

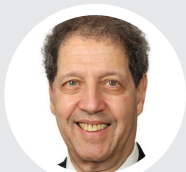
# Mayo Experts Review Treatment Options for Newly Diagnosed Multiple Myeloma



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In this special edition of *Around the Practice®: Institutional Insights*, physicians from the Mayo Clinic in Rochester, Minnesota, discuss topics in newly diagnosed multiple myeloma (NDMM). The investigators specifically focus on different patient populations and discuss patient cases.

The experts are **Shaji Kumar, MD**, professor of medicine and chair of myeloma, amyloidosis, and dysproteinemia; **David Dingli, MD, PhD**, professor of medicine and hematology; **Morie A. Gertz, MD**, Roland Seidler Jr. Professor of the Art of Medicine, Chair Emeritus in the Department of Internal Medicine, and a Mayo Clinic Distinguished Physician; and **Prashant Kapoor, MD**, assistant professor of medicine and oncology and a senior associate consultant in the Division of Hematology.

## Recent Trial Updates in Multiple Myeloma

**KUMAR:** Let's look at updates from the GRIFFIN trial [NCT02874742].<sup>1</sup>

**GERTZ:** GRIFFIN was an important first step in understanding the role of quadruplet therapy. It was a trial that randomly assigned transplant-eligible patients to daratumumab [Darzalex], bortezomib [Velcade], and lenalidomide [Revlimid] plus dexamethasone [DARA-VRd] or to VRd alone. [According to the] most recent update, the 36-month progression-free survival

[PFS] rate in the daratumumab arm was 89%, which was statistically better than in the non-daratumumab-containing arm [HR, 0.46; 95% CI, 0.21-1.01].<sup>1</sup> It spoke volumes in terms of response depth, and a subset of the complete responses [CRs] will be MRD [minimal residual disease] negative. We don't have overall survival [OS] data. We are not able to say that [OS is] impacted, but generally speaking, response depth is a good surrogate in terms of anticipating what will ultimately be seen in PFS.

**KUMAR:** When we use the 4 drugs, are we able to give these patients a limited duration of therapy, then hopefully stop treatment and give them a treatment-free interval? The MASTER trial [NCT03224507] is quite illuminating [in that way].<sup>2</sup>

**DINGLI:** Until now, the paradigm has been that patients are treated continuously with therapy from the time of diagnosis. The MASTER trial is [breaking] new ground because it asks a very important question: Can we use MRD to inform decisions on how long to give therapy? This was a phase 2 trial with approximately 125 patients. The patients were transplant eligible, [and some] were in their early 70s. They were all treated with a quadruplet regimen: daratumumab, carfilzomib [Kyprolis], lenalidomide, and dexamethasone [D-KRd]. Intentionally, this group was divided

into patients in standard-risk and high-risk [groups], with single-hit, double-hit, or higher-risk disease. The patients received 4 cycles of therapy, went on to transplant, and then received 0, 4, or 8 cycles of consolidation with the same quadruplet. The patients were tested at specific points for MRD negativity prior to transplant, meaning after 4 cycles of induction, immediately after transplant, and then every 4 months. The [investigators] showed that the number of patients who developed complete responses, and [who developed] MRD negativity that stayed at the level of  $10^{-5}$ , progressively increased. The study was designed in such a way that if a patient had 2 consecutive MRD-negative results, effectively separated by 4 months, therapy could be held and the patient could go onto observation. The median follow-up is not long—about 18 months. However, we can already see that the patients with standard-risk disease, who accounted for about 43% of the patients in the study, have not progressed. The problem is with patients with double-hit multiple myeloma. Although the response rates were similar to those of standard-risk patients with respect to CR and MRD negativity, the PFS is lower with high-risk disease. At the time of reporting, 27% of patients with double-hit multiple myeloma who were off therapy had progressed. It may be possible to consider the idea of withholding therapy in patients with very deep responses, but we probably need to do more for patients with high-risk disease.

**KUMAR:** Are there certain occasions or patient types in whom you would prefer D-KRd over D-VRd?

**DINGLI:** The question of whether either carfilzomib or bortezomib is superior [to the other] is still being explored. We know that in standard-risk patients, there is no superiority with respect to carfilzomib vs bortezomib. The question remains as to whether carfilzomib will be a superior drug in high-risk patients. In general, I prefer bortezomib-based

regimens because they are simpler. I would consider carfilzomib for some patients with high-risk disease or patients with preexisting neuropathy, but I would generally try to avoid carfilzomib for patients with cardiac comorbidities or severe hypertension.

**KUMAR:** There are other anti-CD38 monoclonal antibodies that also have interesting data, especially from a depth of response standpoint. Let's explore those findings.

**KAPOOR:** At the 2021 [American Society of Hematology] Annual Meeting, a German study group presented data from the phase 3 [GMMG-HD7; NCT03617731] trial that compared a 4-drug regimen of isatuximab [Sarclisa] in combination with VRd vs VRd alone.<sup>3</sup> One of the trial's primary end points was the degree of MRD negativity at the time of transplant or postinduction therapy. This study involved more than 660 patients, all transplant eligible. The initial data were impressive in that the quadruplet led to a deeper response, based on an MRD-negativity rate of about 50% with the 4-drug regimen vs 35% or so with the 3-drug regimen. These are just the initial data presented. The trial schema is interesting in that it's a 2-part trial. Post autologous stem cell transplantation [ASCT], patients would be randomly assigned again to assess the value of adding the anti-CD38 monoclonal antibody, -[isatuximab]-, to lenalidomide maintenance. In that sense, it's somewhat different from the GRIFFIN trial because we don't know whether the value of adding a monoclonal anti-CD38 antibody—in GRIFFIN, daratumumab—was because it was added to the induction, to the maintenance, or to the entire regimen, because both the pretransplant and post-transplant [regimens] involved daratumumab. There is more to come; we just need to wait.

**KUMAR:** Do you see any scenario where you would use an isatuximab-VRd combination in the up-front setting?

**KAPOOR:** I am treating these anti-CD38

monoclonal antibodies as somewhat similar, and I use them interchangeably. Using daratumumab has certain advantages; for instance, the subcutaneous route of administration makes it much easier for nurses as well as patients. Another advantage is that, especially after 6 months, the frequency of administration is once every 4 weeks as opposed to every 2 weeks for isatuximab.

### Treatment Decisions Based on MRD

**KUMAR:** What is your goal for depth of response and does the risk status matter? At what time will you say a patient does not have adequate depth of response prior to a transplant and may need to receive a different therapy?

**KAPOOR:** Depth of response depends on a number of factors. But the question about whether we should necessarily treat the transplant-eligible patients until they have achieved an MRD-negative state is a question that still needs to be answered. Some studies suggest we don't need a deep response to take them to transplant. As long as you achieve MRD negativity at some point and sustain it, you would have good outcomes. The timing of MRD negativity achievement isn't as important as actually achieving MRD negativity and, more importantly, sustaining that MRD-negative state.

**KUMAR:** What is your practice in terms of how long you continue treatment? Do certain indicators [convey that a patient has] received enough therapy?

**GERTZ:** When we are outside of a clinical trial and talking about how long we are treating patients—and this, of course, is an era of maintenance therapy—PFS and response depth aren't the only considerations. Quality of life of the patient is a big driver. We are now expecting patients with standard risk to live for 10 years. If we give indefinite therapy, these patients will spend 10 years on therapy. It depends; if the maintenance therapy is lenalidomide, does that mean they are on apixaban

[Eliquis] or rivaroxaban [Xarelto] for 10 years? Are they having cramps? Are they having intractable diarrhea? What is the level of fatigue associated with lenalidomide? It's not a straight-forward question. For patients who are tolerating the lenalidomide and don't have noticeable adverse effects, it's legitimate to continue therapy indefinitely in a nontrial setting. If you look at the scientific community and what thought leaders are doing, most of the trials at [clinicaltrials.gov](http://clinicaltrials.gov) include indefinite lenalidomide therapy. The trials address whether you are MRD negative, and if 36 months of therapy are completed, then you can be randomly assigned: Half continue therapy and half stop therapy. It reminds me of TKIs [tyrosine kinase inhibitors] in [chronic myeloid leukemia], and it raises the question: How long do you stay on a TKI? Will [that time] be indefinite?

If patients don't achieve MRD-negative status [in a trial], time-limited therapy should not be recommended. Depending on the degree of toxicity, that the patient is experiencing, including financial toxicity, I would be continuing treatment. However, for some patients, the [gastrointestinal] toxicity, cramps, and expense of the novel anticoagulants make it hard for them to justify treatment when they are feeling well, and after being on treatment for 3, 4, or 5 years, they keep asking: How much longer?

**KUMAR:** Do you factor in MRD status when making that decision?

**GERTZ:** [I factor it in only] in a clinical trial. [In that scenario], I am more comfortable discontinuing [therapy], but it has to be partly driven by the patient. You always run the risk of MRD positivity, but they do better when they are MRD negative. I am not seeing a curve in the line and I am not seeing the plateau, so they are going to relapse. I won't feel good if they are MRD negative and I stopped the lenalidomide without their consent, and then they progress 6 or 8 months later.

**CASE 1**

- A 55-year-old woman presented with progressive fatigue and rib pain.
- Laboratory values (March 6, 2022)
  - Hemoglobin: 7.4 g/dl
  - Creatine (Cr): 3.84 mg/dL
  - κ Free light chain (FLC): 278 mg/dL
- Bone marrow biopsy
  - 90% plasma cells
  - Hyperdiploid plasma cell clone based on DNA ploidy results
  - *MYC* rearrangement and monosomies 13 and 14
- Initial treatment
  - She was hospitalized and given bortezomib, cyclophosphamide, and dexamethasone, and 4 therapeutic plasma exchanges.
  - On March 11, 2022, her FLC was 143 mg/dL.
  - Daratumumab was added to treatment.
  - Cyclophosphamide was held for 4 days after an absolute neutrophil count of  $0.3 \times 10^9/L$
- Patient response
  - FLC still above 100 mg/dL after 10 days on treatment
  - Cr: 6.42 mg/dL

**KUMAR:** What different characteristics do we take into consideration when we start therapy for patients with NDMM whom we don't consider transplant eligible?

**GERTZ:** I do recommend a transplant but I would like her kidneys to function better before transplant. I am so uncomfortable about the irreversible loss of renal function as I am waiting for the response to happen.

**KUMAR:** What is the initial treatment of choice in a patient who presents with renal failure?

**DINGLI:** I would use a combination of cyclophosphamide, bortezomib, and lenalidomide, and I would be inclined

to use daratumumab very early because we know that if the patient presents with myeloma kidney, meaning light chain cast nephropathy, lowering the light chains rapidly is quite important to maximize the chance of salvaging kidney function. That would be my approach to try to control her disease: salvage kidney function, improve her performance status, and take her to transplant.

**KUMAR:** What do you think about using IMiDs [immunomodulatory drugs] in this setting?

**KAPOOR:** Speed is of vital importance in a case where a patient presents with renal dysfunction and we want to rapidly decrease the plasma cell burden. In other words, we want to rapidly decrease the free light chains that are potentially damaging to the kidney. It is difficult to obtain IMiDs in a hospital setting because it takes several weeks to get the drugs started, and because the dose of IMiDs can vary depending on the kidney function. When a patient's kidney function is in a state of flux, you cannot rely completely on a fixed-dose IMiD. Ultimately, the patient should be on an IMiD; the fact that the patient has hyperdiploidy is also something that should be taken into account. These patients are likely to respond better to an IMiD but [we] should [give] bortezomib at least twice a week for the first few cycles, and potentially consider high-dose steroids. That is the only scenario where I would use this kind of regimen. Also, we have data on daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone in a different patient population. For [amyloid light chain] amyloidosis, I am comfortable adding daratumumab now that we have more data with this regimen. Overall, I wouldn't necessarily change the approach at this point—although eventually, the patient needs an IMiD, specifically lenalidomide.

**KUMAR:** What do you consider, especially in the setting of renal insufficiency, when you take someone to transplant? Do you want to see a specific level of

renal response before you take them to transplant?

**DINGLI:** We know that patients with renal failure can be transplanted, and outcomes can be quite satisfactory. The problem with this patient would be that if kidney function is not stable and she is getting by without needing dialysis, then a substantial risk exists that the patient will end up on dialysis, and the patient [needs] to understand and accept that risk. We typically say that the risk of going to dialysis in an average patient with myeloma is less than 5%; this patient likely has a 15% or higher risk that she would need dialysis in the peritransplant setting and perhaps long-term. The deeper the response this patient gets, the better the chance is that they could get partial salvage of kidney function. However, it's quite possible that this patient has irreversible kidney scarring, and no matter how well we control the plasma cell clone, her kidney function will not improve.

### CASE 2

- A 76-year-old man presented with worsening anemia and back and hip pain.
- ECOG performance: 3
- Laboratory values
  - Hemoglobin: 8.3 g/dL
  - Creatinine: 1.86 mg/dL
  - Calcium: 9.8 mg/dL
  - Lactate dehydrogenase (LDH): 270.5 U/L
  - $\beta_2$ -microglobulin: 13.16  $\mu$ g/mL
  - Albumin: 3.4 g/dL
  - Monoclonal (M) spike (immunoglobulin [Ig]G  $\kappa$ ): 4.7 g/dL
  - IgG: 6950 mg/dL; IgA: 17 mg/dL; IgM: 23 mg/dL
  - $\kappa$ : 7.73 g/dL
  - $\lambda$ : 0.23 g/dL
  - $\kappa/\lambda$  ratio: 346.64 g/dL
  - Urine protein: small  $\kappa$
- Marrow biopsy showed 80% to 90%  $\kappa$  plasma cells and fluorescence in situ hybridization (FISH) hyperdiploid of +3, +9, +11, and +15.

- CT of the skeleton showed innumerable lytic bone disease throughout the axial and appendicular skeleton.
- She was started on daratumumab, lenalidomide (10 mg), and dexamethasone (20 mg).
- Supportive care
  - The patient was started on acyclovir and trimethoprim/sulfamethoxazole after 1 cycle with improved kidney function.
  - The patient was started on denosumab then switched to zoledronic acid with improved kidney function.
  - Vitamin D and calcium supplements
  - Aspirin for thromboprophylaxis
  - Analgesia: oxycodone (Oxycontin)
  - Vertebroplasty: L4
- Patient follow-up
  - The patient had 10 cycles of therapy at the last follow-up.
- Laboratory values:
  - Hemoglobin: 11.2 g/dL
  - Creatinine: 1.25 mg/dL
  - EGFR: 56 ml/min
  - IgG: 426 mg/dL; IgA: 11 mg/dL; IgM: 35 mg/dL
  - $\kappa$  FLC: 1.26 g/dL
  - $\lambda$  FLC: 0.82 g/dL
  - $\kappa/\lambda$  ratio: 1.54 g/dL
- ECOG performance score: 0 to 1.
- He had a VGPR and has no pain. He continues to work.

**GERTZ:** I'd like to ask 2 questions. First, does anybody use a fluoroquinolone for the first few cycles of therapy based on the [Medical Research Council Myeloma IX] trial data? Second, is this patient transplant eligible now?

**DINGLI:** I did give the patient levofloxacin [Levaquin]. Is the patient transplant eligible? Functionally, he has improved. He has achieved a very good partial response [VGPR]. Technically, he can probably go through transplant safely.

Patients aged up to 79 years can probably be transplanted with very similar outcomes [to those of younger patients]. It becomes a bit of a philosophical choice, in whether the patient is willing to sacrifice a few months of his life to be away from home, and perhaps suffer potential short-term toxicity related to the transplant, or to continue therapy he is tolerating well. I do not know if there is a right or wrong answer for that.

**GERTZ:** Age is no bar; it's performance status. And at a performance status of 3, that patient is not a transplant candidate. We have done transplants in 60 patients aged more than 75 years, and [there has been] no mortality. Of the patients we have selected to transplant, the all-cause transplant-related mortality at day 100 is 0. It's only 60 patients, of course, and the results may be different with 400. This patient had a VGPR and I understand he is 76 years old, but maybe we can get him to a stringent complete response and MRD negativity. I also would have given him a fluoroquinolone.

**KUMAR:** This case illustrates why we don't want to make the determination of transplant eligibility right in the beginning and, instead, [should] wait for a couple of cycles [of therapy] for the disease to respond. [That way, we] have all those disease-related adverse effects or comorbidities out of the way before we make that decision [about] transplant.

### CASE 3

- A 73-year-old woman presented with severe back and left groin pain.
- She was referred for ASCT about a year after multiple myeloma diagnosis.
- ECOG performance score: 3
- She previously had idiopathic dilated cardiomyopathy, left ventricular ejection fraction of about 30%, and dual-chamber implantable cardioverter defibrillator.
- Laboratory values
  - Hemoglobin: 12 g/dL
  - Calcium: 9.6 mg/dL



- Creatine: 0.9 mg/dL
- LDH: 177 U/L
- $\beta_2$ -microglobulin: 2.84  $\mu$ g/mL
- Albumin: 4 g/dL
- M-spike (IgG  $\kappa$ ): 3.8 g/dL
- IgG: 5460 mg/dL; IgA: 32 mg/dL; IgM: 7 mg/dL
- $\kappa$  FLC: 18.4 g/dL
- $\lambda$ : 0.186 g/dL
- $\kappa/\lambda$  ratio: 98.9 g/dL
- Urine 24-hour protein: 51 mg
- Urine M-spike: not quantifiable
- Immunofixation: small  $\kappa$  monoclonal IgG  $\kappa$  in urine
- FISH studies unavailable because no bone biopsy was performed.
- Skeletal survey
  - MRI lumbar spine: L3 compression and L5 focal lesion
  - L5 lesion biopsy:  $\kappa$ -restricted plasma cells
  - Skeletal survey: left superior pubic ramus fracture and pelvic and appendicular lytic lesions
- Initial treatment
  - She initially received radiotherapy to the left superior pubic ramus (15 Gy in 3 fraction) and lumbar regions (24 Gy in 8 fractions).
  - Lenalidomide plus dexamethasone was initiated after radiotherapy but was interrupted due to low white blood cell count. Dose of lenalidomide was reduced.
- Treatment response
  - Performance status improved with induction and heart function remaining unchanged.
  - She attained a CR.
- Maintenance treatment
  - She was deemed ineligible for ASCT and dexamethasone was discontinued.
  - She was advised to remain on lenalidomide monotherapy.

**KUMAR:** A triplet regimen can be considered for frail patients whether we start [all 3 drugs] together or add the third drug [to the other 2] after a period of time depending upon how the performance status improves. This brings up the question of frailty measures. Do you routinely [make such measurements] in the clinic? What instruments would you use?

**DINGLI:** There's been a lot of talk about frailty in multiple myeloma. There are 2 ways to [assess it]: One is the eyeball test, and the other [includes] more formal tests. The IMWG [International Myeloma Working Group] came up with a classification for this based on age, performance status, and activities of daily living, as well as the Charlson Comorbidity Index [CCI]. In general, patients younger than 75 years would have a CCI rating of 1 or less. Patients who are independent [who can perform] activities of daily living are considered not frail. Patients aged more than 80 years or with 2 or more of those other characteristics are considered frail. Generally, I do not use these detailed characteristics. One can ask a few questions and use the ECOG performance status. I look at comorbidities and functional status to make decisions. Another important consideration is the social support that the patient has. A patient who has social support with respect to family and relatives who can help is in a much better position than a patient who doesn't have that type of social support. Sometimes this [factor] is neglected.

**KUMAR:** Would you factor in anything else when you decide if this a high- or a standard-risk patient?

**GERTZ:** Risk for myeloma is not just caused by genetics. That's what we use for trials. That's what the IMWG uses. But there are so many [important] factors that are not ["officially" classified as] high risk. If a patient shows up with multiple liver lesions, biopsy-proven plasmacytoma, and proliferative indexes, this is not a part of IMWG, it's going to be bad news. You know about this plasma. Leukemia is not included among

the high-risk [characteristics], but if you see patients with even small numbers of circulating cells, you're nervous about the situation. We use genetic risk for the purpose of trial stratification, but there are so many other [methods]. You ask if they drove themselves to the office. Did they walk from the parking lot or [did they arrive] in a wheelchair? Questions like that are very relevant in determining their pain level and how much opioid they need to control it. The answers to those questions all factor in as to how much the patient can safely tolerate.

**KUMAR:** We talked a lot about adding a monoclonal antibody in the up-front setting for patients with NDMM. Should we keep some of the effective drugs in store for later therapy, or should we be using all the effective treatments, or as many of them as possible, in the up-front setting to get the best outcomes?

**DINGLI:** We probably all agree that our best shot at treating this disease is with first-line therapy. Historically, if we look at what happens with each subsequent therapy, the duration of the responses and the quality of the responses go down. [There is a] risk every time we lose patients because their performance status worsens, they develop comorbidities, or they don't get subsequent lines of therapy for other reasons.

I'd argue that first-line therapy will probably be the main determinant of a patient's long-term outcome. For example, a patient with standard-risk disease who is transplant eligible can be expected to have a survival of about 10 years. Half of that is decided with first-line therapy. This involves 4 cycles of induction, transplant, and maintenance—perhaps with lenalidomide—and that response is about 4.5 to 5 years. With the first-line therapy, assuming there are no developments in the field, that's half the survival time. One can argue that this is true whether the patient is transplant eligible or not. ■

 For references visit [cancernetwork.com/MM\\_ATP\\_7.22](http://cancernetwork.com/MM_ATP_7.22)