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## GRIFFIN: Daratumumab Plus RVd Improves Responses for Older and Some High-Risk Patients Compared With Triplet Alone in Newly Diagnosed MM

Mary Caffrey

**KEY SUBGROUPS OF PATIENTS** with newly diagnosed, transplant-eligible multiple myeloma (NDMM) who were treated with daratumumab and a well-known triplet regimen had improved responses—including progression free-survival (PFS)—compared with similar patients receiving only

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## Dr Ajai Chari: Patients in High-Risk Subgroups Benefit From Daratumumab Plus Triplet

Interview by Hayden E. Klein

**EVIDENCE-BASED ONCOLOGY™ (EBO)** spoke with Ajai Chari, MD, professor of medicine and director of clinical research in the Multiple Myeloma Program at Mount Sinai in New York, New York, about a post hoc analysis of data from the phase 2 GRIFFIN trial (NCT02874742),

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## **GRIFFIN: Daratumumab Plus RvD Improves Responses for Older and Some High-Risk Patients Compared With Triplet Alone in Newly Diagnosed MM**

(CONTINUED FROM COVER)

the triplet, according to a post hoc analysis of the phase 2 GRIFFIN study (NCT02874742).<sup>1</sup>

The analysis, which was presented during the 64th American Society of Hematology (ASH) Annual Meeting and Exposition December 11, 2022, highlighted stringent complete response (sCR) data for patients 65 years or older and those with high cytogenetic risk.

The findings are the latest involving the quadruplet of daratumumab (Darzalex) combined with lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (D-RvD) in patients with NDMM who are transplant eligible. In August, the final, 4-year data for GRIFFIN were presented at the 2022 International Myeloma Society Annual Meeting, confirming prior results that showed combining the monoclonal antibody with RvD offered improved sCR compared with the triplet. Final results revealed a 55% improved PFS (HR 0.45; 95% CI, 0.21-0.95;  $P = .0324$ ).<sup>2</sup>

Initially in GRIFFIN, 16 patients received the quadruplet, which included daratumumab, to evaluate its safety. The trial had a maintenance phase from cycles 7 to 32, which was updated every 28 days based on pharmacokinetic data. Later in the phase 2 part of the study, 207 patients were randomly assigned to either RvD induction and consolidation, autologous stem cell transplant (ASCT), and maintenance with lenalidomide; or D-RvD, ASCT, and maintenance with daratumumab and lenalidomide.

After a median of 13.5 months, GRIFFIN met its primary end point, with a higher percentage of patients taking D-RvD achieving sCR compared with those taking RvD alone after ASCT consolidation therapy: 42.4% vs 32%, respectively.<sup>3</sup> Updated results presented at ASH 2021 had confirmed these earlier results and that minimal residual disease (MRD) negativity ( $10^{-5}$ ) rates were higher for patients in the daratumumab arm.<sup>4</sup>

### **New Analysis at ASH 2022**

Ajai Chari, MD, professor of medicine and director of clinical research in the Multiple Myeloma Program at Mount Sinai in New York, New York, presented the post hoc analysis on key subgroups (see **Related Interview, page 1**). Subgroups had a similar number of patients in each arm. The subgroups included patients 65 years or older, patients with stage III disease, patients with high cytogenetic risk, patients with revised high cytogenetic risk, patients with 1 high-risk cytogenetic abnormality (HRCA), patients with 3 or more copies of chromosome 1q21 (gain/amp1q), patients with gain/amp1q plus 1 HRCA, and patients with more than 2 HRCAs. Outcomes for patients with baseline extramedullary plasmacytomas were explored, but there were only 3 of those patients in the study, so outcomes could not be evaluated.<sup>1</sup>

Among response evaluable patients, results showed:

- The rate of sCR following maintenance therapy was numerically higher for D-RvD vs RvD among patients 65 years or older (63% vs 40.7%, respectively), with odds ratio (OR) of 2.47 (95% CI, 0.83-7.39).

- Rates of sCR for D-RVd and RVd arms were numerically higher for those with high cytogenetic risk (50.0% vs 38.5%, respectively) (OR 1.60; 95% CI, 0.36-7.07), those with gain/amp1q plus 1 HRCA (55.6% vs 33.3%) (OR 2.50; 95% CI, 0.29-21.40), and those with at least 2 HRCAs (50.0% vs 37.5) (OR, 1.67; 95% CI, 0.25-11.07).
- Rates of sCR were similar for D-RVd and RVd arms among patients with stage III disease (64.3% vs 61.5%, respectively) (OR 1.13; 95% CI, 0.24-5.37), those with revised high cytogenetic risk (56.1% vs 55.6%) (OR, 1.02; 95% CI, 0.42-2.52), those with gain/amp1q (57.6% vs 57.1%) (OR 1.02; 95% CI, 0.37-2.82), and those with 1 HRCA (58.1% vs 60.7%) (OR, 0.90; 95% CI, 0.32-2.54).

Although sCR was the primary end point of GRIFFIN, MRD negativity rates following the end of maintenance favored D-RVd over RVd across all subgroups, and PFS was favored across all subgroups except those with more than 2 HRCAs.

**TREATMENT-EMERGENT ADVERSE EVENTS (TEAES).** Among patients 65 years or older, grade 3/4 TEAEs were seen in 88.9% of patients in the D-RVd arm vs 77.8% of those in the RVd arm. Most common were neutropenia (37.0% vs 29.6%, respectively) and lymphopenia (25.9% vs 11.1%). TEAEs led to discontinuation in 37.0% of patients in the D-RVd arm vs 25.9% in the RVd arm. One patient in the D-RVd arm died of pneumonia, unrelated to treatment.

**RESULTS FOR BLACK PATIENTS.** Of the 207 randomly assigned patients in GRIFFIN, 32 were Black. MM disproportionately affects Black communities in the United States; these patients account for 14% of the US population but 20% of new MM cases.<sup>5</sup> Underenrollment of Black patients in clinical trials is a recognized problem that the FDA and major cancer centers are working to address.<sup>6</sup>

A separate abstract at ASH found that after 48 months Black patients enrolled in GRIFFIN in the D-RVd arm saw significant clinical benefits but had lower PFS rates than White patients.<sup>7</sup> “This may have been attributed to the higher rates of study treatment discontinuation following TEAEs in Black patients,” investigators wrote, calling for more research in this area.

At the end of maintenance, sCR rates among Black patients were 93% in the D-RVd arm vs 39% in the RVd arm ( $P = .0021$ ); among White patients at this point, the sCR rates were 65% in the D-RVd arm vs 50% in the RVd arm ( $P = .0589$ ). At a median follow-up

of 49.6 months, D-RVd reduced the risk of disease progression or death by 61% in Black patients and 53% in White patients, compared with RVd, investigators found.

“For Black patients, estimated 48-month PFS rates were 79% for D-RVd and 65% for RVd; among White patients, estimated 48-month PFS rates were 89% for D-RVd and 74% for RVd,” the investigators wrote.

Janssen funded the GRIFFIN study and is collaborating with the European Myeloma Network on a phase 3 study, PERSEUS (NCT03710603). PERSEUS is not yet recruiting patients.<sup>8</sup> ♦

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## Dr Ajai Chari: Patients in High-Risk Subgroups Benefit From Daratumumab Plus Triplet

(CONTINUED FROM COVER)

which he presented at the 64th American Society of Hematology (ASH) Annual Meeting and Exposition in New Orleans, Louisiana.

GRIFFIN showed that patients with newly diagnosed, transplant-eligible multiple myeloma had improved responses after 4 years if they received daratumumab (Darzalex; Janssen) in combination with the well-established triplet therapy of lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (D-RVd), compared with patients who had the triplet alone.<sup>1</sup> Data that Chari presented at ASH involved key groups: patients older and younger than 65 years of age and certain high-risk patients, including patients with stage III cancer as defined by the International Staging System; patients with certain high cytogenetic risk; and patients with certain high-risk chromosomal abnormalities (See **Related Article, page 1**).<sup>2</sup>

This interview has been edited lightly for clarity.

**EBO:** Can you summarize the post hoc analysis of the final results from the GRIFIN study that were presented during ASH and how they build on prior results?

**CHARI:** The GRIFIN study is important because in the United States we were using RVd—lenalidomide, bortezomib, and dexamethasone, a triplet—for almost a decade before we had a randomized study. Now the question is: If 3 [therapies] are better than 2, are 4 better than 3?

In the past, sometimes that wasn't the case; you added a fourth drug, and you got more [adverse] effects. Here, the question is: Is 4 better than 3? It's a randomized study, unlike a single-arm study that we had [previously]. This study's primary end point was the depth of response, which it met. It showed that the addition of daratumumab during induction consolidation, and for 2 years of maintenance, did lead to deepening of response. Surprisingly, even though it wasn't the primary end point, it did also translate into progression-free survival [PFS], so that's really exciting. I think for many of us who are early adopters, we've decided to adopt this quadruplet induction regimen, and it's doing quite well. So, that's the primary message from the study. Our update at this particular ASH meeting was really about the high-risk and elderly patients. I should mention elderly in the sense that they still got transplanted in the study—so it's not frail elderly, but [patients] aged over 65 and under 65 seem to have the same efficacy and safety profile. That

was good to see. But perhaps the more juicy data from this were talking about the high-risk subgroups. What you can see is that when you look at [minimal residual disease] and PFS, almost everybody benefited from the addition of daratumumab with the notable exception of patients who had persistent disease after 2 years; meaning, these patients had less than a [very good partial response] and also extramedullary disease. Other than that, everybody seemed to benefit with the addition of daratumumab.

**“Every incremental benefit we’re getting is making progress for our patients, because our best chance of getting deep, durable remission is really the first treatment.”**

**EBO:** What do these long-term results tell us about the importance of the initial upfront combination treatment in multiple myeloma?

**CHARI:** They confirm what we believed—that the addition of daratumumab leads to better responses, and we're seeing that the response continues to deepen. As you give the daratumumab and lenalidomide in combination for 2 years, the responses deepen. And we're seeing some of the flattest progression-free survival curves, and flat is getting us closer to cure. I think every incremental benefit we're getting is making progress for our patients, because our best chance of getting a deep, durable remission is really the first treatment. It's really important, although I would add the caveat that it doesn't mean everybody should be getting a quadruplet forever. I think it's induction quad consolidation, and then just doublet maintenance for 2 years afterward...it kind of tapers off. And that's really important, because I think sometimes [clinicians] are a little hesitant to use an upfront anti-CD38 monoclonal antibody because they're like, “Well, what am I going to do

with relapse?” Here, you’re not doing it until they’re refractory to the drug, so there’s every reason why you should be able to reuse it if and when they relapse in the future.

**EBO:** Can it be argued that adding daratumumab up front to the standard triplet is superior from a cost-savings perspective, if it prevents the need for additional treatments in some patients?

**CHARI:** That answer is going to depend on longer-term data. Because right now, I think the maturity of the data is only about 3 years. I know during that time [we’ve been giving] the CD38 monoclonal antibody for almost 2 plus years. So, to see the value, you’re going to need to see, well, how much delay in the progression is there? And does that offset the upfront costs? I think we’ll need a longer follow-up to answer the cost question here.

**EBO:** What comes next in the study of this daratumumab combination in this group of patients with multiple myeloma?

**CHARI:** I think for global regulatory approval, we’ll need that randomized phase 3 [trial], which is called the PERSEUS study [NCT03710603]. It’s daratumumab-RVd vs RVd. Because GRIFFIN was a randomized phase 2 trial, that will be a randomized phase 3 trial. And once we see that, I think

there will be even broader uptake. Of course, we’re going to need to see, ideally, the overall survival benefits [from] the sister study in Europe called CASSIOPEIA [NCT02541383]<sup>3</sup>. Dara-VTd [bortezomib, thalidomide, and dexamethasone] vs VTd showed not only response depth and PFS benefit, but also overall survival benefit. It will be exciting to see if on this side of the Atlantic we get the same results. ♦

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## Disparities in Multiple Myeloma: Quality Improvement Initiative Reveals Gaps Between Oncology Providers, Patients in Views of Costs, Risk of Treatments

Interview by Mary Caffrey

**HOW CAN HEALTH SYSTEMS** close disparities in care? A quality improvement (QI) initiative launched in 2020 sought to examine this question in relapsed/refractory multiple myeloma (R/R MM). The first round of data was collected from 2 large oncology groups in academic settings and focused on patient concerns. In the second phase, the effort drew additional participants from 4 community-based oncology practices, “to greater evaluate disparities with electronic medical records [EMR] audits and team-based audit feedback sessions, to identify factors which could enhance more equitable care,” according to

an abstract presented during the 64th American Society of Hematology (ASH) Annual Meeting and Exposition in New Orleans, Louisiana.

Surveys were completed by 59 hematology/oncology providers and 100 patients with R/RMM, of whom 47 were Black, 50 were White, and 3 were Hispanic. A baseline EMR audit included data from 200 patients with R/R MM. The survey found that patients and providers can view situations very differently; gaps in trust are wide among all patients but especially so between Black patients and their cancer care providers.<sup>1</sup> As part of the QI process, the

oncology provider groups received the survey information, and approximately half the providers developed improvement plans.

While in New Orleans, *Evidence-Based Oncology*<sup>TM</sup> (EBO) spoke with lead author Joseph R. Mikhael, MD, MEd, about the survey findings, the ongoing QI initiative, and the challenges of bringing greater diversity to clinical trials. Mikhael is a professor in the Applied Cancer Research and Drug Discovery Division at the Translational Genomics Research Institute, an affiliate of City of Hope Cancer Center, in Phoenix, Arizona. He is also the chief medical officer for the International Myeloma Foundation and was recently elected treasurer of ASH.

This interview has been lightly edited and condensed for clarity.

**EBO: Can you discuss your earlier QI initiative and how it informed this current effort to identify gaps in MM care?**

**MIKHAEL:** In the world in which we're living now—in multiple myeloma and all diseases—there has been, thankfully, a greater emphasis on understanding health disparities. It really is a multipronged challenge and it's going to require a multipronged solution. Our initiative aimed to understand, from many angles, what may be driving some of that disparity, both in the testing that's done but also in the communication that occurs between providers and their patients.

In our initial look [in 2020], we started to see that there is a difference, almost like “He said, she said.” There are 2 different opinions about literally the same conversation. We wanted to understand the perceptions of patients vs their providers, in their goals of treatment and how they are viewing their current response or achieving those goals of treatment; and what their greatest concerns are about treatment. Early in the study, we started to demonstrate that there was a discordance between the two. Going into this study, we wanted to expand our thinking and our evaluation to incorporate differences in race of the patient, as well as the difference between an academic and a community setting; again, the goal was [to] look at this through a different lens.

**EBO: Your new findings identified discordant beliefs between physicians and patients about the costs of care and the risks of certain treatments. How do these gaps manifest themselves in clinical practice?**

**MIKHAEL:** The study highlights the critical nature of that doctor/patient or health care provider/patient relationship. The essence of this is the study is highlighting the importance of *listening* to our patients and understanding

their perception. That discordance that we demonstrated was almost a historical discordance, in which the physician assumes that the patient is most concerned about their finances, when the patient's concerns may be very different—and may include the toxicities they may experience and the quality-of-life impairment that they may have.

There's no doubt there are patients for whom the cost of their treatment is their greatest concern. But as a physician, I can't go in assuming that based on demographic information, or racial and ethnic background, or really anything about the patient until I have listened to them. And so, how that manifests in the clinic is that a physician may or may not even ask those questions; he or she may just make the assumption. If I were to boil down the whole of this study, it is to remind our health care provider colleagues that we should not make assumptions about patients—that we really must listen to their concerns, what their goals of therapy are, so that we can engage in a genuine dialogue as opposed to a monologue.

**EBO: Would you say that manifests itself in not offering a more expensive treatment or an option to join a clinical trial?**

**MIKHAEL:** Absolutely. It's one thing to assume in one's mind. But then, what actions come out of that assumption are exactly as you've outlined. Assumptions about someone's financial situation may translate into simply assuming that the patient cannot have this agent that typically has a greater co-pay; the provider may just assume the person's not interested in a clinical trial. Conversely, they may assume that a certain toxicity is just going to be an issue for them and it doesn't really matter if they can't drive, because we just know that the drug is *so* important. I'm going to minimize that ocular toxicity to the patient, because I didn't realize that this patient's whole lifestyle is based on their ability to drive, for example. These aren't theoretical phenomena. It's one thing to demonstrate a discordance on paper, but this really influences the selection of treatments—and that was part of what we tried to demonstrate in this study. In future studies, we will have to see the downstream effect of those kinds of assumptions.

**EBO: You found that only 14% of Black patients felt completely involved in their treatment decisions, and only a little more than half of White patients feel completely involved. What has been the reaction to these findings?**

**MIKHAEL:** We did have follow-up after the audit and the interviews; we also had follow-up discussions with the health care teams, which I think is one of the most powerful parts of this study. It is one thing to capture the objective data, but then

we reflect on [those] data. I may be making assumptions in the clinic, but if someone never points this out to me, then how can I ever make a change? That's the idea of a [QI] project—the *improvement* aspect to it. And to no surprise, the results were received with some raised eyebrows, with some wondering [whether] this was really happening. And the reality is, in some of the granularity of this study, the health care provider said, “Oh, yes, we have discussed clinical trials with the patient.” But when you ask the patient the same question, a significantly smaller minority will remember that. To me, it highlights the difference between information and communication, as one has said the information is being given out, and yet these numbers are showing to us that our patients are not feeling engaged in that discussion. That is even more so within the Black population; there are many historical reasons why that is so. The small number of those who felt fully engaged is worrisome, but it is even more worrisome when we see the difference between the 2 races. Again, that emphasizes the point that communication and engaging the patient [are] fundamental to patients achieving their goals of therapy. The studies are highlighting that we're just not doing that well.

**EBO:** Can you elaborate on the efforts by about half the physicians to address disparities and develop more personalized approaches to patient care? What are specific steps the groups will take?

**MIKHAEL:** When we look at their approaches, I put them in 2 categories: there was a general awareness, and then there [are] specific tactics. One thing to come from a study like this is just the sheer recognition that this is a problem. Maybe I say the phrase ‘clinical trial,’ but I don't take time to really *explain* it. Maybe, in general, I'm not looking to my patient carefully enough to see [whether] they're taking in what I'm saying, because I'm so busy typing on my computer.

So, there was a general response: “I want to do this better.” But then there were also very specific tactics, such as taking courses on shared decision-making, and developing, for lack of a better word, a checklist to ensure that in patient interactions, when discussing a new therapy or a clinical trial or autologous stem cell transplant, maybe I need to have a more rigid checklist that I'll keep with me to ensure that I've taken time to ask the explicit question, “What are your goals of treatment as a patient?” and discuss what that may mean.

**EBO:** Here at ASH, we covered a study of an investigational therapy in MM and saw that in phase 1 approximately 14% of the patients were Black, but by phase 2 the percentage of Black patients

**had dropped to 8%. How should FDA or other stakeholders respond to these situations?**

**MIKHAEL:** This is a large part of my life....I've had 3 meetings today about participation of African Americans in clinical trials in myeloma. A few essential points: First, many of my colleagues have commented that it's amazing how much more time the presenters at ASH this year have been spending on their demographic slide. Because it is raising awareness that we need to know who these patients are.

In the United States, roughly 14% of the population [is] African American, which includes me; I'm of African descent. But we know that 20% of [patients with] myeloma...are African American. So, we want to be careful not to just say, “Oh, well, the standard must be 20%,” because it will vary in different regions. But the first step in solving the problem is to recognize that there was a problem, and then recognizing that this problem is not something that can be corrected overnight.

There are many realms of this problem, from the essence of systemic racism to the way the health care system is built, to trust within the health care system, to insurance—be it underinsured or lack of insurance—which affects the African American population more.

And there are much more nitty-gritty, pragmatic issues within hematology/oncology. Some are the things that we address in this QI initiative, such as communication. When we look at centers across this country that enroll greater numbers of African American patients in clinical trials or autologous stem cell transplant, they have a history of trust, they have a history of community engagement—not only when they have something that they want from the community, but also to build a sense of health within that community. And their teams reflect the diversity of their population.

I advocate very strongly that every single clinical trial going forward in multiple myeloma should have a diversity officer, and not for window dressing, but to genuinely ask, “Is everything we are doing in this trial encouraging all minority populations to be a part of this trial?” Or do all the materials have a picture of a 70-year-old White man on it? What about the wording of the trial, in the way it's being presented? What is happening at the individual physician or health care provider level? Am I practicing culturally sensitive care to recognize that someone may be hesitant to enroll in a clinical trial for a whole host of reasons? What specific strategies can I take? And listening to patients is the most important strategy.

We know that myeloma is a different biology; the disease is twice as common in African American [individuals]. And yet, mortality is twice as high in the African American population with myeloma expected survival being half that in the Black population than it is in the White population.

So, you can see that this is a complex issue, but I'm very encouraged that this is on the radar, that people are thinking about it. And it's going to take work at the regulatory level, at the industry level, at the lay community level, and at the health care provider and health care system levels to be able to address this issue. I think we've come a long way in the [past] 24 months, but we have a long way to go and I'm quite positive about the future.

#### **EBO:** What are the next steps planned in your QI initiatives in MM?

**MIKHAEL:** We are sitting now to discuss what the next phase will be. There [are] still a lot of data to mine out of [this phase]—we didn't get into a lot of the detail about the differences between an academic and a community center, the differences that were seen in the reporting of cytogenetics, and so on. I would like to see us not only write up this work, but also propose a greater understanding of what the solutions were that each of these groups produced. We're using this as an opportunity to share more broadly what can be implemented in other places; we're ensuring that our physicians in particular have more formal training in shared decision-making—because nurses often are very

good at this—and understand the concepts of cultural humility or culturally sensitive care. Physicians provide great care to every patient, but they must view each patient individually and have that ability to listen, despite how busy we are in clinic. We're hoping that part of our QI study will lead to more initiatives. And we are considering expanding it to more centers. One of the limitations in our study was that there was a minority of African American providers in these studies, and most of these centers, the physicians and advanced practitioners were White. It would be interesting to reproduce some of the same work we've done in a context where we have African American providers and see [whether] that discordance still presents, in light of what I said before, since part of the multipronged solution is to create a workforce of providers caring for... patients [with myeloma] that comes from the community. ♦

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## Allogeneic Stem Cell Transplant Shows Minimal OS, PFS Benefits in Patients With MM

Rose McNulty

**MOST PATIENTS WITH** multiple myeloma (MM) did not significantly benefit from treatment with allogeneic stem cell transplant (allo-SCT) in a study presented as an abstract at the 64th American Society of Hematology Annual Meeting and Exposition, held December 10-13, 2022, in New Orleans, Louisiana.

Although allo-SCT is increasingly used to manage MM and other hematological conditions, there have been mixed efficacy results in the context of MM. Some patients with treatment-resistant disease experience remission following allo-SCT, whereas others have adverse reactions due to opportunistic infections and graft-vs-host effects. Despite its increased use in this patient population in recent years, there are no clear guidelines surrounding allo-SCT treatment in patients with MM.

The retrospective study included 89 patients who were diagnosed with MM and had received allo-SCT following an autologous stem cell transplant (ASCT) at Mayo Clinic in Rochester, Minnesota, between 2000 and 2022. The median age was 51.3 years. The main outcomes of interest included overall survival (OS) and progression-free survival (PFS) after allo-SCT.

There were 2 reported indications for allo-SCT in the cohort: relapsed or progressive disease (91%) and high risk in remission (9%). Information on risk stratification, according to International Myeloma Working Group criteria, was available for 94% of patients. Among those patients, 63% were considered to be standard risk and 32% were high risk. Overall, 55% of patients underwent myeloablative allo-SCT, whereas 45% underwent nonmyeloablative allo-SCT.

## The findings suggest allogeneic stem cell transplant may not significantly benefit most patients with multiple myeloma. Alternatives such as CAR T-cell or bispecific T-cell engager therapies may be feasible.

The median follow-up time was 11.5 years, the median OS was 1.7 years, and the median PFS was 0.8 years. OS was 46%, 26%, and 16% at 2, 4, and 8 years, respectively. In this population, OS was not significantly impacted by age, sex, race, allo-SCT indication, or myeloablative regimen. Patients who were considered high risk at diagnosis had an OS of 32% at 2 years, 18% at 4 years, and 7.1% at 8 years, whereas standard-risk patients had an OS of 52% at 2 years,

27% at 4 years, and 20% at 8 years. However, the findings regarding OS in the 2 risk stratification groups were not statistically significant.

At 2, 4, and 8 years of follow-up, PFS was 27%, 16%, and 7.9% overall, with no significant variations due to age, race, allo-SCT indication, risk group, or conditioning regimen. Male patients showed slightly higher PFS at 2, 4, and 8 years.

The findings suggest that allo-SCT may not significantly benefit most patients with MM. Less than 20% of patients in the study cohort experienced long-term survival after treatment with allo-SCT following ASCT, and most patients had experienced disease progression or death by 2 years post treatment. Newer alternatives, such as chimeric antigen receptor T-cell therapy or bispecific T-cell engager therapy, may be feasible alternatives to allo-SCT in this population, the authors noted. ♦

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## Population-Based Study Finds Increased Risk of Stroke, Heart Attack in Patients With MM

Rose McNulty

A REAL-WORLD STUDY of patients with multiple myeloma (MM) in the United States found that heart attack and stroke risks are significantly higher in this patient population compared with the general population. The findings were presented as an abstract at the 64th American Society of Hematology Annual Meeting and Exposition held December 10-13, 2022, in New Orleans, Louisiana.

Patients with MM are at an increased risk of arterial and venous thrombosis, but the authors report a lack of real-world studies exploring the association between MM and arterial thrombosis in the United States. The retrospective study aimed to characterize the risk of stroke and heart attack in this patient population using a database of patient

records spanning 26 health care systems in 50 states (IBM Explorys).

Sex, age (older than 65 years), hypertension, hyperlipidemia, diabetes, smoking status, and atrial fibrillation were also evaluated as risk factors for heart attack and stroke in the study. A multivariable logistic regression factoring in these covariates was conducted to determine the associations between MM and heart attack, as well as stroke.

A total of 70,434,190 patients were included in the cohort, 67,920 of whom were diagnosed with MM between 1999 and 2022. Most patients (77%) were older than 65 years and 52% were men. Regarding comorbidities, 19% of patients in the cohort were obese, 67% had

hypertension, 53% had hyperlipidemia, 31% had diabetes, and 21% had atrial fibrillation.

In the MM cohort, 600 patients experienced a stroke and 5370 experienced a heart attack (0.88% and 7.9% of the MM group, respectively). The risk of stroke was substantially higher in the MM group compared with patients who did not have MM, even after adjusting for confounding risk factors (odds ratio [OR], 1.51; 95% CI, 1.43-1.59). Patients with MM were also more likely to experience a heart attack compared with the general population (OR, 1.36; 95% CI, 1.32-1.39).

The study is the largest real-world assessment of arterial thrombotic events among patients with MM in the United States. Overall, individuals with MM were 51% more likely

to have a stroke and 36% more likely to have a heart attack compared with patients who did not have MM. However, further research is needed to identify at-risk individuals and to risk stratify these patients. “Given the enormity of the risk, physicians should consider optimizing modifiable risk factors in all patients with multiple myeloma,” the authors concluded. ♦

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## Diagnosis of Second Primary Malignancies Is Associated With Prolonged Survival Among Patients With MM

Matthew Gavidia

**INCIDENCE OF CERTAIN** second primary malignancies (SPMs) were associated with increased overall survival (OS) among patients with multiple myeloma (MM), according to abstract findings presented at the 64th American Society of Hematology Meeting and Exposition.<sup>1</sup>

There is significant literature regarding the incidence of SPMs in patients with MM, in which therapies used to treat the disease, such as immunomodulatory drugs, have been implicated to increase risk of specific SPMs.<sup>2</sup> Despite survival rates of patients with MM continuing to improve, and subsequently increasing long-term risk of SPMs among survivors, researchers note that there remains a relative paucity of data regarding prognosis and mortality in this population.

Aiming to determine outcomes of patients with MM who receive a diagnosis of SPM, authors conducted a retrospective analysis of real-world data from the American Society of Clinical Oncology (ASCO) CancerLinQ MM registry, which includes records from more than 100 oncology practices and hospitals in the United States.

Eligible patients with MM included those who received their diagnosis between 2009 and 2021 with *International*

*Classification of Diseases, Ninth Revision (ICD-9)* and *Tenth Revision (ICD-10)* codes utilized for SPM diagnoses of interest: acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), breast cancer, colorectal cancer, nonmelanoma cutaneous cancers, melanoma, non-Hodgkin lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), lung cancer, prostate cancer, and any SPM.

The primary end point assessed was OS from the date of initial MM diagnosis, which was compared between patients with MM vs without a later diagnosis of a SPM. A total of 34,234 patients met inclusion criteria, of whom 10.62% developed any SPM (n = 3634).

“Analyses were conducted with STATA version 17.0 (College Station, Texas); critical alpha level was set at .05. Kaplan-Meier curves were generated to demonstrate OS. Median OS and HRs were calculated for all patients later diagnosed during the reporting period with a SPM vs without, and by specific SPMs vs all patients without that SPM,” researchers explained.

Findings indicated that all patients who subsequently received a diagnosis of an SPM reported a median OS of

130 months compared with 103 months in those without such a diagnosis (HR, 0.741; 95% CI, 0.6900-0.796;  $P < .001$ ).

When comparing survival rates by specific SPMs, median OS was shown to be prolonged in patients who later received a diagnosis of certain SPMs vs those without any SPM:

- median OS of patients with MM who received a diagnosis of nonmelanoma cutaneous cancers vs those without an SPM (141 months vs 105 months; HR, 0.472; 95% CI, 0.398-0.559;  $P < .001$ )
- median OS of patients with MM who received a diagnosis of breast cancer vs those without an SPM (median OS not reached vs 105 months; HR, 0.584; 95% CI, 0.475-0.717;  $P < .001$ )
- median OS of patients with MM who received a diagnosis of prostate cancer vs those without an SPM (median OS not reached vs 105 months; HR, 0.599; 95% CI, 0.483-0.743;  $P < .001$ )
- median OS of patients with MM who received a diagnosis of NHL vs those without an SPM (median OS not reached vs 105 months; HR, 0.702, 95% CI, 0.594-0.831;  $P < .001$ )
- median OS of patients with MM who received a diagnosis of DLBCL vs those without an SPM (median OS not reached vs 106 months; HR, 0.712; 95% CI, 0.516-0.984;  $P = .04$ )
- median OS of patients with MM who received a diagnosis of melanoma vs those without an SPM (median OS not reached vs 105 months; HR, 0.743; 95% CI, 0.611-0.904;  $P = .003$ )

Conversely, survival was worse in patients who received a diagnosis of AML (67 months vs 106 months; HR, 1.522; 95% CI, 1.267-1.828;  $P < .001$ ) and lung cancer (76 months vs 106 months; HR, 1.374; 95% CI, 1.157-1.632;  $P < .001$ ) than those without any SPM. Survival was not shown to be significantly affected in patients who received a diagnosis of colorectal cancer, ALL, or CLL.

Researchers acknowledged that findings show many factors could explain why patients who received a

diagnosis of any SPM were more likely to live longer than patients who did not receive a diagnosis of an SPM. This could reflect patients with more indolent disease biology or those who received better treatments, resulting in higher longevity and immortal time bias.

They noted that further study and results analyzing the timing of SPM diagnosis (post MM) and its subsequent impact on OS are forthcoming and will be presented.

**Researchers acknowledged findings show many factors could explain why patients who received a diagnosis of secondary primary malignancy were more likely to live longer than patients who did not receive such a diagnosis.**

“The finding that both AML and lung cancer as SPMs resulted in shorter survival is consistent with what would be expected in the general population, and serves as a good internal control. In summary, this study is the first to shed light on prognosis of patients with MM diagnosed with various SPMs,” the authors concluded. ♦

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