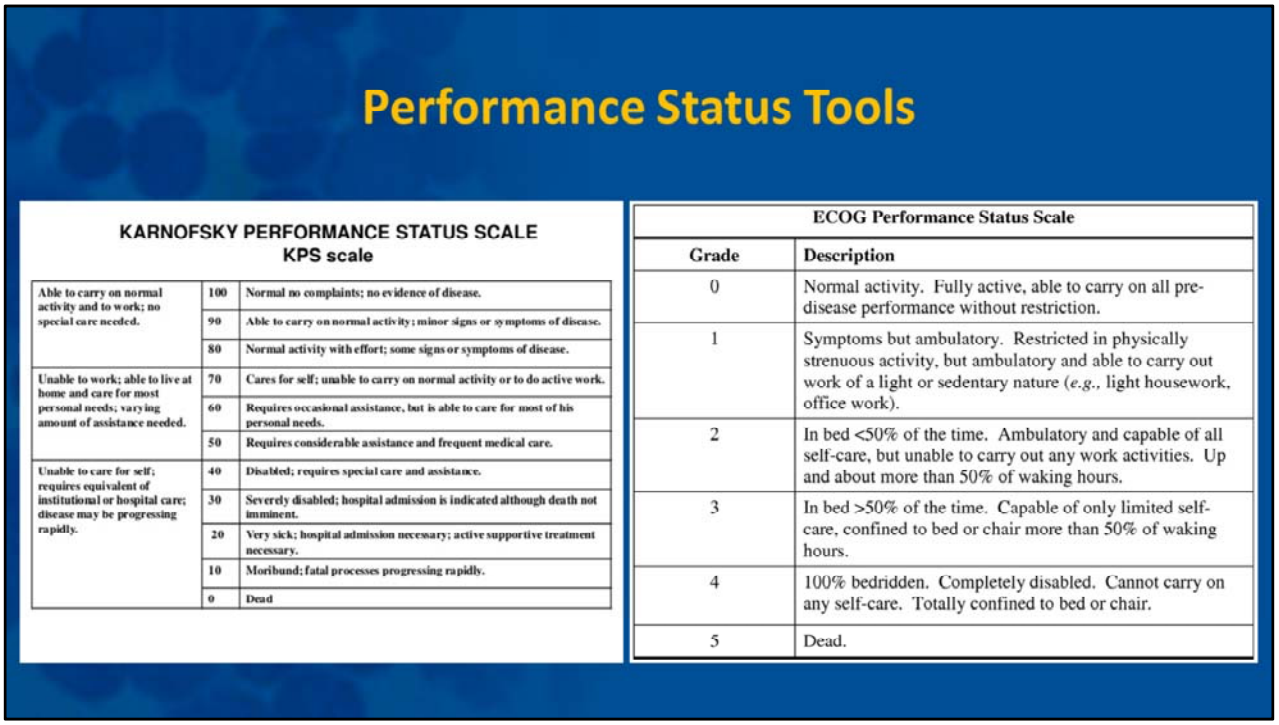


So, how do we assess performance status? There are two main tools that are often used when assessing performance status. The Karnofsky score and the ECOG score. The Karnofsky score goes from 0 to 100, 0 being dead and 100 being completely normal and no complaints or no evidence of disease, and it goes in gradations of 10 in decreasing amounts relative to the relative disability a patient has as they have less and less ability to care for themselves and undergo their activities of daily living. The ECOG performance status is a simpler performance status assessment that goes from 0 to 5. The Eastern Cooperative Oncology Group status starts at 0, which is completely normal; 1 is where you have some limitations based on your disease; 2 is where you have more limitations and spend a significant amount of time in bed, but less than 50% of the time; 3 is where you spend more than 50% of your time in bed; 4 is where you are completely dependent upon others for your activities of daily living. It is worthwhile when assessing your patients at each evaluation to decide where they fit along these scales, either Karnofsky or ECOG, to help evaluate what therapy may be most appropriate for them.

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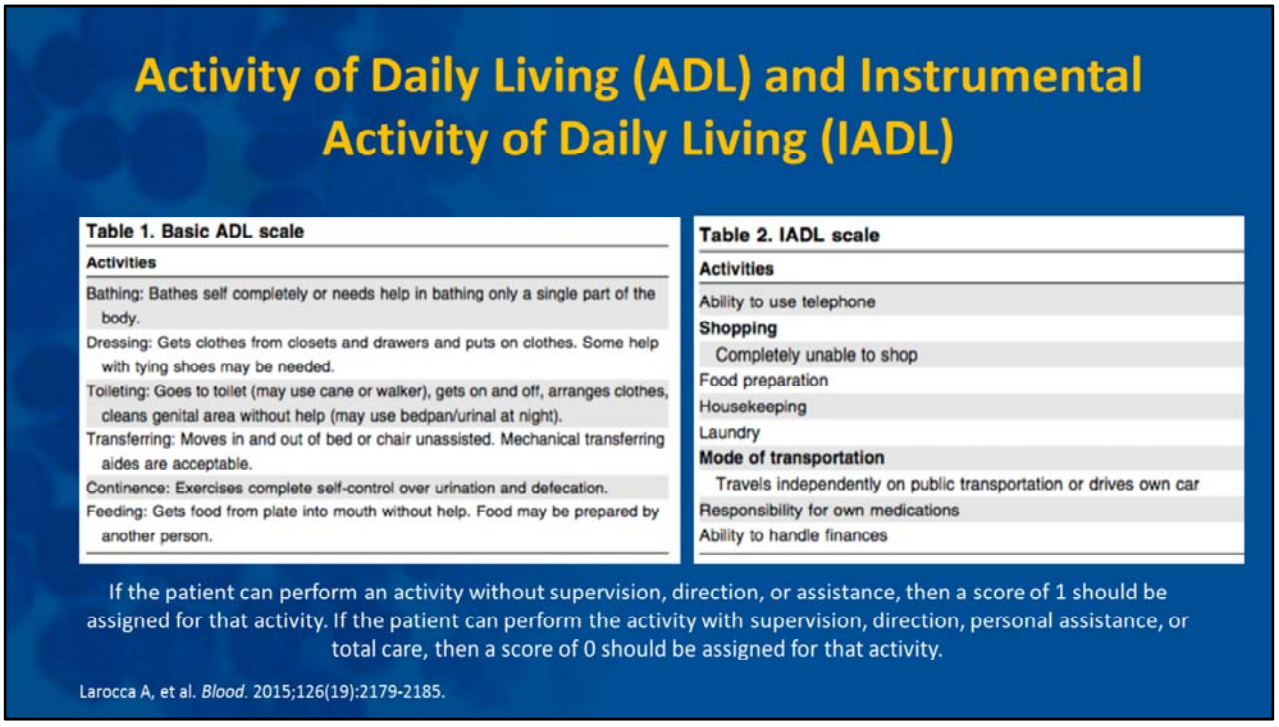


So, we talked a little bit about activities of daily living, and it is worthwhile to review what they are. The activities of daily living involve things such as basic care for oneself, bathing, clothing, and toileting. These are the ADLs, the activities of daily living. Alongside of the activities of daily living assessment is the IADL, the instrumental activities of daily living. These factors are one step above the basic functions that we all need to survive. The ability to use a telephone and communicate with the outside world, the ability to shop for oneself, manage one's own medications, laundry, housekeeping, and the ability to manage your travel back and forth to clinic. Again, these are things that other people can help with, but it is worthwhile to assess these on a global scale for each of our patients. Which of these they are able to do, which are these that they are not able to do, and which of these factors do they require help from other people in order to achieve? Again, these psychosocial aspects may play heavily into your choice of therapy, specifically relating to route of administration. Some of our patients may be able to perform all of their ADLs but may not have the ability to travel back and forth for frequent visits. For these patients, an oral chemotherapy regimen may be more appropriate.

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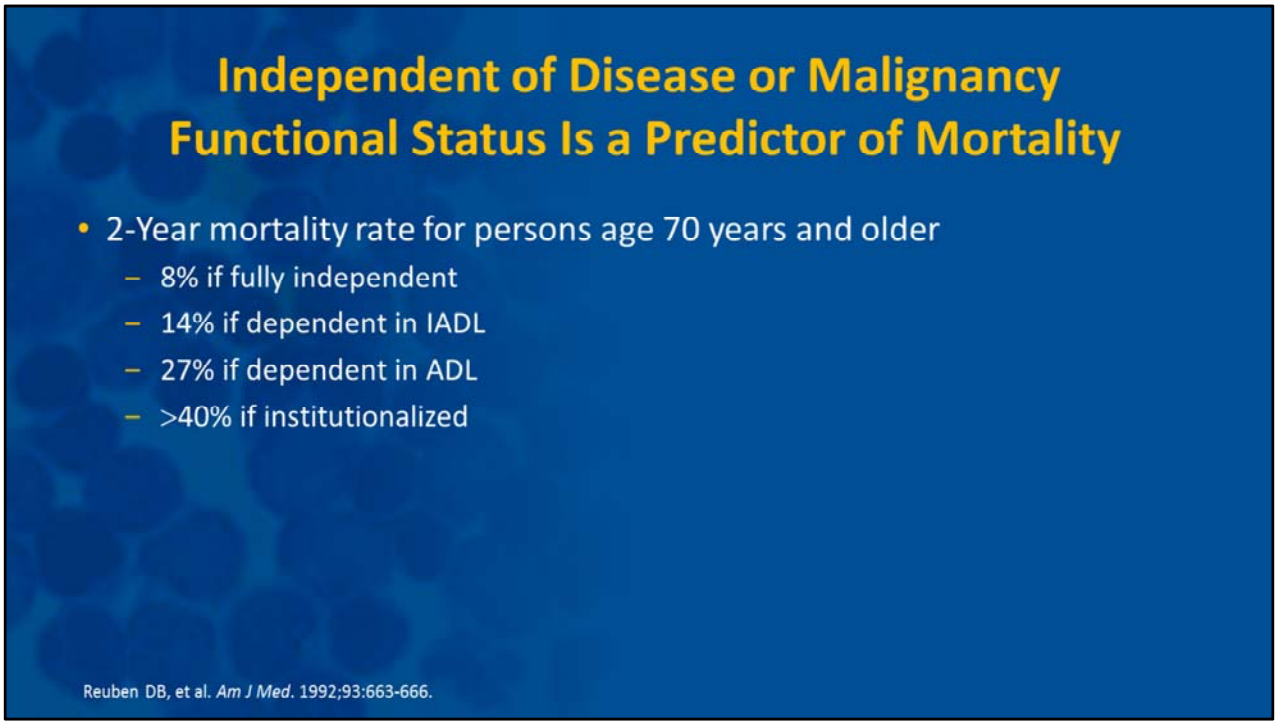


The concept of functional status has been studied far and above, specifically myeloma or even malignancy in general. Reports done in the 1990s looked at functional status as an independent risk for mortality in elderly patients, and if we look across the board, the 2-year mortality rate for patients age 70 and older, if we look from fully independent to independent in IADLs, independent from an ADL standpoint or institutionalized whereas they are completely unable to do any of the ADLs or IADLs, we can see a gradual worsening in their mortality across the first 2 years. Now, literally looking separate from disease status or other comorbid status, if we simply look at patients who have poor performance status, their mortality is very high, up to 40% the first 2 years for a patient age 70 and older. Again, as an independent risk factor of their disease, it is worthwhile to evaluate this. Much research has been done in multiple myeloma in terms of looking at adverse outcomes related to cytogenetic abnormalities or disease-specific abnormalities. It is just as important to evaluate a patient's individual functional status and their individual frailty as a factor to decide how you want to best control their disease.

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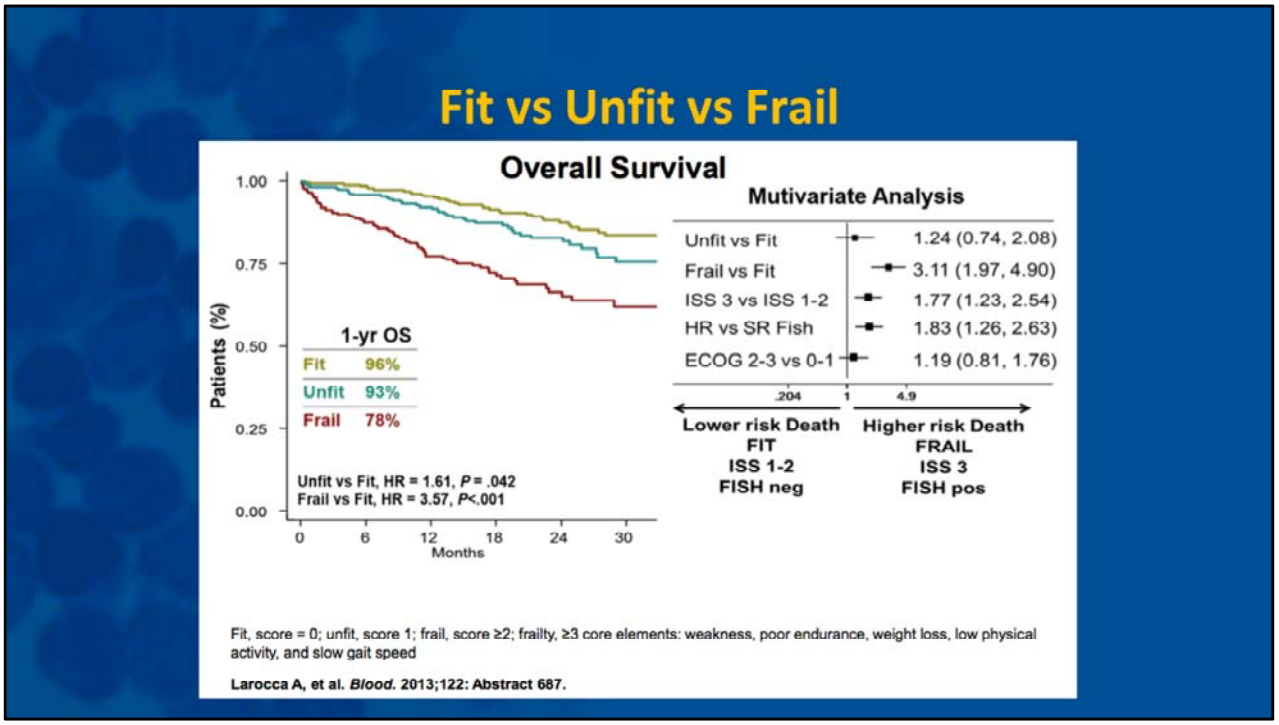


Now, if we separate patients between fit, unfit, and frail, we can see how the overall survival curves really separate out, and if we look on the right, we can see that in the multivariate analysis, patients who were fit had a lower ISS, that is International Stage 1 and 2 and FISH that was negative for high-risk cytogenetic features, those patients had a lower risk of death. Contrarily, patients who had FISH cytogenetic findings consistent with high-risk disease, higher ISS stage, ISS 3 or were found to be frail had a worse overall survival. Again, we see this as an independent risk factor for outcomes in a multivariate analysis. It is something that we need to be very conscious of when we approach our patients and discuss what their prognosis is.

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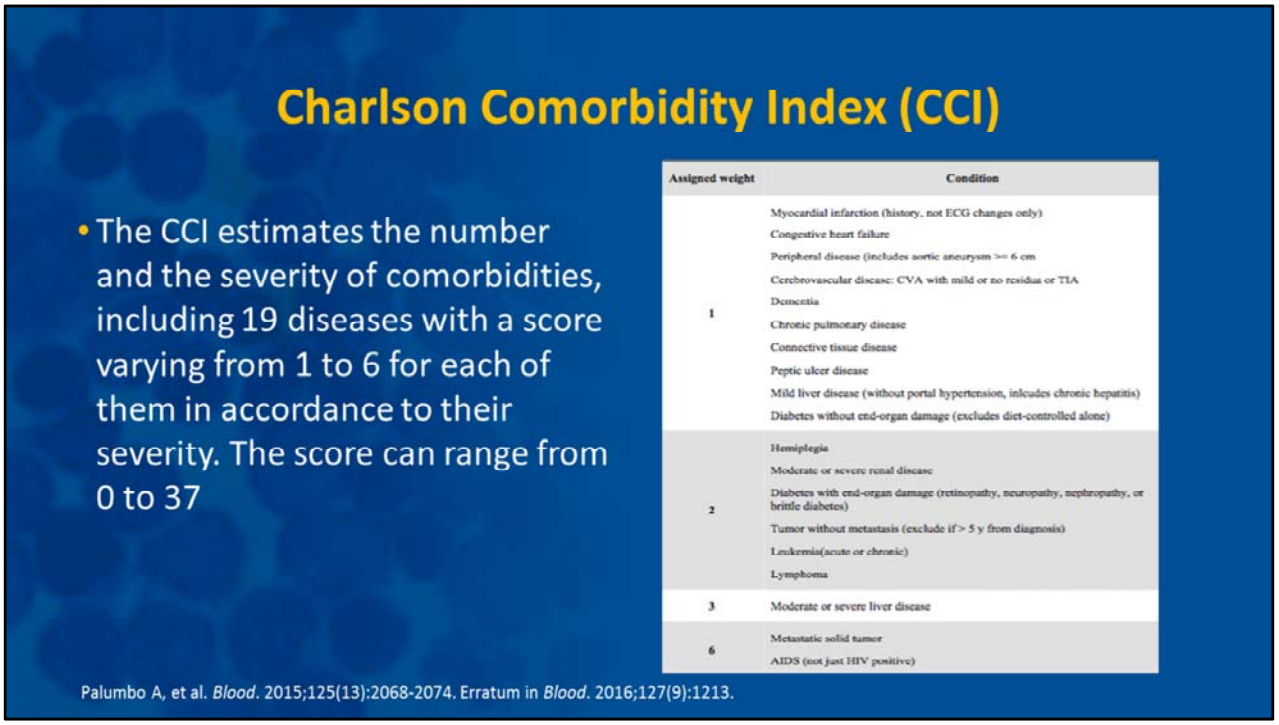


So, how do we go about evaluating fitness and frailty in a general level? Much of us in the clinic do this from a gut instinct or kind of once-over view of our patients and make some basic determinations about fitness or frailty. There actually have been developed a variety of indices to help formally and rigorously evaluate a patient's fitness or frailty, one of them being the Charlson Comorbidity Index. The Charlson Comorbidity Index evaluates a patient based of a variety of comorbidities ranging from dementia, chronic obstructive pulmonary disease, all the way up to other malignancies and AIDS. Basically, the patient is evaluated and each different comorbid condition is assigned a point score, and the score is totaled somewhere between 0 and 37, with the higher weight scores being patients with more significant comorbidities.

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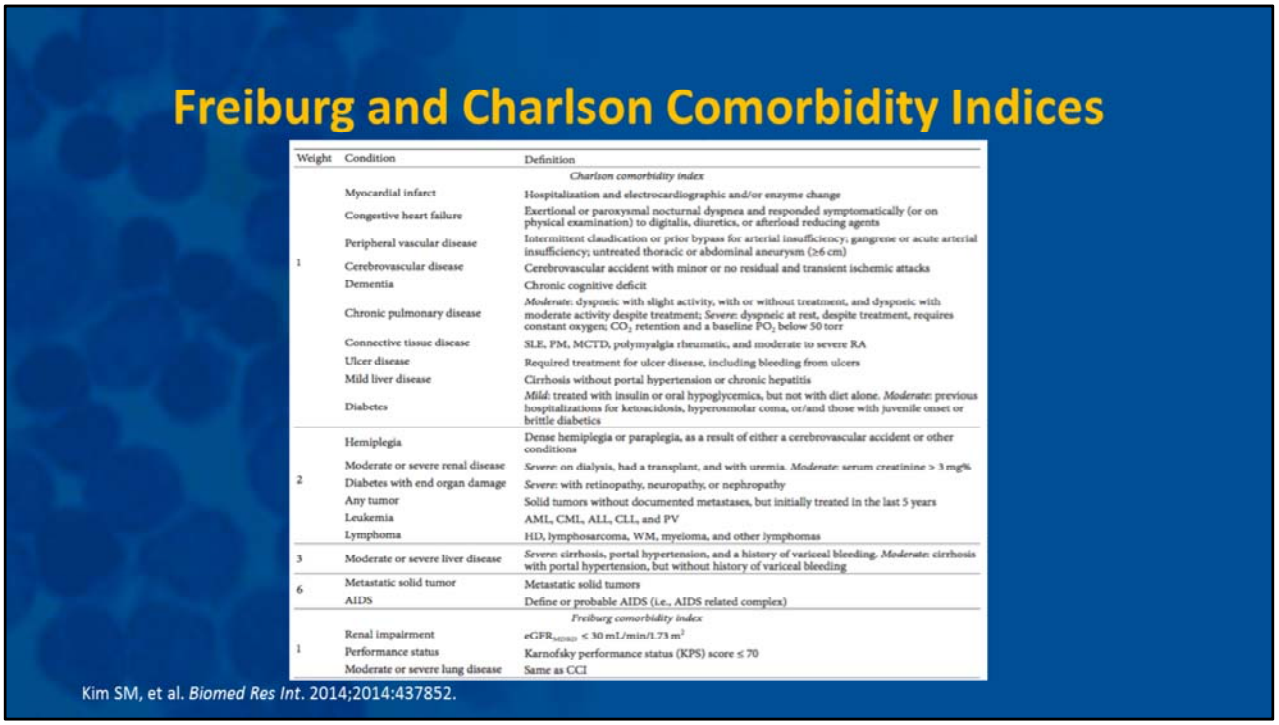


The Charlson Comorbidity Index is quite large and quite cumbersome, so other indices have been developed to simplify matters, the most notable being the Freiburg Comorbidity Index. The Freiburg Comorbidity Index evaluated comorbid conditions and really boiled it down to the three most important ones for assessment of patient's fitness or frailty. Number one being renal impairment, so an estimated glomerular filtration rate of less than 30; performance status, a Karnofsky score of less than 70; or moderate or severe lung disease which has been defined in the Charlson Comorbidity Index. These three factors together help to determine whether or not a patient is fit or frail at some level

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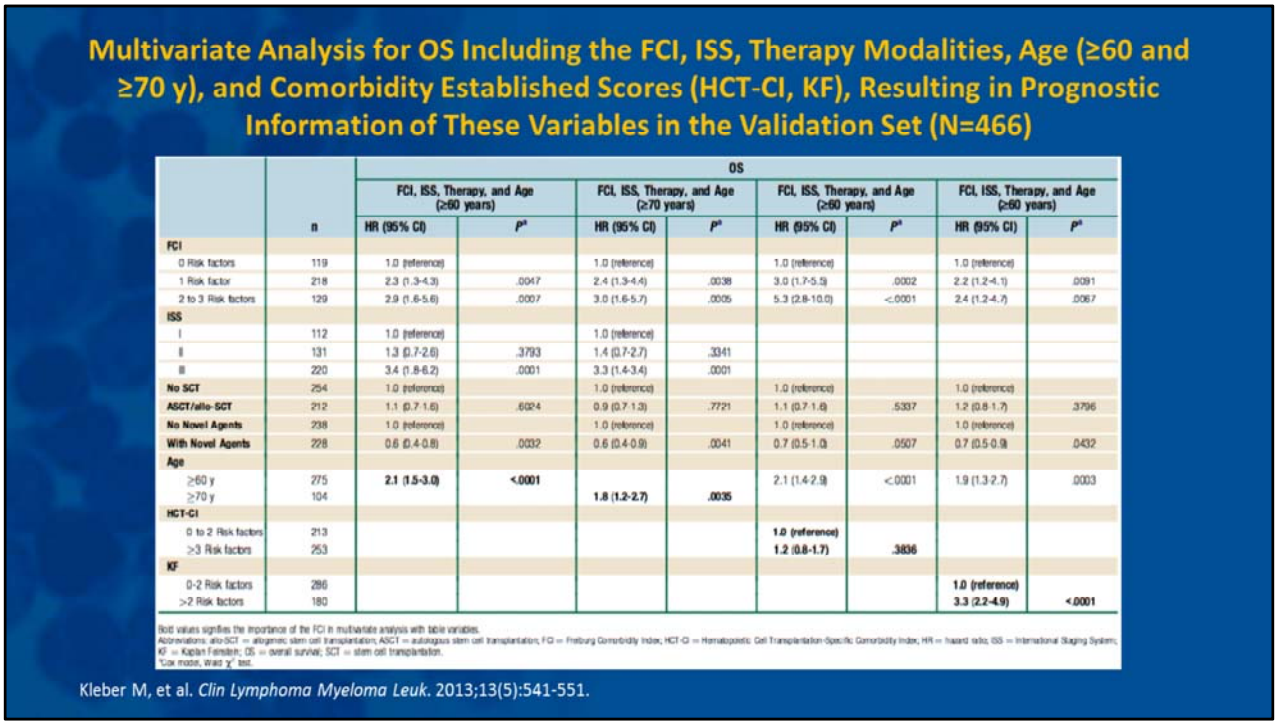

**Multivariate Analysis for OS Including the FCI, ISS, Therapy Modalities, Age (≥60 and ≥70 y), and Comorbidity Established Scores (HCT-CI, KF), Resulting in Prognostic Information of These Variables in the Validation Set (N=466)**

| | | OS | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | FCI, ISS, Therapy, and Age (≥60 years) | | FCI, ISS, Therapy, and Age (≥70 years) | | FCI, ISS, Therapy, and Age (≥60 years) | | FCI, ISS, Therapy, and Age (≥60 years) | |
| | n | HR (95% CI) | P* | HR (95% CI) | P* | HR (95% CI) | P* | HR (95% CI) | P* |
| **FCI** | | | | | | | | | |
| 0 Risk factors | 119 | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | |
| 1 Risk factor | 218 | 2.3 (1.3-4.3) | .0047 | 2.4 (1.3-4.4) | .0038 | 3.0 (1.7-5.5) | .0002 | 2.2 (1.2-4.1) | .0091 |
| 2 to 3 Risk factors | 129 | 2.9 (1.6-5.6) | .0007 | 3.0 (1.6-5.7) | .0005 | 5.3 (2.8-10.0) | <.0001 | 2.4 (1.2-4.7) | .0067 |
| **ISS** | | | | | | | | | |
| I | 112 | 1.0 (reference) | | 1.0 (reference) | | | | | |
| II | 131 | 1.3 (0.7-2.6) | .3793 | 1.4 (0.7-2.7) | .3341 | | | | |
| III | 220 | 3.4 (1.8-6.2) | .0001 | 3.3 (1.4-3.4) | .0001 | | | | |
| **No SCT** | 254 | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | |
| **ASCT/allo-SCT** | 212 | 1.1 (0.7-1.6) | .6024 | 0.9 (0.7-1.3) | .7721 | 1.1 (0.7-1.6) | .5337 | 1.2 (0.8-1.7) | .3796 |
| **No Novel Agents** | 238 | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | |
| **With Novel Agents** | 228 | 0.6 (0.4-0.8) | .0032 | 0.6 (0.4-0.9) | .0041 | 0.7 (0.5-1.0) | .0507 | 0.7 (0.5-0.9) | .0432 |
| **Age** | | | | | | | | | |
| ≥60 y | 275 | **2.1 (1.5-3.0)** | **<.0001** | | | 2.1 (1.4-2.9) | <.0001 | 1.9 (1.3-2.7) | .0003 |
| ≥70 y | 104 | | | **1.8 (1.2-2.7)** | **.0035** | | | | |
| **HCT-CI** | | | | | | | | | |
| 0 to 2 Risk factors | 213 | | | | | **1.0 (reference)** | | | |
| ≥3 Risk factors | 253 | | | | | **1.2 (0.8-1.7)** | **.3836** | | |
| **KF** | | | | | | | | | |
| 0-2 Risk factors | 286 | | | | | | | **1.0 (reference)** | |
| >2 Risk factors | 180 | | | | | | | **3.3 (2.2-4.9)** | **<.0001** |

Bold values signifies the importance of the FCI in multivariate analysis with table variables.
Abbreviations: allo-SCT = allogeneic stem cell transplantation; ASCT = autologous stem cell transplantation; FCI = Freiburg Comorbidity Index; HCT-CI = Hematopoietic Cell Transplantation-Specific Comorbidity Index; HR = hazard ratio; ISS = International Staging System; KF = Kaplan Feinstein; OS = overall survival; SCT = stem cell transplantation.
*Cox model, Wald $\chi^2$ test.

Kleber M, et al. *Clin Lymphoma Myeloma Leuk*. 2013;13(5):541-551.

Now, the Freiburg Comorbidity Index has been evaluated and validated in relation to the management of patients with multiple myeloma. So, across a multivariate analysis, we can look at overall survival rates of patients with varying factors related to their disease, as in whether or not they received novel therapies, whether or not they received high-dose therapy and autologous stem cell transplant, what their International Staging System is, and no matter which point you are looking at, we can see where patients with lower Freiburg Comorbidity Index, the more fit patients will do better than those with the higher Freiburg Comorbidity Index.

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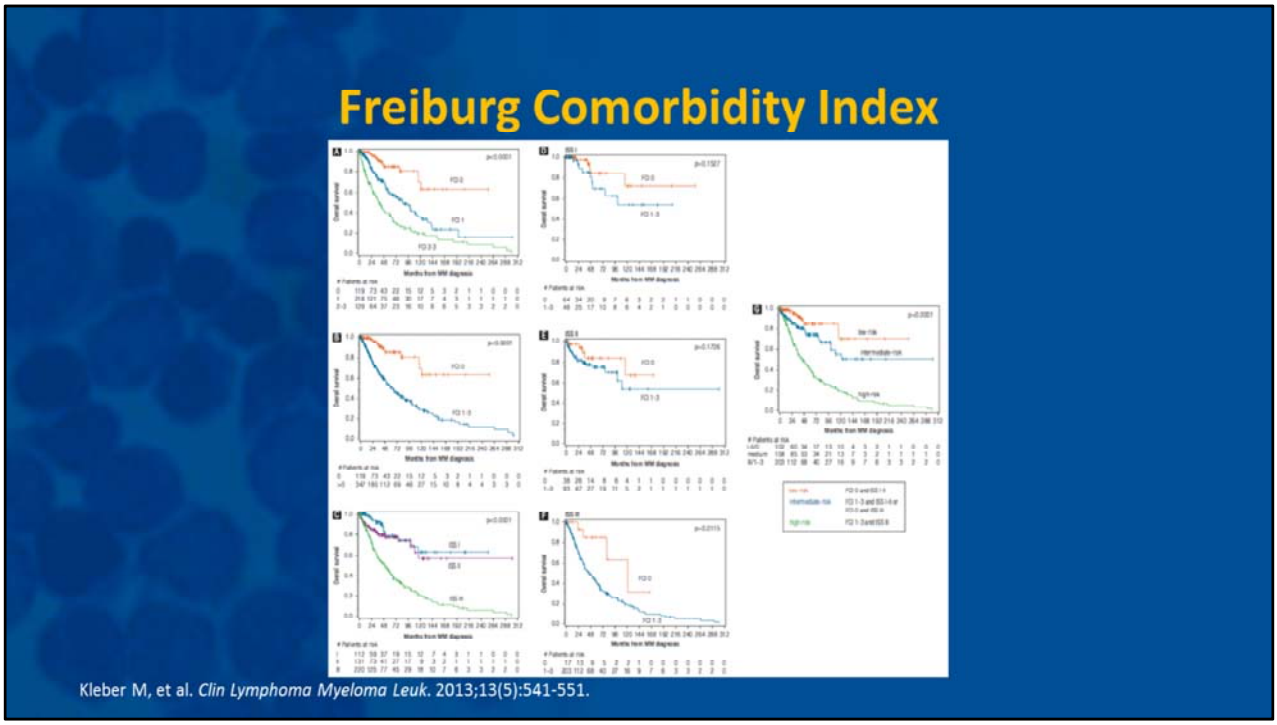


Again, this is evaluated for patients with ISS stage 1, ISS stage 2, and ISS stage 3. So, ISS stage for ISS stage. The patients who are more fit had a lower Freiburg Comorbidity Index and did better overall in regards to not only progression-free survival but overall survival. Again, something that is key and important when discussing with our patients what their prognosis is, is to factor in not only their disease but their own comorbidity index in terms of their overall functional status.

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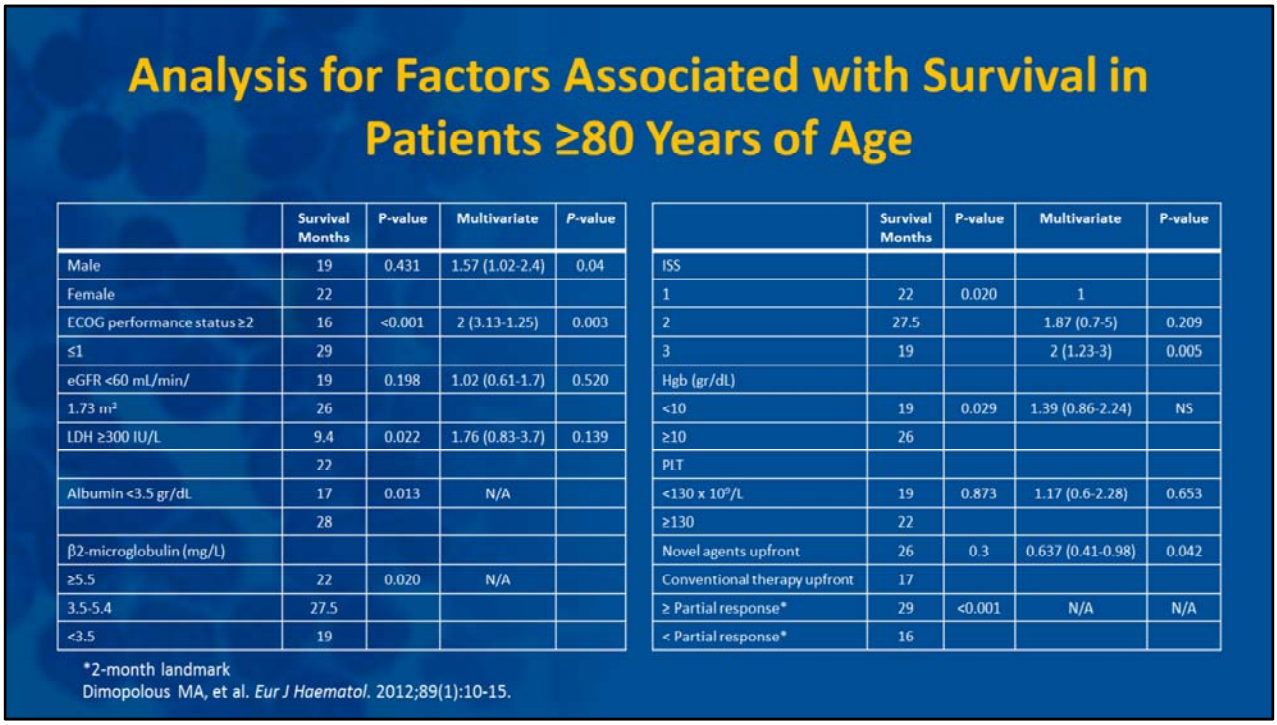

## Analysis for Factors Associated with Survival in Patients ≥80 Years of Age

| | Survival Months | P-value | Multivariate | *P*-value |
|---|---|---|---|---|
| Male | 19 | 0.431 | 1.57 (1.02-2.4) | 0.04 |
| Female | 22 | | | |
| ECOG performance status ≥2 | 16 | <0.001 | 2 (3.13-1.25) | 0.003 |
| ≤1 | 29 | | | |
| eGFR <60 mL/min/ | 19 | 0.198 | 1.02 (0.61-1.7) | 0.520 |
| 1.73 m² | 26 | | | |
| LDH ≥300 IU/L | 9.4 | 0.022 | 1.76 (0.83-3.7) | 0.139 |
| | 22 | | | |
| Albumin <3.5 gr/dL | 17 | 0.013 | N/A | |
| | 28 | | | |
| β2-microglobulin (mg/L) | | | | |
| ≥5.5 | 22 | 0.020 | N/A | |
| 3.5-5.4 | 27.5 | | | |
| <3.5 | 19 | | | |

| | Survival Months | P-value | Multivariate | P-value |
|---|---|---|---|---|
| ISS | | | | |
| 1 | 22 | 0.020 | 1 | |
| 2 | 27.5 | | 1.87 (0.7-5) | 0.209 |
| 3 | 19 | | 2 (1.23-3) | 0.005 |
| Hgb (gr/dL) | | | | |
| <10 | 19 | 0.029 | 1.39 (0.86-2.24) | NS |
| ≥10 | 26 | | | |
| PLT | | | | |
| <130 x $10^9$/L | 19 | 0.873 | 1.17 (0.6-2.28) | 0.653 |
| ≥130 | 22 | | | |
| Novel agents upfront | 26 | 0.3 | 0.637 (0.41-0.98) | 0.042 |
| Conventional therapy upfront | 17 | | | |
| ≥ Partial response* | 29 | <0.001 | N/A | N/A |
| < Partial response* | 16 | | | |

*2-month landmark

Dimopolous MA, et al. *Eur J Haematol*. 2012;89(1):10-15.

So, what about patients who are of advanced age? And it is worthwhile to note that age does not equal frailty. We all have seen patients in our clinic who are running marathons in their mid-80s, and we have all seen those patients who are far younger but with significant comorbidities and limitations, and it is worthwhile to note that age in and of itself is not the end-all be-all of a frailty assessment. However, patients with advanced age, it is worthwhile to take close attention to make sure that we are aware of the general metabolic changes of a patient who is of advanced age in relation to drug metabolism, polypharmacy, and other factors. And there are specific factors that have been evaluated in association with survival for patients over the age of 80 with multiple myeloma, most notably on the list, ECOG performance status, so those patients with an ECOG performance status of greater than or equal to 2 had a worse survival overall. The other thing that is worthwhile to note is exposure to novel therapies. Now, we live in a golden age "in myeloma" where we have access to many different drugs and lots of novel therapies. It is worthwhile to note that patients who are of advanced age, the standard of care, at least in this country, is really no longer melphalan/prednisone, but we do have the availability of well-tolerated highly efficacious novel therapies including immunomodulatory agents, proteosome inhibitors, and monoclonal antibodies. It seems that patients who received these novel therapies despite fitness or frailness will do well overall, but again worthwhile to consider all factors when approaching a treatment decision for your patient.

# Performance Status Adaptive Therapy in Multiple Myeloma


So, Dr. Palumbo and his group has done a lot of work in evaluating assessments for patients who are older or more frail with multiple myeloma to ensure that this is not done by "gut instinct" but is done in some rigorous fashion so that we can make some general statements about how to approach patients who are older or more frail with multiple myeloma.

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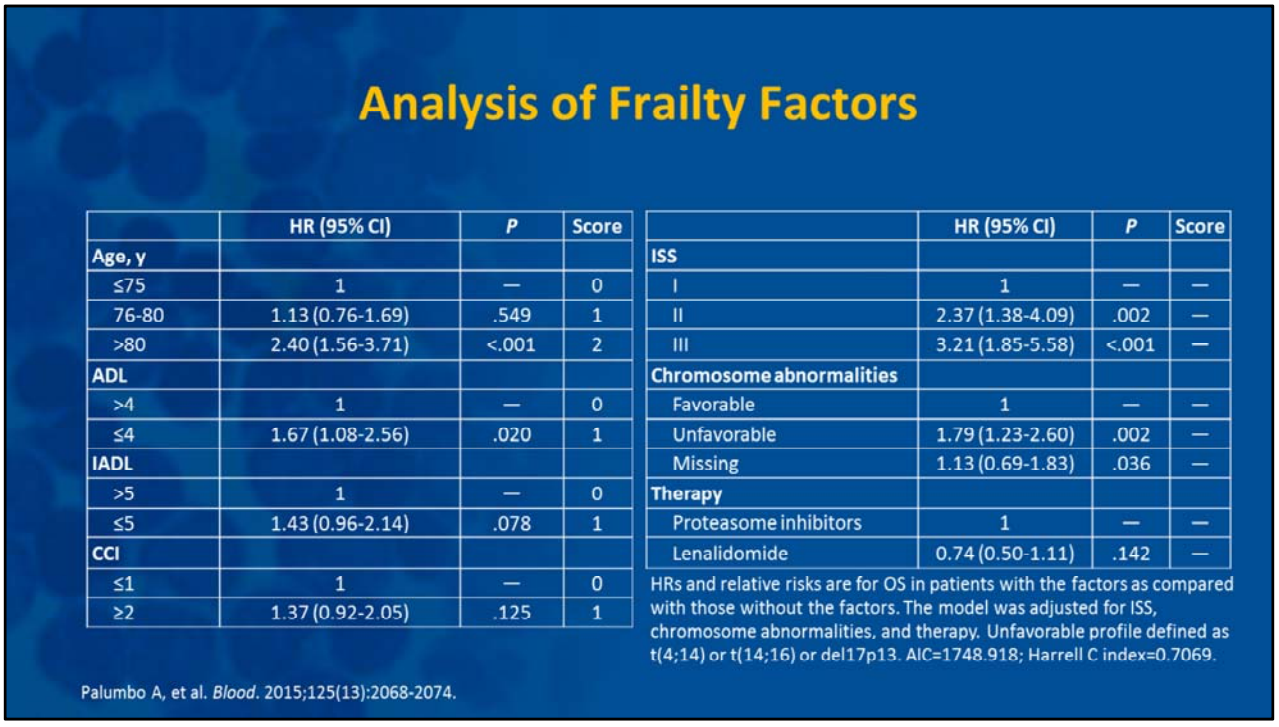


| | HR (95% CI) | *P* | Score |
|---|---|---|---|
| **Age, y** | | | |
| ≤75 | 1 | — | 0 |
| 76-80 | 1.13 (0.76-1.69) | .549 | 1 |
| >80 | 2.40 (1.56-3.71) | <.001 | 2 |
| **ADL** | | | |
| >4 | 1 | — | 0 |
| ≤4 | 1.67 (1.08-2.56) | .020 | 1 |
| **IADL** | | | |
| >5 | 1 | — | 0 |
| ≤5 | 1.43 (0.96-2.14) | .078 | 1 |
| **CCI** | | | |
| ≤1 | 1 | — | 0 |
| ≥2 | 1.37 (0.92-2.05) | .125 | 1 |

| | HR (95% CI) | *P* | Score |
|---|---|---|---|
| **ISS** | | | |
| I | 1 | — | — |
| II | 2.37 (1.38-4.09) | .002 | — |
| III | 3.21 (1.85-5.58) | <.001 | — |
| **Chromosome abnormalities** | | | |
| Favorable | 1 | — | — |
| Unfavorable | 1.79 (1.23-2.60) | .002 | — |
| Missing | 1.13 (0.69-1.83) | .036 | — |
| **Therapy** | | | |
| Proteasome inhibitors | 1 | — | — |
| Lenalidomide | 0.74 (0.50-1.11) | .142 | — |

So, when evaluating patients for frailty, it is worthwhile to consider their age. Again, age in and of itself is not the end-all be-all, but there is difference between a patient who is 60, 70, 80, and beyond, evaluating a patient's activities of daily living and their ability to perform them, either independently or with the help of others, their instrumental activities of daily living, the Charlson Comorbidity Index, the International Staging System, chromosomal abnormalities, and therapies. So again, looking at the analysis of frailty factors from Dr. Palumbo's work, we see that patients who are older tend to be more frail, and again as a general sense of frailty, patients who are unable to perform their activities of daily living are more frail. Patients who are unable to independently perform their instrumental activities of daily living are more frail, and the outcomes for patients again with higher International Staging System disease will have worse outcome in general.

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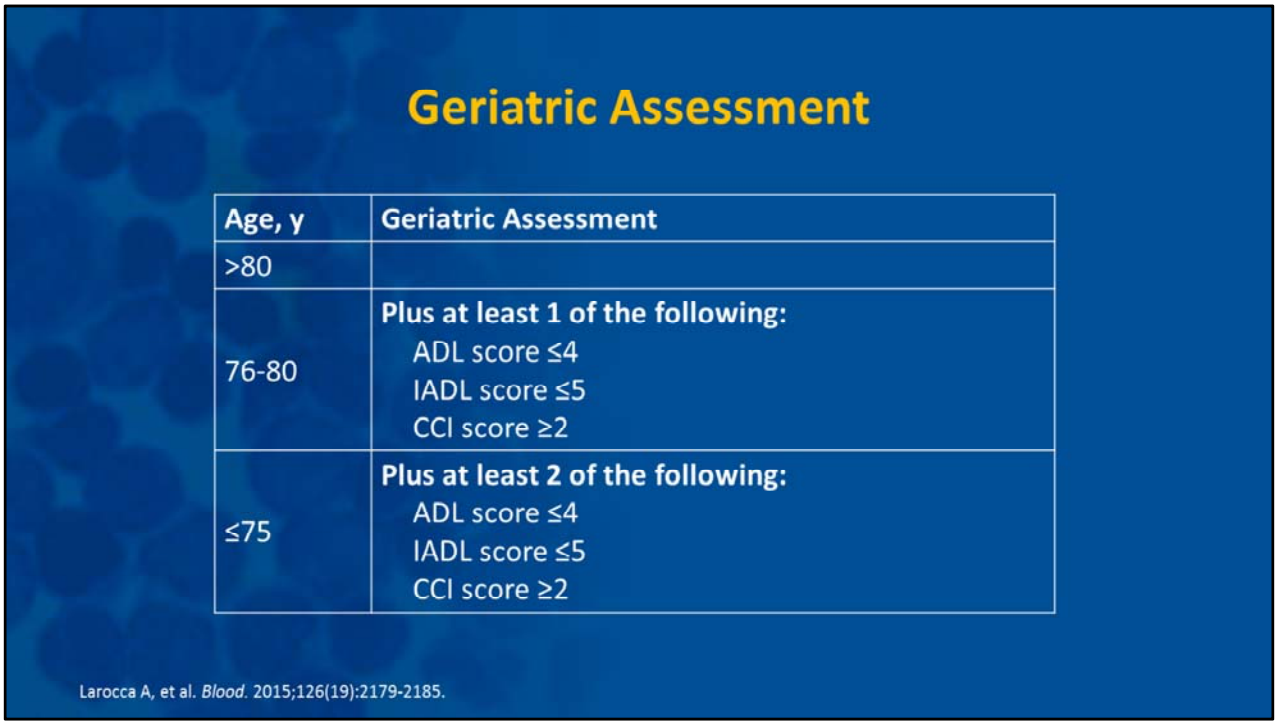


So, how do we approach geriatric assessment? I believe this graph here represents a good balance to combine not only the age but a patient's performance status and a comorbidity index. So, here we evaluate patients who are "geriatric" over the age of 80 need to really be thought of in somewhat of a different light as a general basis. If they are between the ages of 76 and 80, we consider them more frail if they are of this age group and at least one of the following, either a Charlson Comorbidity Index of greater than 2, an IADL score of less than or equal to 5, and an ADL score of less than or equal to 4. If they are under the age of 75, they should have at least two of these before being considered frail.

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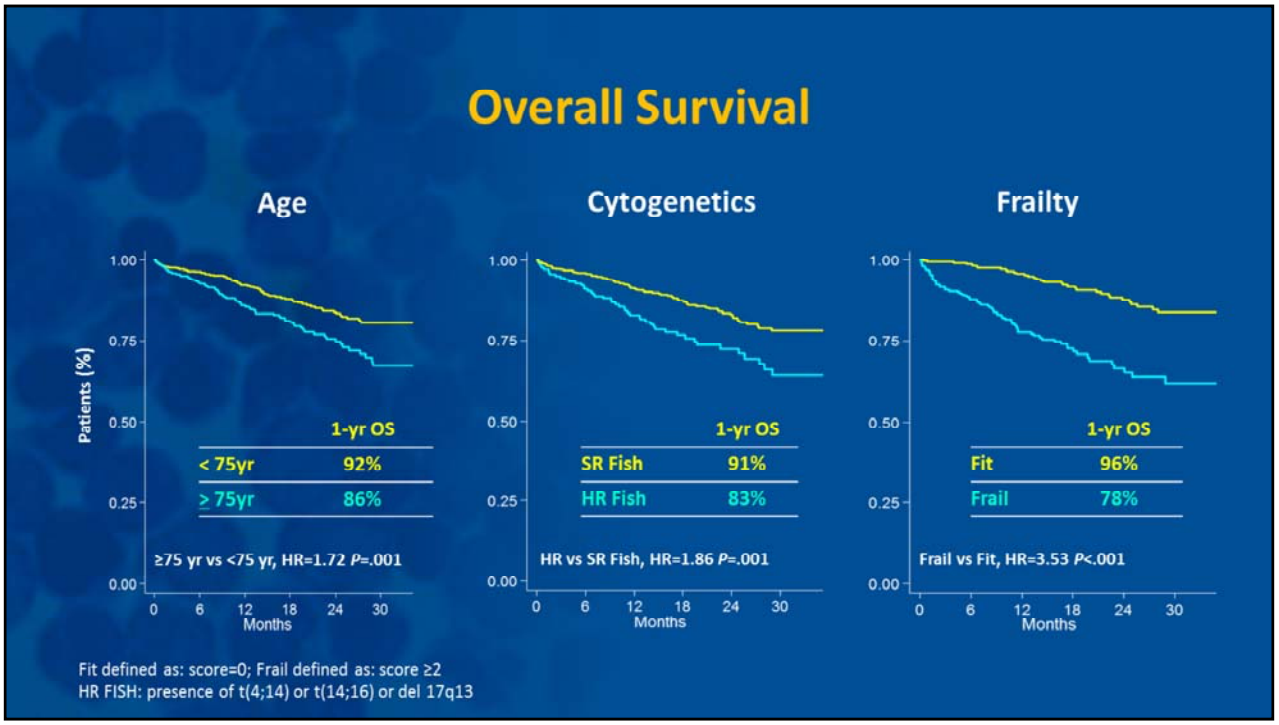


And again, when we look at overall survival across age groups, across cytogenetic groups, and across a frailty assessment, we see that the overall survival curves really do separate, and it is worthwhile to note that we see in many papers that are published that age may play a factor. Again, it is not the only factor, but we can see overall survival differs here based on age over or under the age of 75. Again, much of this is not disease related but simply a fact of decreased actuarial predicted survival of more elderly patients. Cytogenetics has clearly been described as a factor in evaluating patients' overall survival, finding that patients with cytogenetically high-risk disease, despite various interventions, will overall have a worse overall survival. And frailty, clearly here looking at the 1-year overall survival of fit versus frail patients of 96% versus 78%, again worthwhile to discuss with your patient regarding their goals of care and their therapeutic approach.

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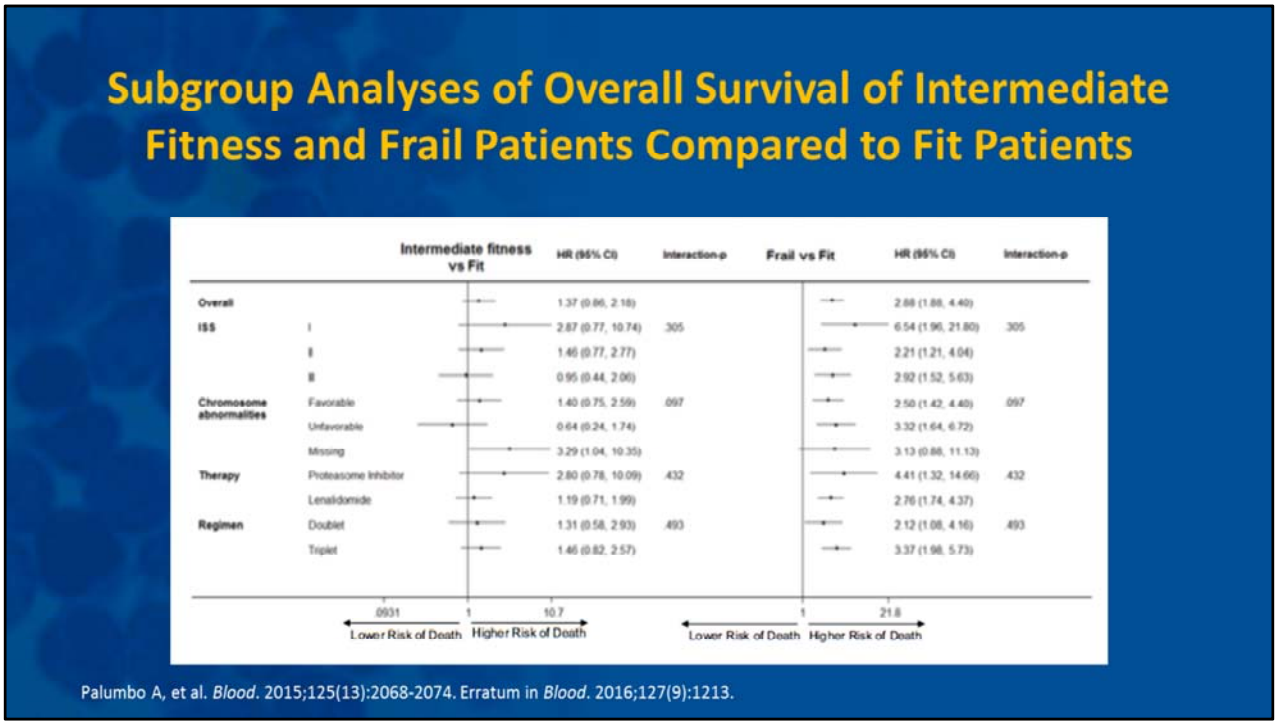
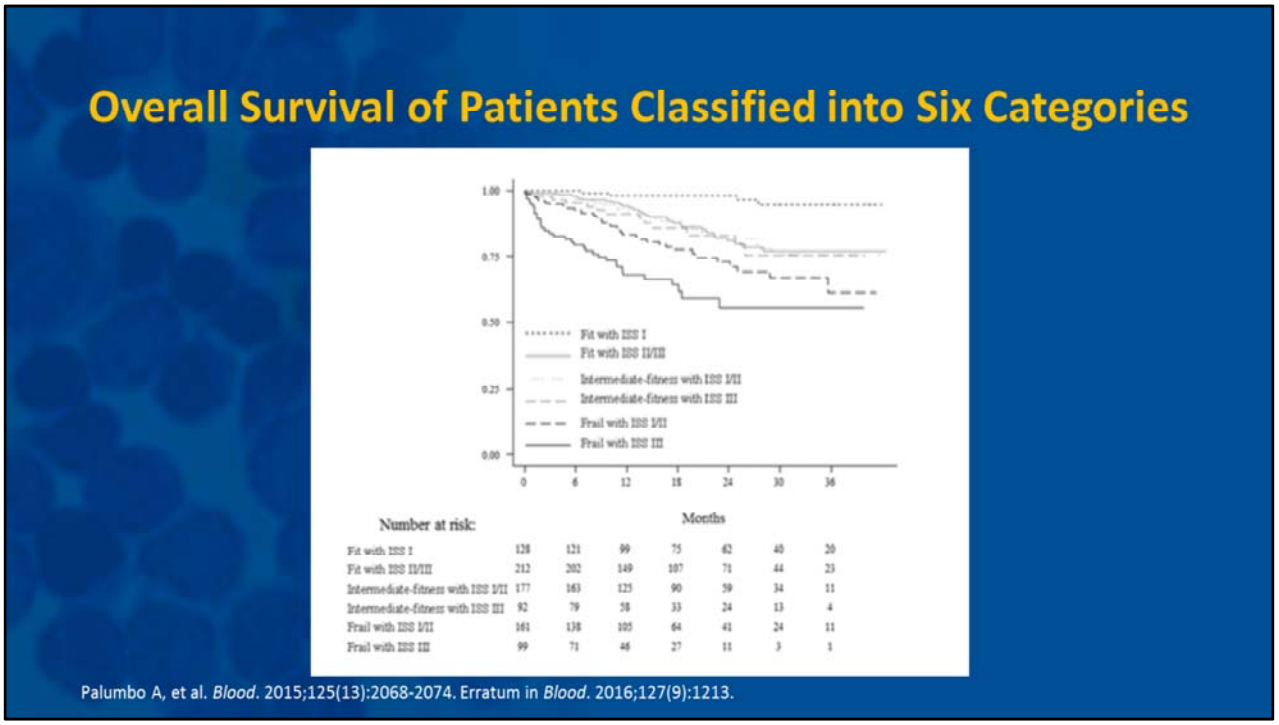



Palumbo A, et al. *Blood*. 2015;125(13):2068-2074. Erratum in *Blood*. 2016;127(9):1213.

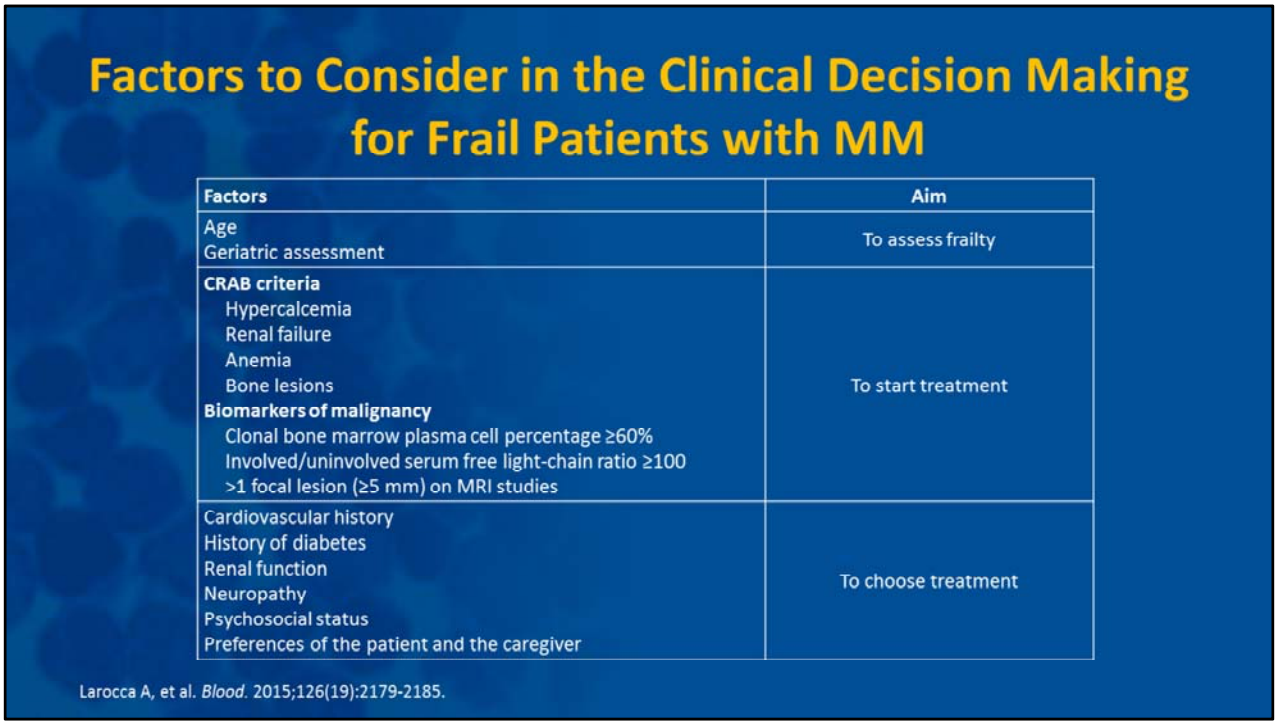
We can also evaluate our patients not in an all-or-none fashion but in subgroups relating to intermediate fitness versus fit, or fit versus frail. Here, in the Forest plot, we can evaluate the intermediate fitness versus fit patients and see that certain approaches will lean us one way or the other toward higher risk of death or lower risk of death, but on the whole, when you compare intermediate fitness patients versus fit patients, most of the ranges do cross the midline. When we look over to the right of the screen in the fit versus frail patients, we can see that almost all the incidences, whether it is International Staging System, chromosomal abnormalities, or therapeutic choice, those patients who were deemed to be frail had a higher risk of death overall.

# Performance Status Adaptive Therapy in Multiple Myeloma




Again, we can combine these different concepts of patient factors and disease factors to separate out our patients into different categories in terms of their overall survival. So, the best patients are obviously the fit patients with ISS stage 1 disease, and as we progress with different combinations toward the frail patient with ISS stage 3, we see a marked difference in their overall survival.

# Performance Status Adaptive Therapy in Multiple Myeloma




So, there are certain factors to consider when making the decision to treat a patient with myeloma. So, if you have a patient who warrants therapy or you feel warrants therapy, what are the factors that we need to take into account? Obviously, the first one is to assess the patient. What is their age, what is their geriatric assessment, meaning is this patient older and more frail or they are younger and more fit, what are your goals of therapy? Is your goal of therapy palliative, is your goal of therapy simply disease control? All of these factors need to work into your thinking. What about CRAB criteria? The classic way that we consider when patients are warranting systemic therapy is by fitting the CRAB criteria. Hypercalcemia, renal dysfunction, anemia, or lytic bone disease. These still remain the classic core manifestations of myeloma to warrant therapy. However, recently, we have established that there is a group of patients with high-risk smoldering disease who will have such a high likelihood of progressing to symptomatic disease that they warrant therapy. The so-called SLiM CRAB criteria. Si for bone marrow plasmacytosis greater than 60%, LI for a light chain ratio of greater than 100, or M for MRI lesions greater than one focal lesion. Again, all these factors need to be taken into account when deciding whether or not to assess whether or not a patient warrants chemotherapeutic intervention. How do we choose the individual treatment? Here it is worthwhile to evaluate their comorbidities. History of diabetes may play a role in how you dose your steroids as almost every therapy for myeloma involves corticosteroids. What about cardiovascular risk, renal function, and neuropathy? Now that we have a almost plethora of drugs to choose from, at least in the upfront setting, it is worthwhile to evaluate all of these when instituting therapy. Certain therapeutic agents have a higher risk of neuropathy. Certain drugs are tolerated better from a renal dysfunction standpoint or a bone marrow standpoint, and this will help us choose our individualized therapy.

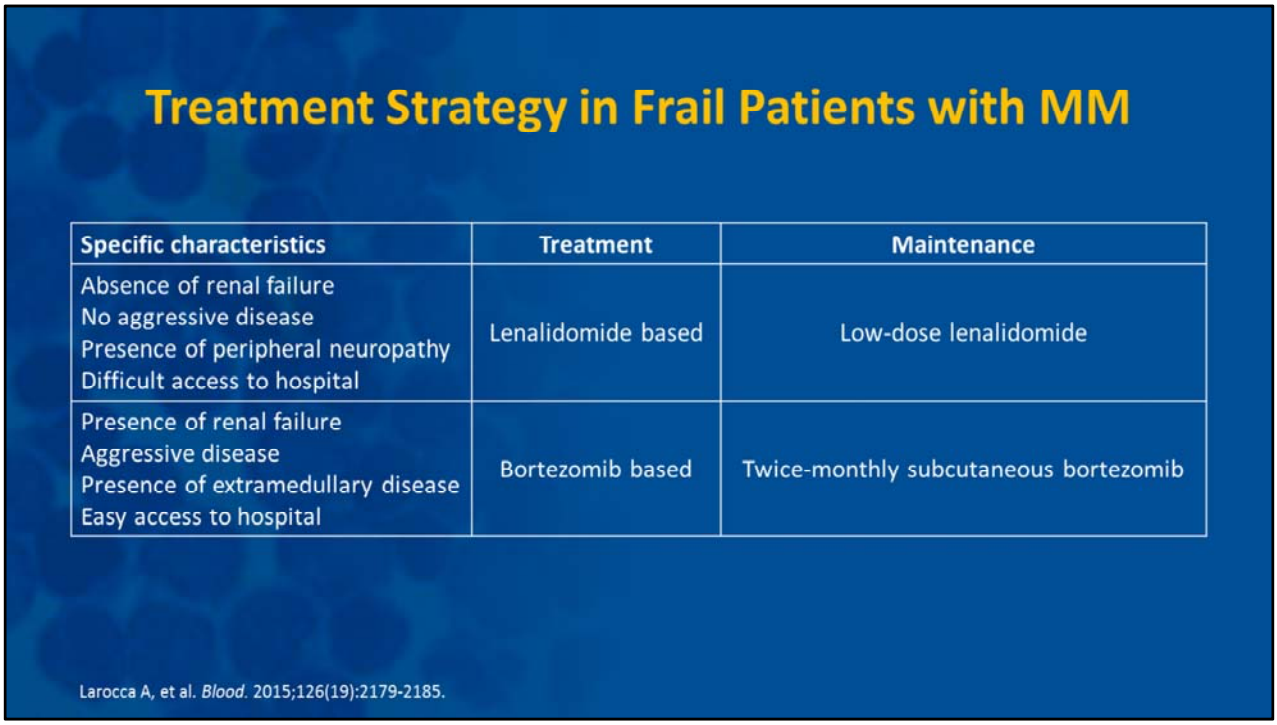

So again, when we have a patient who is more frail where the decision to start therapy is not an easy one and not a definite one, what are your goals? And number one, if the patient is having evidence of active CRAB symptoms, this is something that we need to treat in order to prevent progressive end-organ dysfunction. One of the difficult things may be to rule out confounding factors. Again, not all renal dysfunction in a myeloma patient is related to the myeloma. This could be related to a longstanding metabolic disease such as hypertension or diabetes. What about bone lesions? Again, many of our patients are quite elderly, and osteoporosis and osteopenia and fractures from bone mineral density lost over years may be confused with aggressive lytic bone disease. It is worthwhile to evaluate these functions on a system-by-system basis to make sure that you are not instituting therapy in a patient who is more frail simply because they fit one of the CRAB symptoms. These symptoms may be related to other factors. The other thing may be if someone is on the cusp, but they are quite frail, to delay therapy until they absolutely need it to prevent end-organ dysfunction. You may have somebody that fits criteria for treatment by the SLiM CRAB criteria; however, they may be quite frail, and they may be quite frail related to a recent hospitalization or related to their overall functional status. In these patients, it may be worthwhile to delay therapy until such time as the risk-benefit analysis is such that it makes sense to institute some type of intervention, and again, these decisions need to be made on a patient-by-patient basis. There are guidelines that we can use and general concepts we can use, but patient-by-patient decisions are necessary to avoid unnecessarily treating patients and to avoid undue toxicity.

# Performance Status Adaptive Therapy in Multiple Myeloma

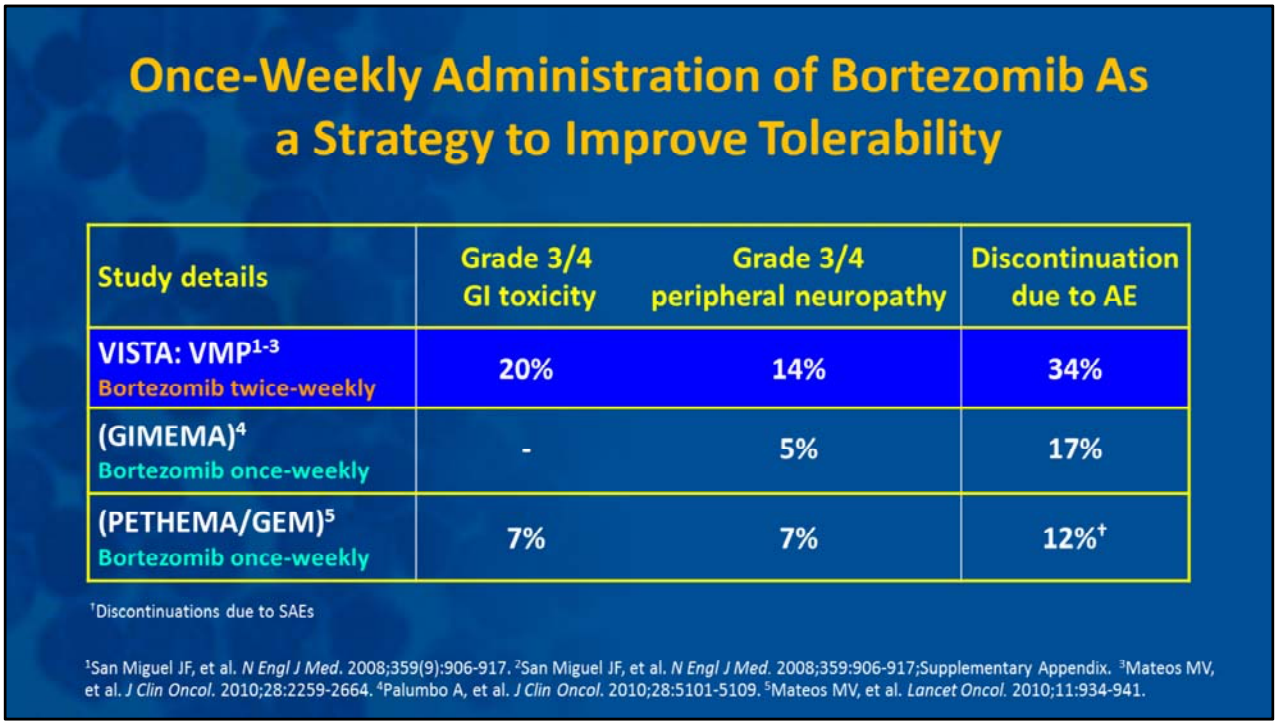

So, what are our goals of therapy? Now, again if we treat, we are looking for things such as quality of response, depth of response, and for our younger fit patients, one of the things that has become part of the mainstay of our therapy is continuous therapy, either in the upfront fashion as a maintenance after autologous transplant or in the relapse setting. There is evidence mounting that continuous therapy is better to prevent disease progression and clonal evolution, but we have to balance this with the other side of things by controlling symptoms. Now, again, symptoms can be related to disease or general comorbidities of the patient. Avoiding toxicities is an important one. Preventing neuropathy is key in an elderly patient group as well as preventing consequences of bone marrow dysfunction and renal dysfunction. Maintaining independent status. If you have a patient who is barely maintaining independent status as it is and you provide them worsening fatigue from therapy or neuropathy that limits their ability to undergo their activities of daily or their IADLs, you may be doing them a disservice, so this needs to be balanced. Overall, it is all about preserving quality of life, especially in the disease that for the most part remains incurable.


So, there are specific therapeutic interventions we should consider in the management of a frail multiple myeloma patient. So, there are certain characteristics that may lean us in one way or another.

# Performance Status Adaptive Therapy in Multiple Myeloma

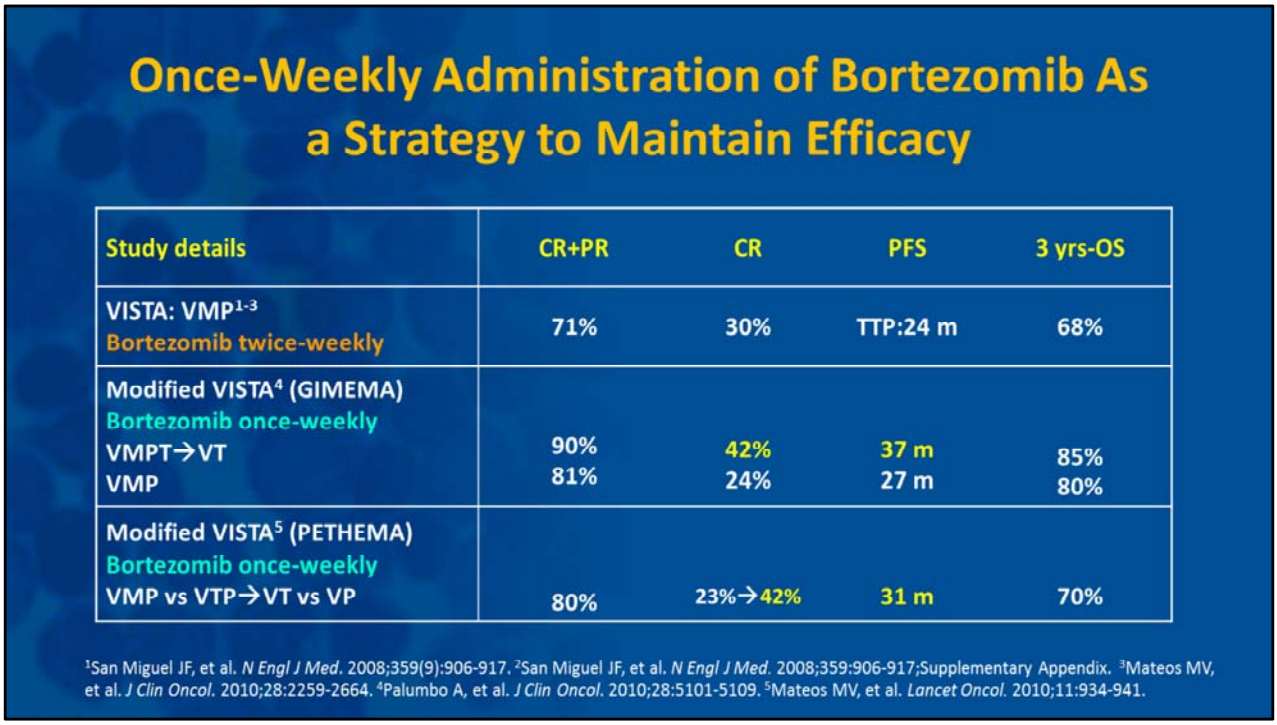



So, let's think about certain characteristics that would lean us toward a lenalidomide-based therapy. Now, again, as lenalidomide is cleared by the kidneys, patients with worse renal function will have delayed clearance, and as a result, enhanced marrow toxicity of lenalidomide. So, lenalidomide therapy is probably best considered for patients with no renal dysfunction. Now, again, even patients with advanced renal dysfunction can be dosed with the drugs, but it needs to be closely monitored and dose adjusted. Because lenalidomide may take somewhat longer to work than a bortezomib-based regimen, these should be patients who have perhaps less aggressive disease, and because lenalidomide is generally not associated with peripheral neuropathy, if you have a frailer patient who already has preexisting sensory peripheral neuropathy from diseases such as diabetes, this may be your drug of choice. If you get them in control with the drug and want to achieve a maintenance approach, something to consider is low-dose lenalidomide in this group of patients. Now, if you have a patient who has a progressive renal dysfunction as a result of myeloma, aggressive disease, or presence of extramedullary disease, proteasome inhibitor inhibition may be your mainstay of therapy, and here you may choose bortezomib for your upfront therapy of choice. Now, once you get them into control, you may want to consider either a weekly or every-other-week dosing schedule for your bortezomib to better control their disease in a long-term fashion and to allow them the ease of coming back and forth to clinic at a reduced level.



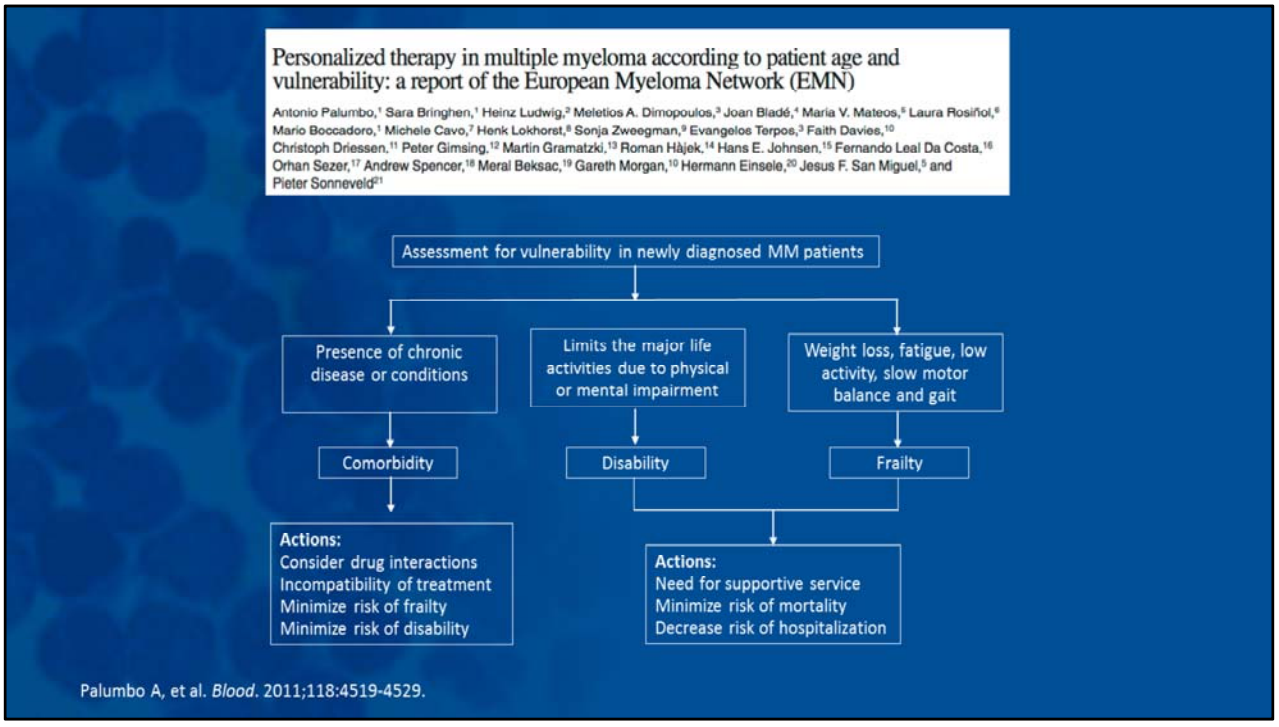

So, what about the overall dosing strategy for bortezomib? The classic way that bortezomib has been administered dates back to the VISTA trial where bortezomib was given on a twice-weekly basis on days 1, 4, 8, and 11, on a 21-day dosing schedule. Now, in this study, there was a significant number of patients who developed peripheral neuropathy and had to discontinue the drug due to neuropathy as a manifestation of sensory peripheral neuropathy or GI toxicity due to autonomic neuropathy. Now, again, this data has to be taken with a grain of salt as the VISTA data implored intravenous bortezomib, and we now know that subcutaneous bortezomib has a far lower incidence of peripheral neuropathy. Now, one of the ways that may be worthwhile to control a more frail patient with myeloma is by administrating once-weekly bortezomib. Now, in a once-weekly fashion, we see that the discontinuation rate due to adverse events is significantly lower and 17% and 12% in the GIMEMA and the PATHEMA studies. Now, again, this may be a way for patients who have less aggressive disease to control them long term.

# Performance Status Adaptive Therapy in Multiple Myeloma



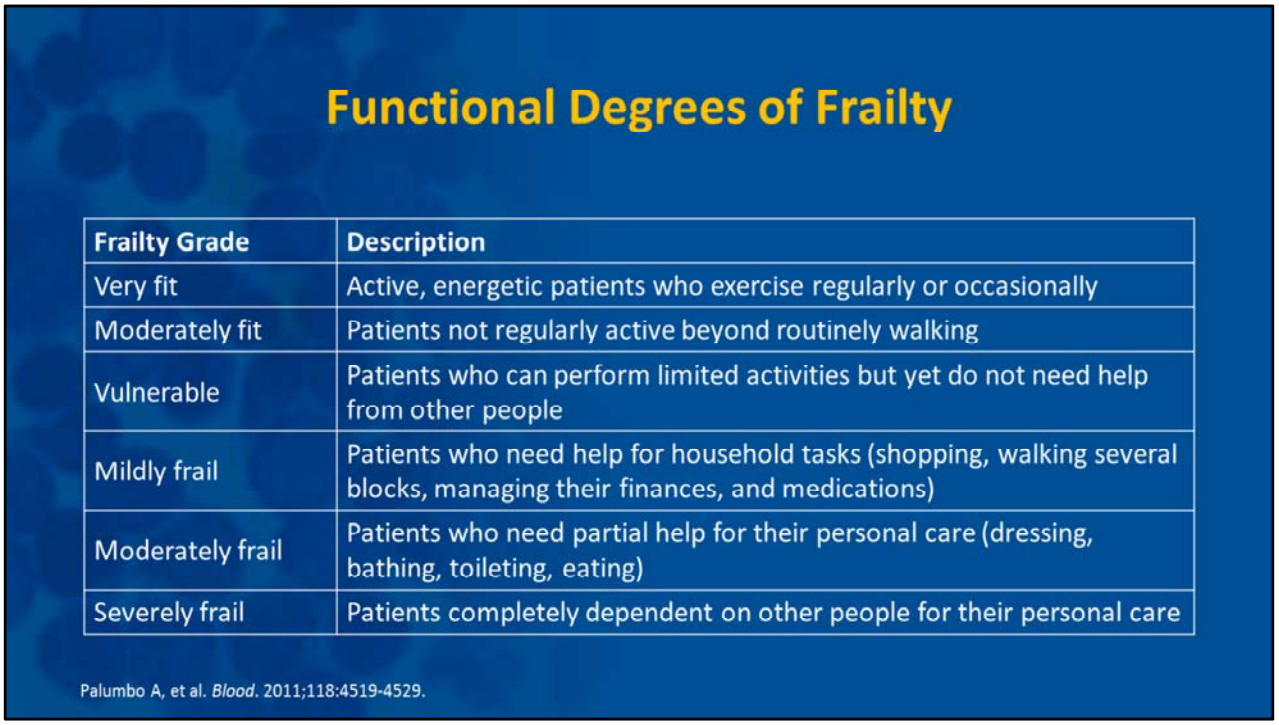

What about the efficacy of doing once weekly? Now again, I think we all have those patients in clinic that have progressed on once-weekly bortezomib that we can recapture with twice weekly. So, there probably is some difference in terms of their immediate efficacy. However, for some of our more frail patients, we may be able to maintain them on once-weekly dosing bortezomib for a prolonged period of time, whereas in the initial stages they may not respond as deeply. If you can maintain a patient on long-term therapy, their studies with bortezomib and other novel therapies have shown that long-term continuous therapy provides deeper and deeper responses over time, so this may be a way to control our more frail patients without having to come back and forth twice a week, without the higher risk of peripheral neuropathy, and because we can administer this over a long periods of time, over time those MRs become PRs, the PRs become VGPRs, and the VGPRs becomes CRs. Here, we can see a variety of different approaches to using bortezomib in a twice-weekly or once-weekly fashion, and again, we can see very high overall survival rates even with the once-weekly fashion. This may be due to the fact that if the drug is better tolerated from a back and forth standpoint visiting the clinic as well as a peripheral neuropathy standpoint, we may be able to maintain patients on therapy for longer periods of time, ultimately receiving deeper responses, and ultimately leading to better overall survival.

# Performance Status Adaptive Therapy in Multiple Myeloma



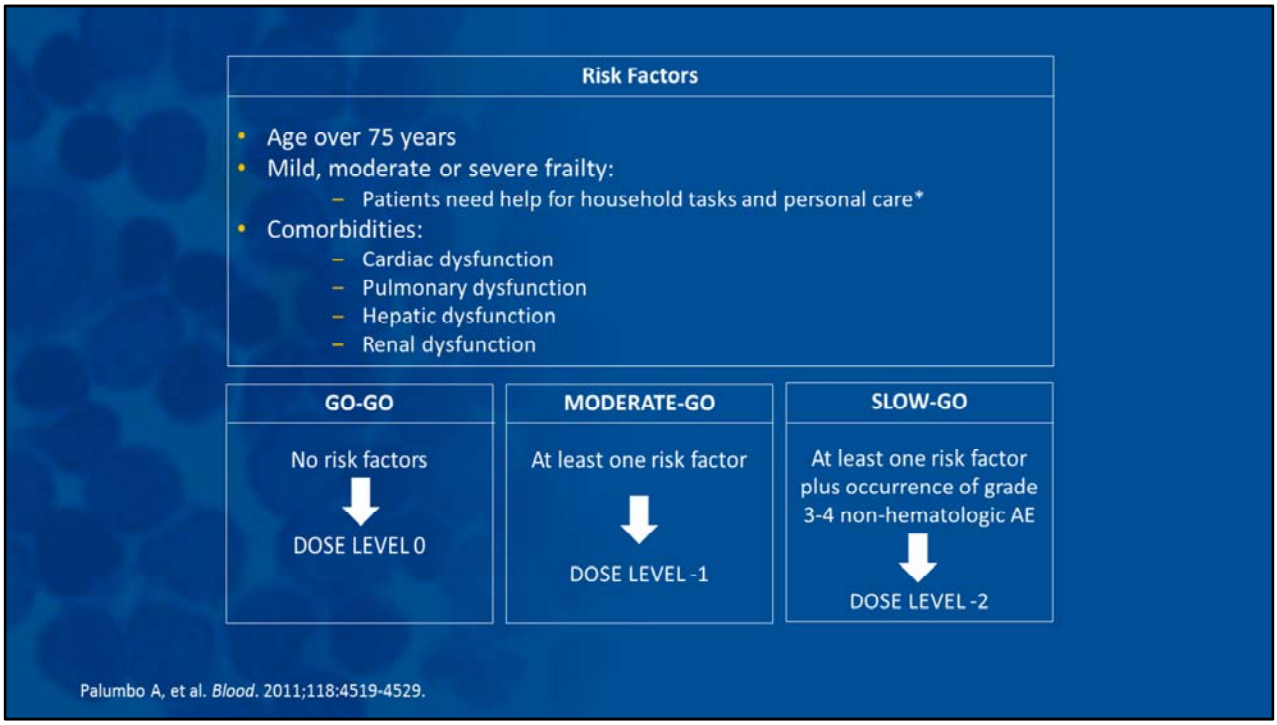

So, how do we evaluate our patients in a pragmatic standpoint? So, Palumbo's group again evaluated a personalized approach to treating frail myeloma patients. Now, we can evaluate them in terms of comorbidities, in terms of their other diseases and the drugs they need for drug-drug interaction. In terms of their disabilities, patients may have significant physical or mental disabilities, especially with advanced age. And frailty again, weight loss and fatigue need to be taken into account as well as patient's motor skills, gait, ability to transfer, and the need for supportive therapy.

# Performance Status Adaptive Therapy in Multiple Myeloma



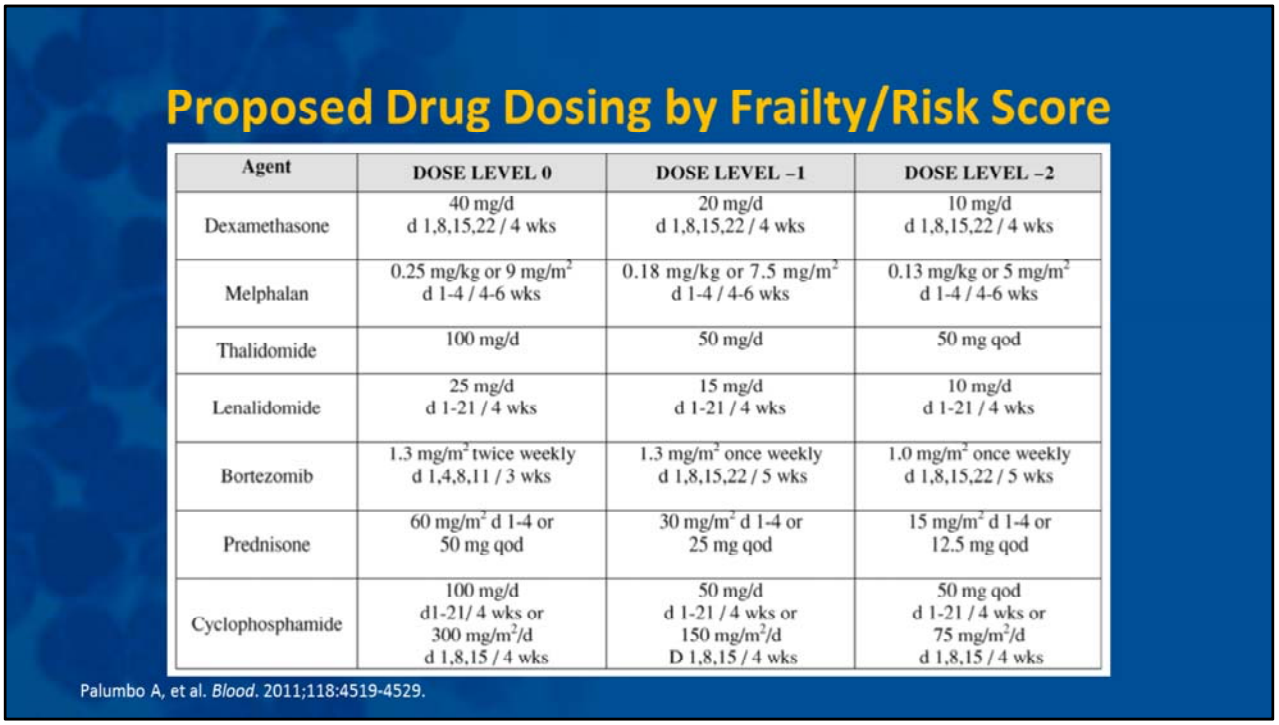

So, there are a variety of functional degrees of frailty, all the way from the very fit , our younger, active, and energetic patients who exercise regularly or occasionally and have no visible outward signs of deficiency from their myeloma, all the way to moderately fit, vulnerable, mildly frail, moderately frail, and ultimately severely frail patients who are completely dependent upon other people for their activities of daily living.

# Performance Status Adaptive Therapy in Multiple Myeloma




So, Dr. Palumbo's group evaluated a go-go, a moderate-go, and a slow-go category for patients with varying degrees of frailness in regard to how they may be approached from a treatment standpoint, looking at things such as age, age over 75, mild, moderate, or severe frailty, and comorbidities such as cardiovascular dysfunction, renal dysfunction, or hepatic dysfunction. For those patients who had no risk factors, we dosed them at a dose level 0. For patients who fit in the moderate-go category, at least one of these risk factors, they were dosed at a dose level of -1, and for those patients with at least one risk factor plus things such as recurrent grade 3 or 4 adverse events, they were treated at dose level -2 on the slow-go category.

# Performance Status Adaptive Therapy in Multiple Myeloma



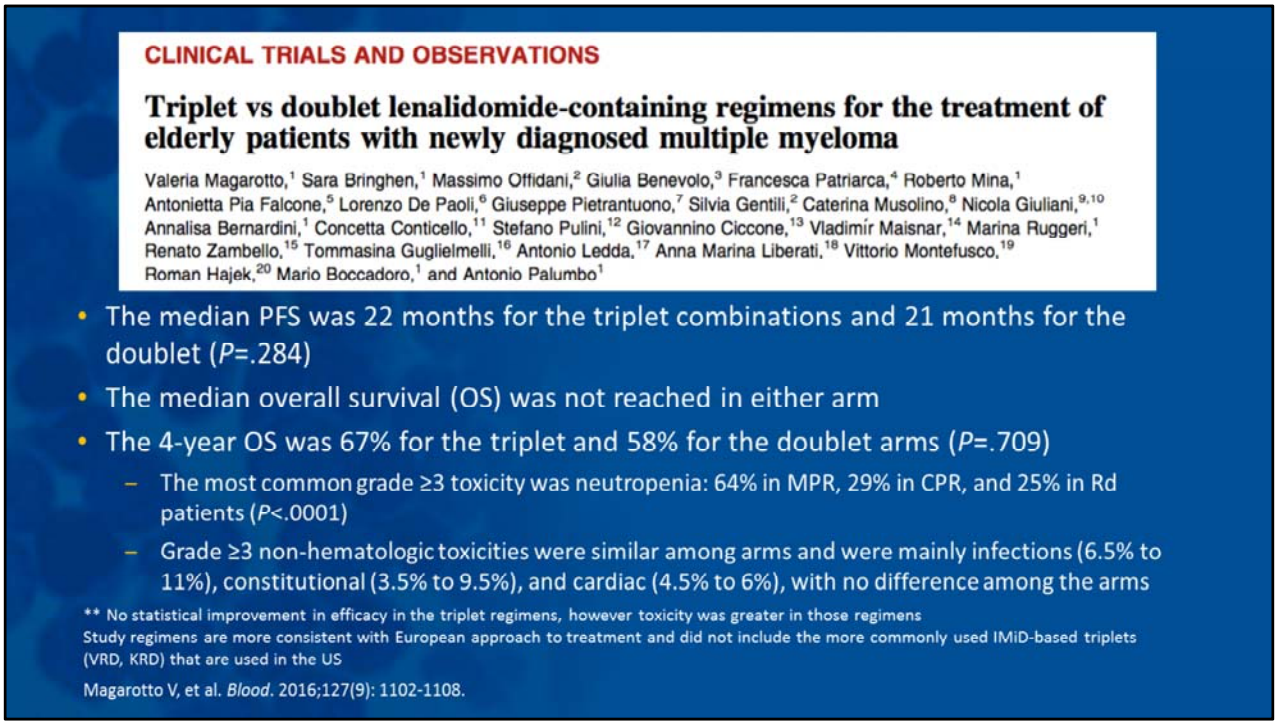
## Proposed Drug Dosing by Frailty/Risk Score

| Agent | DOSE LEVEL 0 | DOSE LEVEL –1 | DOSE LEVEL –2 |
|---|---|---|---|
| Dexamethasone | 40 mg/d<br>d 1,8,15,22 / 4 wks | 20 mg/d<br>d 1,8,15,22 / 4 wks | 10 mg/d<br>d 1,8,15,22 / 4 wks |
| Melphalan | 0.25 mg/kg or 9 mg/m$^2$<br>d 1-4 / 4-6 wks | 0.18 mg/kg or 7.5 mg/m$^2$<br>d 1-4 / 4-6 wks | 0.13 mg/kg or 5 mg/m$^2$<br>d 1-4 / 4-6 wks |
| Thalidomide | 100 mg/d | 50 mg/d | 50 mg qod |
| Lenalidomide | 25 mg/d<br>d 1-21 / 4 wks | 15 mg/d<br>d 1-21 / 4 wks | 10 mg/d<br>d 1-21 / 4 wks |
| Bortezomib | 1.3 mg/m$^2$ twice weekly<br>d 1,4,8,11 / 3 wks | 1.3 mg/m$^2$ once weekly<br>d 1,8,15,22 / 5 wks | 1.0 mg/m$^2$ once weekly<br>d 1,8,15,22 / 5 wks |
| Prednisone | 60 mg/m$^2$ d 1-4 or<br>50 mg qod | 30 mg/m$^2$ d 1-4 or<br>25 mg qod | 15 mg/m$^2$ d 1-4 or<br>12.5 mg qod |
| Cyclophosphamide | 100 mg/d<br>d1-21/ 4 wks or<br>300 mg/m$^2$/d<br>d 1,8,15 / 4 wks | 50 mg/d<br>d 1-21 / 4 wks or<br>150 mg/m$^2$/d<br>D 1,8,15 / 4 wks | 50 mg qod<br>d 1-21 / 4 wks or<br>75 mg/m$^2$/d<br>d 1,8,15 / 4 wks |

Palumbo A, et al. *Blood*. 2011;118:4519-4529.

Now, this list is not exhaustive by any stretch of the imagination. However, this represents some of the core therapies that are still used to manage our patients with myeloma. Dexamethasone, melphalan, immunomodulatory agents, as well as cyclophosphamide and bortezomib. Here, we can see the dose level 0 is where we use as a starting point for the majority of our fit patients, dosing dexamethasone at a 40 mg level, thalidomide at a 100 mg level, lenalidomide at 25 mg, bortezomib at the standard 1.3 mg twice-weekly on days 1, 4, 8, and 11, prednisone at 60 mg, and cyclophosphamide at 300 mg/m$^2$. As we looked at dose level 1 and dose level 2, we can see how we can bring these doses down for each of the individual drugs for patients that we deem more frail, so bring the dexamethasone from 40 down to 20 or 10, from bringing the lenalidomide from 25 down to 15 or 10, and from cyclophosphamide 300 mg/m$^2$ down to 150 or even 75. Bortezomib is interesting because there is a variety of ways to dose reduce, not just by drug dose or by dosing schedule. So, patients who are classically dosed at 1.3 mg/m$^2$ on a twice-weekly basis, as we deem them more unfit or more frail, we can either change the dosing schedule and bring them down to once-weekly dosing or even bring down the total dose from 1.3 mg/m$^2$ down to 1 mg/m$^2$.

# Performance Status Adaptive Therapy in Multiple Myeloma



CLINICAL TRIALS AND OBSERVATIONS

**Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma**

Valeria Magarotto,[1] Sara Bringhen,[1] Massimo Offidani,[2] Giulia Benevolo,[3] Francesca Patriarca,[4] Roberto Mina,[1] Antonietta Pia Falcone,[5] Lorenzo De Paoli,[6] Giuseppe Pietrantuono,[7] Silvia Gentili,[2] Caterina Musolino,[8] Nicola Giuliani,[9,10] Annalisa Bernardini,[1] Concetta Conticello,[11] Stefano Pulini,[12] Giovannino Ciccone,[13] Vladimír Maisnar,[14] Marina Ruggeri,[1] Renato Zambello,[15] Tommasina Guglielmelli,[16] Antonio Ledda,[17] Anna Marina Liberati,[18] Vittorio Montefusco,[19] Roman Hajek,[20] Mario Boccadoro,[1] and Antonio Palumbo[1]

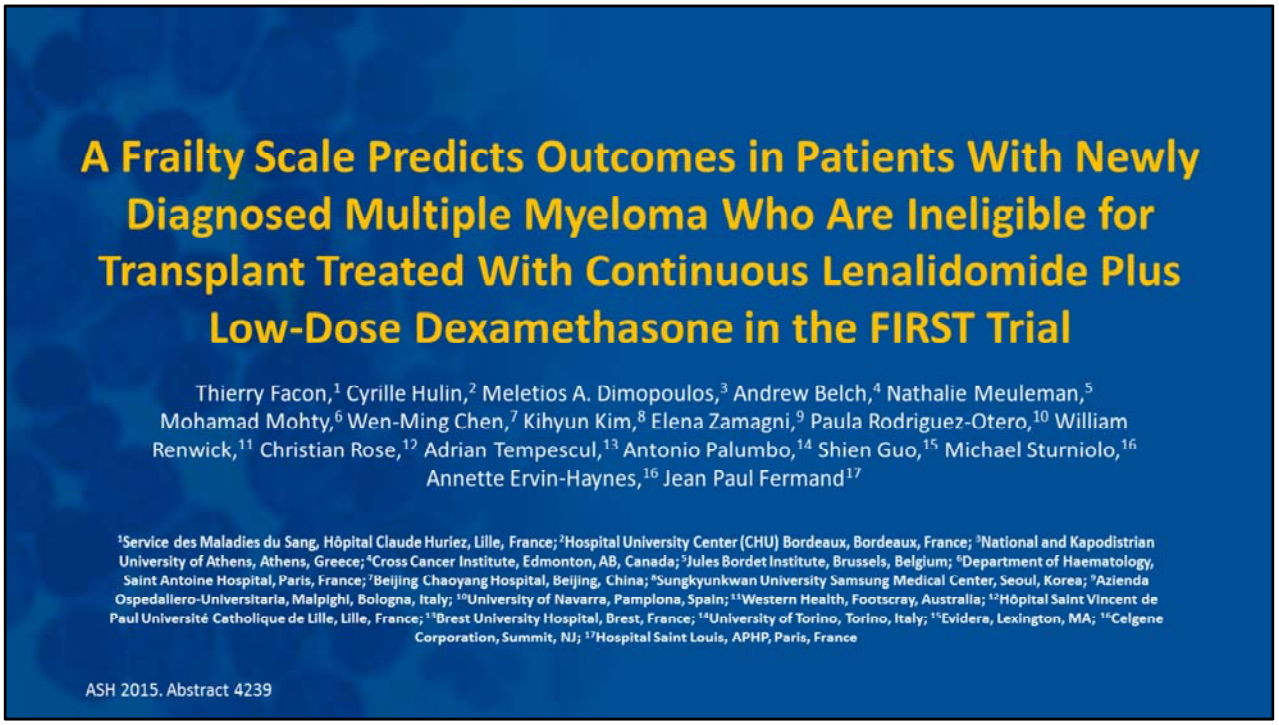
- The median PFS was 22 months for the triplet combinations and 21 months for the doublet (*P*=.284)
- The median overall survival (OS) was not reached in either arm
- The 4-year OS was 67% for the triplet and 58% for the doublet arms (*P*=.709)
  - The most common grade ≥3 toxicity was neutropenia: 64% in MPR, 29% in CPR, and 25% in Rd patients (*P*<.0001)
  - Grade ≥3 non-hematologic toxicities were similar among arms and were mainly infections (6.5% to 11%), constitutional (3.5% to 9.5%), and cardiac (4.5% to 6%), with no difference among the arms

** No statistical improvement in efficacy in the triplet regimens, however toxicity was greater in those regimens
Study regimens are more consistent with European approach to treatment and did not include the more commonly used IMiD-based triplets (VRD, KRD) that are used in the US

Magarotto V, et al. *Blood*. 2016;127(9): 1102-1108.

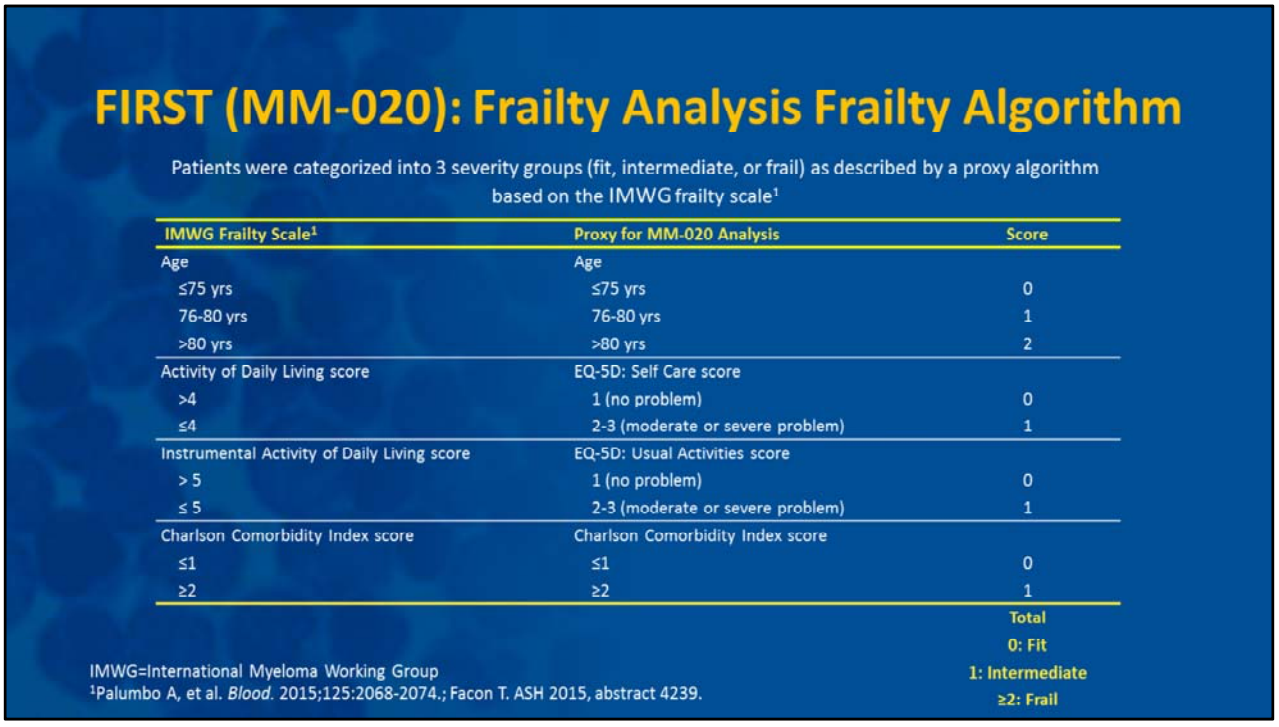
Now, one of the big hot buttons in myeloma of late has been the concept of doublets versus triplets. There have been a variety of trials that have come out recently including the ASPIRE trial, the TOURMALINE trial, and the ELOQUENT trial, who have all demonstrated the benefit of triplet regimens over doublet regimens. And the question is, is this true for everybody? Now, there was a study done in Europe looking at triplets versus doublets for elderly patients with newly diagnosed myeloma. Now, if we look across this study which utilized a variety of doublet- and triplet-based regimens, the median progression-free survival was similar in both groups. The overall survival was not reached in both arms. The 4-year overall survival was 67% for the triplet and 58% for the doublet arms. This was not statistically significant. Now, grade 3 and above non-hematologic toxicities were similar. However, hematologic toxicities were clearly worse in the triplet arms. So, grade 3 or more neutropenia was seen at 64% in the MPR group, 29% in the CPR, and 25% in the lenalidomide-dexamethasone group. This was statistically significant. Now again, we have to take this with a grain of salt. There was no statistical improvement in efficacy between the triplets or doublets for patients who were older and/or more frail, and there was a significant increase in toxicity. However, these regimens that were utilized in this trial, while more common in Europe, are less utilized in the United States, so the triplet regimens such as MPR and CPR are not the frequently used triplets used in the United States such as VRD, KRD, and CyBorD, so it is always worthwhile to individualize therapy to our specific patient. However, this is food for thought that although triplet regimens are better for many of our patients, that may not necessarily be true for our more frail patients.

# Performance Status Adaptive Therapy in Multiple Myeloma



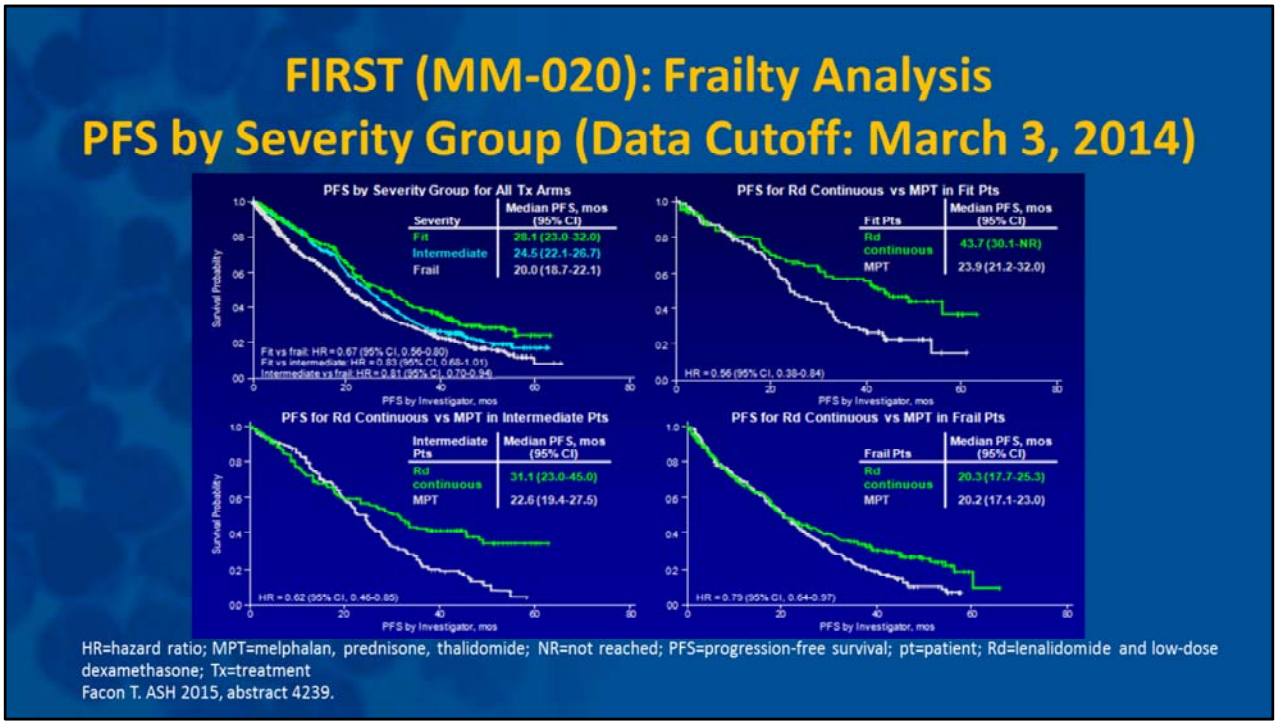

So, one of the big trials that has come out in the last few years has been the FIRST trial, the MM-020 trial, and this trial looked at an upfront approach to non-transplant eligible patients comparing melphalan, prednisone, and thalidomide for 18 months versus lenalidomide and dexamethasone for 18 months versus lenalidomide and dexamethasone in a continuous fashion until lack of tolerability or progression.

# Performance Status Adaptive Therapy in Multiple Myeloma




And frailty was taken into this and subgroup analysis to evaluate whether or not this was true, not only for our fit patients who are not transplant candidates but the frail patients, those who really are not candidates for transplant and may have significant other factors that may limit our ability to give them aggressive therapy. And here we looked at a variety of scores and correlates between patients who receive therapy on the FIRST trial from a frailty standpoint relating to age, their ability to undergo their ADLs, IADLs, and as well as the Charlson Comorbidity Index.

# Performance Status Adaptive Therapy in Multiple Myeloma

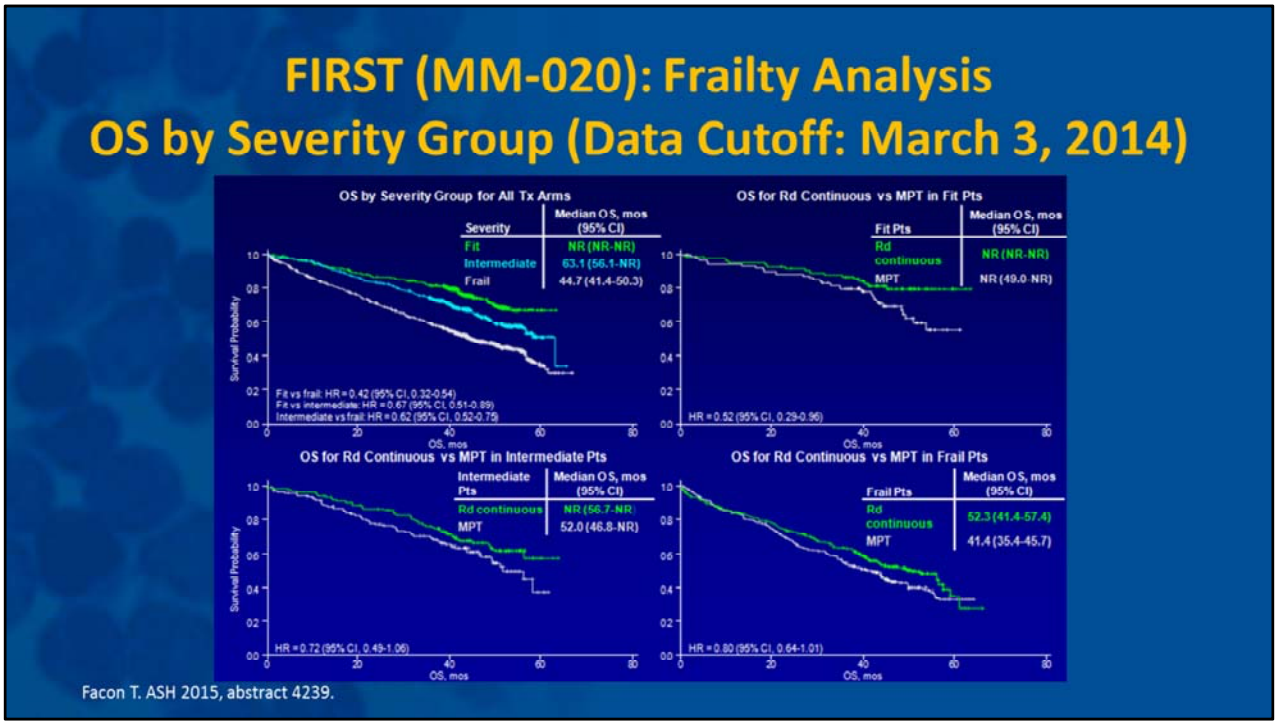



HR=hazard ratio; MPT=melphalan, prednisone, thalidomide; NR=not reached; PFS=progression-free survival; pt=patient; Rd=lenalidomide and low-dose dexamethasone; Tx=treatment

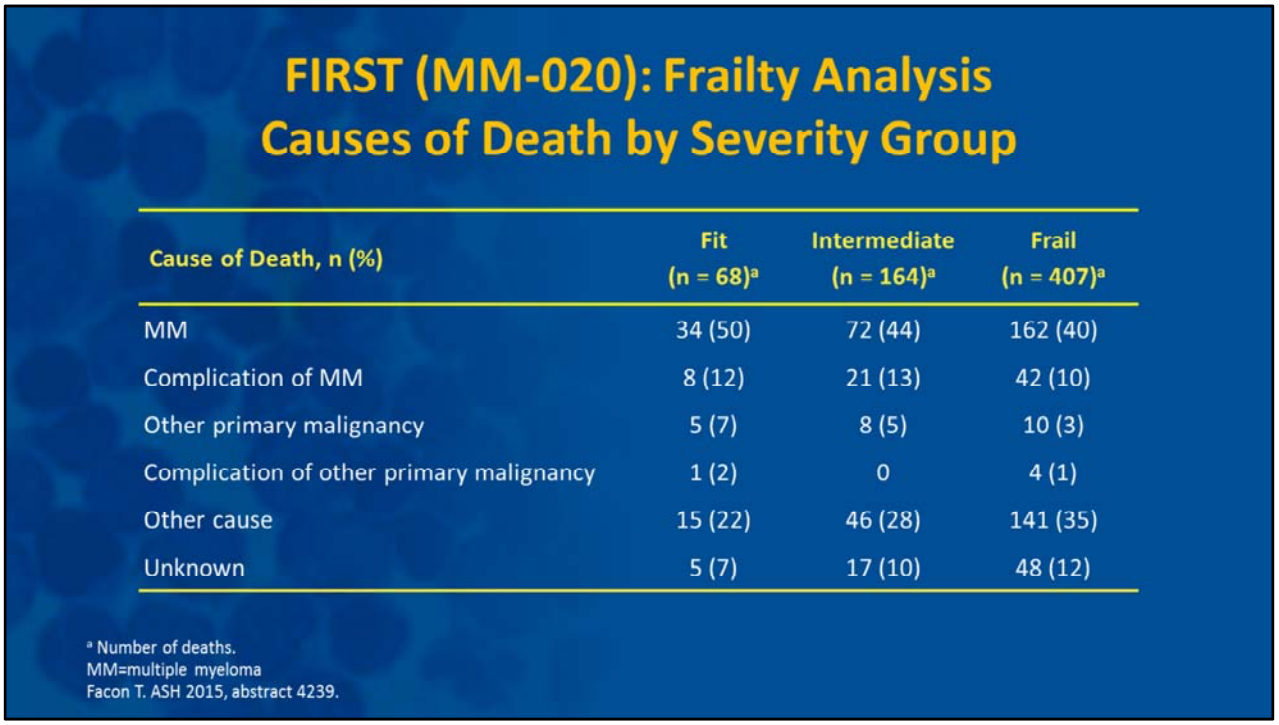
Facon T. ASH 2015, abstract 4239.

When the analysis was done by PFS for severity group, we found that obviously the patients who are more fit did better. However, if you look across from the RD continuous and all arms, the RD continuous patients still did better. So, even though this is a more "aggressive approach" in so far as you are giving a patient constant therapy, we can see that the progression-free survival was improved for patients who received continuous lenalidomide and dexamethasone. Again, this represents a new age in myeloma where we have well-tolerated oral therapies that we can give for long periods of time, and again one of the things that has been demonstrated time and time again is continuous therapy, if it can be achieved and maintained, provides for better disease control, deeper responses, and ultimately improved overall survival.

# Performance Status Adaptive Therapy in Multiple Myeloma




We can see that in the overall survival breakdown of the FIRST trial for patients who received RD continuous versus MPT, and again, even for our frail patients, this has been maintained. So again, just because our patient is frail does not mean that we have to back off completely. We can provide continuous therapy, and one of the ways we might approach that is with lenalidomide and dexamethasone.



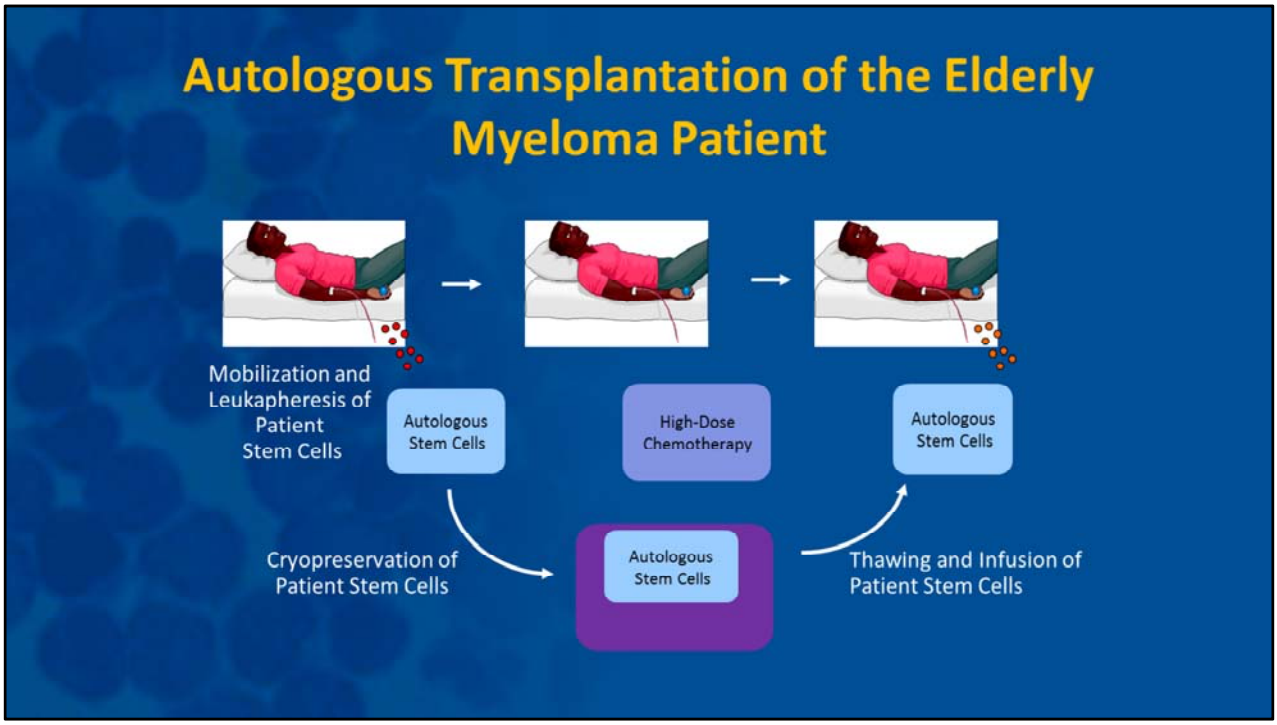
## FIRST (MM-020): Frailty Analysis
## Causes of Death by Severity Group

| Cause of Death, n (%) | Fit (n = 68)[a] | Intermediate (n = 164)[a] | Frail (n = 407)[a] |
|---|---|---|---|
| MM | 34 (50) | 72 (44) | 162 (40) |
| Complication of MM | 8 (12) | 21 (13) | 42 (10) |
| Other primary malignancy | 5 (7) | 8 (5) | 10 (3) |
| Complication of other primary malignancy | 1 (2) | 0 | 4 (1) |
| Other cause | 15 (22) | 46 (28) | 141 (35) |
| Unknown | 5 (7) | 17 (10) | 48 (12) |

[a] Number of deaths.
MM=multiple myeloma
Facon T. ASH 2015, abstract 4239.

When we look at causes of death in the frailty analysis for the FIRST trial, if you compare fit versus intermediate versus frail, we can see that the fit patients had a higher cause of death from myeloma. This makes sense that the patients who were able to maintain therapy and did not succumb to death from other causes ultimately succumbed to their myeloma, whereas other causes of death outside of their myeloma were higher in the frail group. Again, this is worthwhile to balance when adjusting for therapies in our frail patients.

# Performance Status Adaptive Therapy in Multiple Myeloma

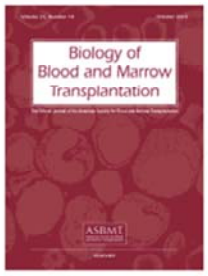



Now, just because a patient is older or just because they are frail does not mean that we should ignore one of the best therapies that has ever been developed for multiple myeloma, autologous stem cell transplant. Although classically viewed as a standard of care for younger fit patients, there may be a subgroup of older and/or frail patients who will benefit from this approach. This approach allows for improved outcomes and survivals without the need for ongoing therapy in many patients.

# Performance Status Adaptive Therapy in Multiple Myeloma

Cost-Effectiveness of Autologous Hematopoietic Stem Cell Transplantation for Elderly Patients with Multiple Myeloma using the Surveillance, Epidemiology, and End Results—Medicare Database

Gunjan L. Shah [1,*], Aaron N. Winn [2,3], Pei-Jung Lin [2], Andreas Klein [4], Kellie A. Sprague [4], Hedy P. Smith [4], Rachel Buchsbaum [4], Joshua T. Cohen [2], Kenneth B. Miller [4], Raymond Comenzo [4], Susan K. Parsons [4,5]




Biology of Blood and Marrow Transplantation
Volume 21, Issue 10

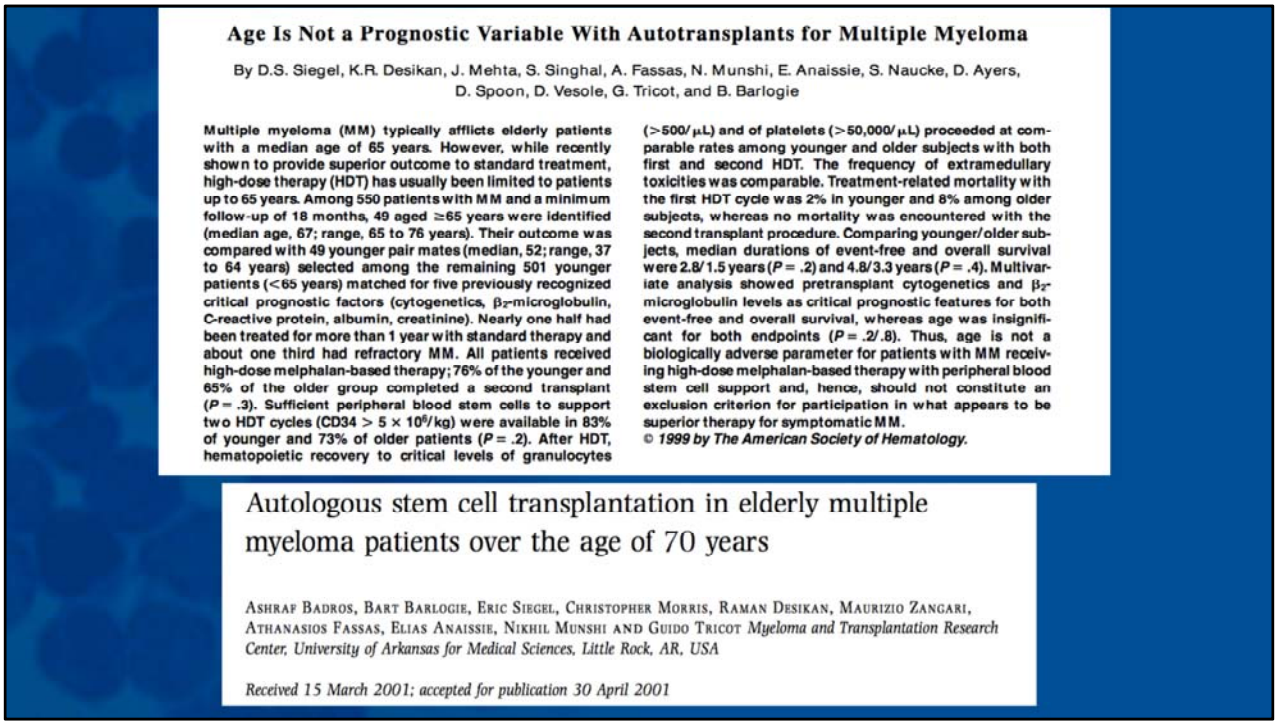
**Table 2**
Median Monthly Cost

| | Transplantation | Nontransplantation |
|---|---|---|
| Living more than 2 years | n = 234 | n = 180 |
| First year after diagnosis* | $8337 | $2607 |
| Middle years | $2435 | $2088 |
| Last year | $8114 | $6809 |
| Living less than 2 years | n = 36 | n = 90 |
| Monthly† | $13,106 | $6756 |

Total cost of care per month during each time frame. Significant differences were seen only in the first year after diagnosis for patients living longer than 2 years and monthly for those living less than 2 years.
* $P < .001$.
† $P = .013$.

So, again, it is worthwhile to approach a patient who at the surface may appear more old or and more frail that autologous stem cell transplant still may represent an option for some of these patients. Now this has been evaluated across a variety of modalities, but it does still represent a potential option for some of our patients in regard to managing their disease from a long-term standpoint.

# Performance Status Adaptive Therapy in Multiple Myeloma



**Age Is Not a Prognostic Variable With Autotransplants for Multiple Myeloma**

By D.S. Siegel, K.R. Desikan, J. Mehta, S. Singhal, A. Fassas, N. Munshi, E. Anaissie, S. Naucke, D. Ayers, D. Spoon, D. Vesole, G. Tricot, and B. Barlogie

Multiple myeloma (MM) typically afflicts elderly patients with a median age of 65 years. However, while recently shown to provide superior outcome to standard treatment, high-dose therapy (HDT) has usually been limited to patients up to 65 years. Among 550 patients with MM and a minimum follow-up of 18 months, 49 aged ≥65 years were identified (median age, 67; range, 65 to 76 years). Their outcome was compared with 49 younger pair mates (median, 52; range, 37 to 64 years) selected among the remaining 501 younger patients (<65 years) matched for five previously recognized critical prognostic factors (cytogenetics, $\beta_2$-microglobulin, C-reactive protein, albumin, creatinine). Nearly one half had been treated for more than 1 year with standard therapy and about one third had refractory MM. All patients received high-dose melphalan-based therapy; 76% of the younger and 65% of the older group completed a second transplant ($P = .3$). Sufficient peripheral blood stem cells to support two HDT cycles (CD34 > $5 \times 10^6$/kg) were available in 83% of younger and 73% of older patients ($P = .2$). After HDT, hematopoietic recovery to critical levels of granulocytes (>500/μL) and of platelets (>50,000/μL) proceeded at comparable rates among younger and older subjects with both first and second HDT. The frequency of extramedullary toxicities was comparable. Treatment-related mortality with the first HDT cycle was 2% in younger and 8% among older subjects, whereas no mortality was encountered with the second transplant procedure. Comparing younger/older subjects, median durations of event-free and overall survival were 2.8/1.5 years ($P = .2$) and 4.8/3.3 years ($P = .4$). Multivariate analysis showed pretransplant cytogenetics and $\beta_2$-microglobulin levels as critical prognostic features for both event-free and overall survival, whereas age was insignificant for both endpoints ($P = .2/.8$). Thus, age is not a biologically adverse parameter for patients with MM receiving high-dose melphalan-based therapy with peripheral blood stem cell support and, hence, should not constitute an exclusion criterion for participation in what appears to be superior therapy for symptomatic MM.



Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years

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If we look at age as an independent risk factor, it turns out that age in and of itself is not an independent risk factor ora  prognostic endpoint for patients with auto transplants in myeloma, and although in Europe the standard is not to proceed with autologous stem cell transplant in patients over the age of 65, there are a number of patients who have advanced age over the age of 70 and yes even over the age of 80 who may benefit from autologous stem cell transplantation. At our center, our oldest patient has been the age of 85. Now again, this was an exceptionally fit 85-year-old; however, again, it is worthwhile to understand the fact that older age or elderly status does not equal frailty and that we need to make individual decisions on our patients and do so in a rigorous standpoint.

# Performance Status Adaptive Therapy in Multiple Myeloma

Autologous stem cell transplantation in patients of 70 years and older with multiple myeloma: Results from a matched pair analysis

Shaji K. Kumar,* David Dingli, Martha Q. Lacy, Angela Dispenzieri, Suzanne R. Hayman, Francis K. Buadi, S. Vincent Rajkumar, Mark R. Litzow, and Morie A. Gertz

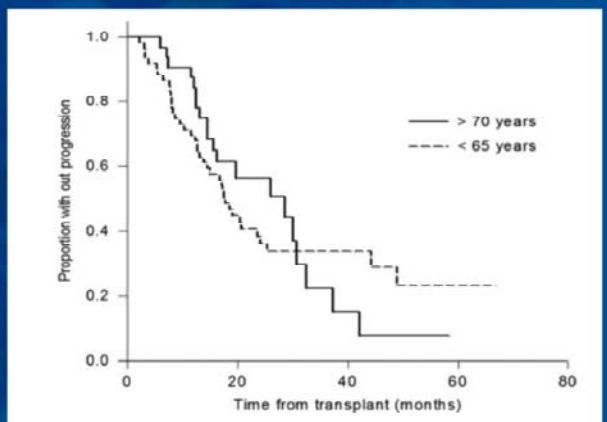



Figure 2. Kaplan–Meier curves demonstrating median overall survival for the two groups following stem cell transplantation.

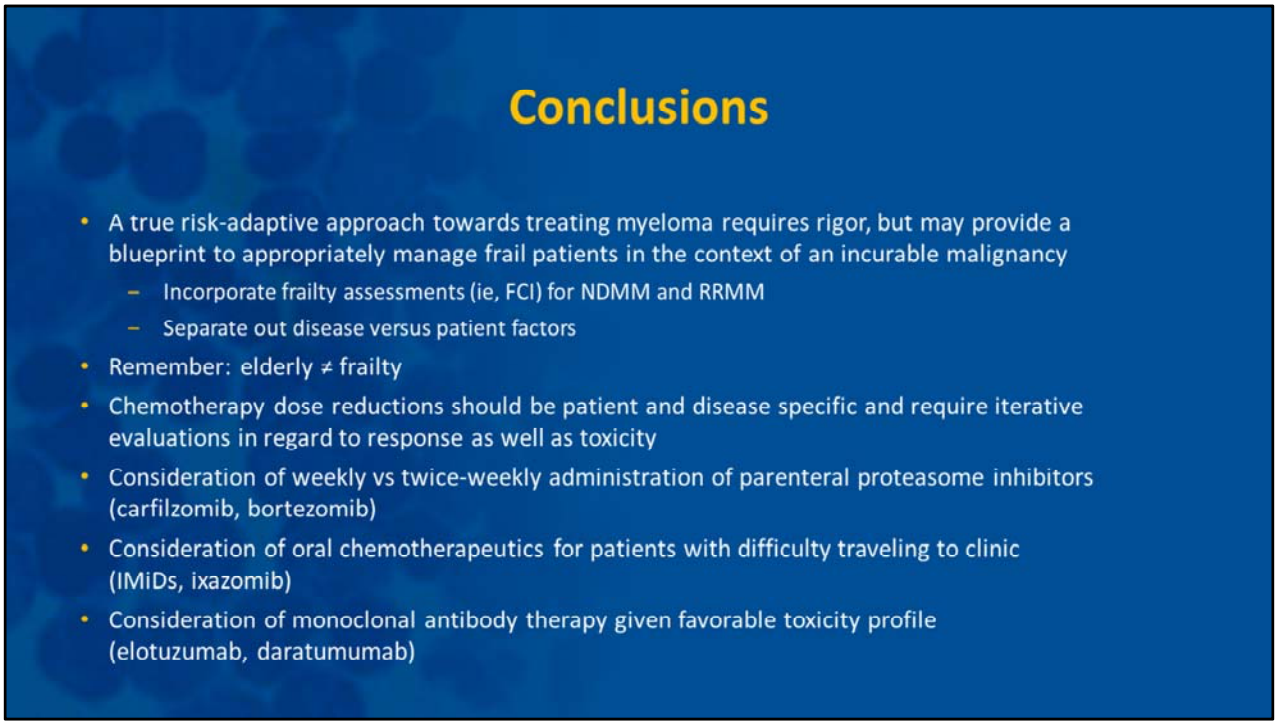
**TABLE II. Baseline Features at Transplant**

| Characteristics | Elderly (≥70) ($n$ = 33) Median (range) | Control (≤65) ($n$ = 60) Median (range) | $P$-value |
|---|---|---|---|
| Age at diagnosis (years) | 71.2 (66.7–75.3) | 54.3 (36.9–64.3) | <0.01 |
| Age at transplant (years) | 71.7 (70–75.8) | 55.6 (37.3–64.9) | <0.01 |
| M protein level (gm/dl) | 0.7 (0–6.1) | 1.3 (0–5.7) | 0.9 |
| LDH (U/l) | 184 (92–332) | 187 (74–393) | 0.5 |
| CRP (mg/dl) | 0.4 (0.1–6.4) | 0.4 (0.1–9.2) | 0.4 |
| BM plasma cell % | 13.6 (0.2–52) | 13.2 (1–78) | 0.4 |
| Creatinine (mg/dl) | 1.1 (0.7–6.5) | 1.0 (0.7–4.3) | 0.04 |
| CD34 collected | 8.3 (3–33.5) | 10 (2–27.8) | 0.28 |
| | $n$ (%) | $n$ (%) | |
| Transplant <12 months from diagnosis | 28 (85) | 48 (80) | NS |
| Male gender | 25 (76) | 38 (63) | 0.3 |
| $\beta_2$ microglobulin >3.5 μg/ml | 11 (33) | 11 (18) | 0.2 |
| Bone disease | 28 (85) | 45 (75) | 0.3 |
| Response to initial therapy | 25 (72) | 58 (80) | 0.4 |
| Relapsed/refractory disease at transplant | 15 (45) | 24 (40) | NS |
| Conditioning | | | |
| Mel 200 | 23 (70) | 57 (95) | 0.001 |
| Mel 140 | 10 (30) | 3 (5) | |

Kumar SK, et al. *Am J Hem.* 2008;83(8);614-617.

When approaching the concept of autologous stem cell transplant in our older patients, there are factors that we need to take into account so that we do not simply transplant absolutely everybody. There are a variety of factors that are worthwhile to take into account, and we can see here about the different baseline features of those patients who are elderly versus the control group in this study. Obviously, the elderly group had a higher age at diagnosis and time of transplant, but other things that came out were conditioning regimen. Obviously, patients of advanced age are felt to potentially need a lower dose of high-dose melphalan, and many of these patients receive melphalan at 140 mg/m$^2$ as opposed to the standard dose of 200 mg/m$^2$. Again, it is worthwhile to always evaluate not just the chronologic age of the patient but the physiologic age of the patient along with their comorbidity indices and general functional status.

# Performance Status Adaptive Therapy in Multiple Myeloma




So, what conclusions can we draw? At the end of the day, we have many options of how to treat multiple myeloma, and a true risk adaptive approach is needed to help employ the optimal therapy for each one of our patients regardless of age, frailty status, or comorbidity. This is something that requires rigor, and in general, it is probably a better thing not to simply guess at it but actually employ one of the indices such as the Freiburg Comorbidity Index with regard to our patients with newly dosed myeloma as well as relapse and refractory myeloma in order to choose the best therapy. This need to be an iterative process and should be evaluated at all points regularly during our therapy as this may change. Again, it is worthwhile to separate out what are disease-specific factors versus patient-specific factors. Remember, elderly does not equal frailty. You can have a younger patient who is more frail or an older patient who is more fit. So again, it is worthwhile to take into account other things besides age when deeming somebody frail. Chemotherapy dose reductions are a key component to long-term management of any disease, especially multiple myeloma. These dose reductions do not have to be made de facto off the top simply related to age, but should be a function of disease-specific factors, patient-specific factors, and comorbidities. When considering dose reductions or dose adjustments, there are variety of ways to do this, not simply by lowering the dose but by adjusting the schedule of dosing of our drugs. Take for example bortezomib, although the standard dosing is twice weekly, some of our patients may benefit from once-weekly dosing with bortezomib. With the newer-generation proteasome inhibitor such as carfilzomib, again the standard dosing is twice weekly. However, there has been a variety of data published with once-weekly dosing including the recently published CHAMPION trial by Dr. James Berenson employing a once-weekly dosing strategy for elderly or frail patients.

Furthermore, we need to consider patient's access to medical care. Traveling back and forth to the clinic may be difficult for patients, not only twice a week but even once a week. For some of these patients we may consider oral chemotherapy options. Classically, this was melphalan and prednisone, but I think we have seen with the FIRST trial and many other studies that lenalidomide and dexamethasone represents perhaps a better choice and a well-tolerated choice, and now with the advent of orally bioavailable proteasome inhibitors, ixazomib-based therapies also represent an oral option for patients who cannot come back and forth to the clinic readily. We have also had a variety of new drugs approved in the last year including daratumumab and elotuzumab. These monoclonal antibodies have a well-tolerated toxicity profile, something to take into account in our older and more frail patients due to their lack of causing significant marrow suppression, asthenia, or neuropathy. These drugs may be able to provide a great cornerstone of therapy for the patient who is more frail.