

# Multiple Myeloma Frontline Treatment Options

When you're [diagnosed with multiple myeloma \(MM\) \(/node/984/\)](#), the first step is frontline, or first-line, treatment. First-line treatment for MM is the first step in managing the disease and improving your quality of life. This initial therapy aims to reduce the number of myeloma cells, relieve symptoms, and improve your overall health. This page will guide you through the different options and help you understand what to expect.



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## WITHDRAW CONSENT

To determine the best treatment plan for multiple myeloma, your doctor will order several tests, including blood and urine testing, radiologic imaging, and tissue (bone marrow) biopsy. The results of these tests may indicate a [precursor condition \(/what-are-mgus-smm-mm\)](/what-are-mgus-smm-mm) known as monoclonal gammopathy of undetermined significance (MGUS), or they may indicate the indolent condition of [smoldering multiple myeloma \(SMM\) \(/node/1005\)](/node/1005). If you have active myeloma, your doctor will look for specific signs called [myeloma-defining events \(/medical-conditions\)](/medical-conditions) (MDEs) to determine if treatment is needed right away.

## How Is Multiple Myeloma Treated?

Multiple Myeloma treatment typically involves combinations of medications to get the [deepest and most durable \(/resource-library/international-myeloma-working-group-imwg-uniform-response-criteria-multiple\)](/resource-library/international-myeloma-working-group-imwg-uniform-response-criteria-multiple) response. When needed, medication combinations will be adjusted or changed for continued management. Each new combination is called a line of therapy (LOT). The first LOT for active myeloma is called initial, frontline, or induction treatment.



## When Should You Begin Treatment for Your Multiple Myeloma?

For some people, starting treatment comes after diagnosis. For others, treatment begins after evaluation of symptoms arising from [CRAB features \(/medical-conditions\)](/medical-conditions) that have led to a diagnosis of myeloma. Although it is important to get treatment started to prevent further medical complications such as infections and kidney or bone damage, there may be time to discuss treatment options available, including [participating in a clinical trial \(/clinical-trial-search\)](/clinical-trial-search).

Sometimes, [emergency situations \(/resource-library/myelosuppression-bone-disease-acute-renal-failure-evidence-based-recommendations\)](/resource-library/myelosuppression-bone-disease-acute-renal-failure-evidence-based-recommendations) may require immediate medical attention. Kidney failure, high blood calcium, active infection, or vertebral fracture that presses on the nerves or spinal cord are examples of emergency situations that require immediate intervention. Treatment is directed at the immediate medical issue to preserve renal function, reduce blood calcium, treat infect,

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ahead:

[Patient Handbook \(https://issuu.com/international-myeloma-foundation/docs/patient-handbook-en?fr=sM2MwYzQ2MzkwMTY\)](https://issuu.com/international-myeloma-foundation/docs/patient-handbook-en?fr=sM2MwYzQ2MzkwMTY)

[Urgent Problems at Diagnosis \(/medical-conditions\)](/medical-conditions)

[Understanding Your Test Results \(/resource-library/understanding-your-test-results\)](/resource-library/understanding-your-test-results)

[Understanding Clinical Trials in Myeloma \(/resource-library/understanding-clinical-trials-myeloma\)](/resource-library/understanding-clinical-trials-myeloma)

## Why Should You Consult With a Myeloma Expert?

Myeloma is a complex diagnosis with rapidly changing treatment options. A myeloma expert can provide valuable guidance, answer your questions, help you access clinical trials, and make you aware of the latest treatment advances. These specialists can work with your local hematologist to review your plan of care and provide additional recommendations.



## Frontline Treatment Options for Multiple Myeloma

This section will guide you through the different multiple myeloma treatment options, helping you make informed decisions with your healthcare team.

### The “Triplet,” or Three-Drug Regimen

The “triplet” (three-drug) VRd regimen combines three different drug classes used to treat myeloma:

The proteasome inhibitor Velcade® (bortezomib)

The immunomodulatory agent Revlimid® (lenalidomide)

The steroid dexamethasone, known as VRd

Each drug has a different way of attacking myeloma, and each enhances the activity of the other drugs in this combination therapy.

VRd was accepted as the standard-of-care (SOC) regimen based on data from the phase III Southwest Oncology Group (SWOG) 0777 clinical trial, in which VRd

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balanced between the two treatment groups.

In May 2020, Blood Cancer Journal published a longer-term follow-up of SWOG 0777. At a median follow-up of 84 months, VRd for induction therapy resulted in a statistically significant and clinically meaningful improvement in PFS as well as better OS, demonstrating that VRd continues to represent an appropriate standard of care irrespective of a patient's age. In December 2022, the post-hoc analysis of 471 study patients aged < 65 years at enrollment demonstrated a median PFS of 55.4 months with VRd and 36.6 months with Rd.

### **The Use of Four Drugs for Frontline Treatment**

Recent research has shown that adding a fourth drug to the VRd regimen can improve outcomes for some patients. These quadruplet regimens are now considered standard of care (SOC) treatment for both transplant-eligible and transplant-ineligible patients.



The notion of adding Darzalex to the VRd regimen was introduced by the [GRIFFIN phase II clinical trial \(/node/5902\)](#) in 2019. At the June 2022 annual meeting of the American Society of Clinical Oncology (ASCO), the post hoc analysis of sustained minimal residual disease (MRD) from the GRIFFIN clinical trial demonstrated that the addition of Darzalex to VRd [DVRd] induction and consolidation therapy, followed by Revlimid maintenance therapy, may lead to durable MRD-negativity in ASCT-eligible patients with NDMM, high-risk cytogenetics, ISS stage III myeloma, and those who achieve complete response (CR) or stringent complete response (sCR).

At the December 2023 annual meeting of the American Society of Hematology (ASH), the primary results of the [PERSEUS phase III clinical trial \(/node/10577\)](#) of DVRd in ASCT-eligible patients with NDMM demonstrated that DVRd, with subcutaneous (SQ) injection of Darzalex Faspro, significantly improved PFS and increased depth of response (DpR) with consistent and clinically meaningful benefit across clinically relevant subgroups. The safety profile was consistent.

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For younger and fit individuals, frontline therapy is a three-step process that comprises one line of therapy (LOT):

- Induction:** Initial treatment to reduce the myeloma burden.
- Autologous Stem Cell Transplant (ASCT):** A procedure to replace damaged bone marrow with healthy stem cells.
- Maintenance:** Long-term treatment to keep the myeloma in remission

As of July 30, 2024, the [United States Food and Drug Administration \(U.S. FDA\)](#) approved Darzalex (daratumumab or dara) in combination with Velcade (bortezomib), Revlimid (lenalidomide) and dexamethasone (Dara-VRd or D-VRd [\(/news-events/multiple-myeloma-news/fda-approves-darzalex-faspro-plus-VRd\)](#) ). This approval was based on results from the PERSEUS trial (NCT03710603) and marks D-VRd as the SOC induction therapy for newly diagnosed multiple myeloma patients eligible for autologous stem cell transplant.



Results from the PERSEUS trial show statistically significant benefit in progression-free survival (PFS) and depth of response, both complete response (CR) and minimal residual disease (MRD)-negative status (MRDneg), when dara is added to VRd:

|                            | D-VRd | VRd   |
|----------------------------|-------|-------|
| PFS (48 months)            | 84.3% | 67.7% |
| CR or better               | 87.9% | 70.1% |
| MRDneg (10 <sup>-5</sup> ) | 75.2% | 47.5% |
| MRDneg (10 <sup>-6</sup> ) | 65.1% | 32.2% |

Source: [Sonneveld P, Dimopoulos MA, Boccadoro M, et al. ...PERSEUS Trial Investigators. "Daratumumab, Bortezomib, Lenalidomide, and Dexamethas](#)

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patients achieved MRD-negativity with Isa-VRd plus ASCI, while less than half achieved MRD-negativity with the VRd regimen without Sarclisa.

At a median follow-up of 48 months, 18 weeks of Isa-VRd induction therapy – without consolidation therapy – resulted in a 30% reduction in risk of progression or death when compared with VRd, regardless of which maintenance therapy was received by the patient. As of July 2025, the Isa-VRd combination is approved in Europe and is being reviewed for approval in the United States.

### **Standard Induction Therapy — Dara-VRd for Transplant-Eligible Patients**

The PERSEUS study confirms the clinical benefits of adding daratumumab to standard VRd therapy. It shows significant improvements in depth of response and long-term disease control, supporting its use in combination regimens for newly diagnosed multiple myeloma patients.

 Daratumumab in combination with VRd is considered the preferred regimen by the National Comprehensive Cancer Network (NCCN) guidelines ([https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician\\_gls/pdf/myeloma.pdf](https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf)) for primary treatment of myeloma for those who are transplant candidates.

These drugs are administered as follows:

Darzalex (daratumumab) is given by subcutaneous injection

Velcade (bortezomib) is given by subcutaneous injection

Revlimid (lenalidomide) is a pill taken by mouth

Dexamethasone, a steroid taken as a pill by mouth or can be given intravenous (IV)

### **Additional Induction Therapy Options for Transplant-Eligible Patients**

Kyprolis (carfilzomib) combined with Revlimid (lenalidomide) and dexamethasone (Dexa), may be used instead of VRd in patients with higher risk features such as

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Revlimid (lenalidomide) may be replaced due to medical need or drug availability. Alternative combinations for frontline therapy for people considered eligible for ASCT include:

Darzalex, Velcade, Thalomid® (thalidomide) (/thalomid-thalidomide), and dexamethasone (DVTd): This combination is administered like the DVRd combination. Thalomid is an immunomodulatory drug (IMiD) and can be taken as a pill by mouth as well.

Darzalex, Velcade, Cytosan® (cyclophosphamide) (/cyclophosphamide), dexamethasone (DVCd or Dara-CyBorD). Cytosan is an alkylating agent, a form of chemotherapy for myeloma cancer, that can be taken as a pill by mouth.

Darzalex, Velcade, dexamethasone (DVd)



Before undergoing ASCT, a person will receive 4-6 cycles of induction therapy to gain control over myeloma cells and to show the myeloma is responsive to therapy.

## **The Stem Cell Transplant Process**

The use of autologous stem cell transplant (ASCT) (/autologous-stem-cell-transplant) in the upfront setting is part of a multi-step treatment plan and is considered SOC. Alkeran (Melphalan) is intensive chemotherapy and is given IV. There are additional steps to this process involving eligibility determination, stem cell collection, high-dose chemotherapy followed by stem cell infusion, engraftment, and recovery.

## **Maintenance Therapy**

Following recovery from ASCT, approximately 2-3 months, use of maintenance therapy to maintain control over myeloma is recommended. Medications used for induction are also used for maintenance with changes in dose and schedule.



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## Patients

Stay informed about the four-drug combination for transplant-eligible patients with the following resources:

[Understanding DARZALEX and DARZALEX FASPRO \(/resource-library/understanding-darzalex-faspro\)](/resource-library/understanding-darzalex-faspro)

[Understanding the VRd Regimen for Newly Diagnosed Myeloma \(/resource-library/understanding-vrd-regimen\)](/resource-library/understanding-vrd-regimen)

[Understanding Stem Cell Transplant in Myeloma \(/resource-library/understanding-stem-cell-transplant-myeloma\)](/resource-library/understanding-stem-cell-transplant-myeloma)

[Understanding KYPROLIS® \(carfilzomib\) for Injection \(/resource-library/understanding-kyprolis\)](/resource-library/understanding-kyprolis)

[Tip Card: Alkylating Agents \(/resource-library/tip-card-alkylating-agents\)](/resource-library/tip-card-alkylating-agents)

[Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. \(https://pubmed.ncbi.nlm.nih.gov/38084760/\)](https://pubmed.ncbi.nlm.nih.gov/38084760/) (Sonneveld, et al., NEJM, 2024;390(4):301-313.)



## For Transplant-Ineligible Patients

ASCT is a rigorous treatment process — not all people will be eligible or able to undergo this process due to frailty or age. Some may choose to delay or decline ASCT based on personal circumstances and preferences.

At the December 2024 annual meeting of ASH, the final analysis presented of progression-free survival (PFS) from the first randomization in Part 1 of the [GMMG-HD7 phase III clinical trial \(/node/11528\)](/node/11528) of VRd vs. Sarclisa® (isatuximab) plus VRd, or Isa-VRd, induction therapy for transplant-eligible patients with NDMM.

Isa-VRd led to deeper minimal residual disease (MRD)-negative response post-transplant when compared with VRd alone. At a median follow-up of 48 months, 18 weeks of Isa-VRd induction therapy – without consolidation therapy – re-



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are not eligible (TIE) for autologous stem cell transplant (ASCT). This [FDA approval of the Isa-VRd regimen \(/news-events/multiple-myeloma-news/fda-approves-sarclisa-isatuximab-with-vrd-for-ndmm\)](#) was based on the results of the IMROZ phase III clinical trial, which demonstrated longer PFS in ASCT-ineligible patients with NDMM who received Isa-VRd, when compared to patients who received VRd alone.

**The IMROZ Clinical Trial**

The [IMROZ phase III trial \(/node/10852\) \(NCT03319667 \(https://clinicaltrials.gov/study/NCT03319667\) \)](#) evaluated the quadruplet combination of isatuximab with bortezomib, lenalidomide, and dexamethasone (Isa-VRd) compared to the triplet combination of bortezomib, lenalidomide, and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma (NDMM) who are transplant-ineligible (TI).



The addition of isatuximab to the VRd regimen also shows statistically significant benefit in progression-free survival (PFS) and depth of response, both complete response (CR) and minimal residual disease (MRD)-negative status (MRDneg), when Sarclisa (isatuximab) is added to VRd.

|                                 | Isa-VRd | VRd   |
|---------------------------------|---------|-------|
| <b>PFS (60 months)</b>          | 63.2%   | 45.2% |
| <b>CR or better</b>             | 74.7%   | 64.1% |
| <b>MRDneg (10<sup>-5</sup>)</b> | 55.5%   | 40.9% |

The FDA approval of Isa-VRd validates the complex biology of myeloma, which can be better controlled with multiple drugs that have different mechanisms of action (MoA), the process through which a drug induces its effect in the body.

Source: [Facon T, Dimopoulos MA, Leleu XP, et al. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. Pub](#)

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Society of Clinical Oncology (ASCO) demonstrated impressive improvement in PFS. This study evaluated 446 patients who were 80 years of age or younger.

An independent review committee assessed PFS efficacy using criteria by the IMF International Myeloma Working Group (IMWG). The median PFS (mPFS) was not reached in the Isa-VRd arm of the study; it was 54.3 months in the VRd arm. In the Isa-VRd arm, 63% of study patients In the Isa-VRd arm were still in remission at 4 years vs. 45% of patients in the VRd arm.

**The BENEFIT Phase III Trial**

The BENEFIT phase III trial ([/node/10867](#)) ([NCT04751877](#) (<https://clinicaltrials.gov/study/NCT04751877>) ) reinforced the use of the quadruplet combination of Isa-VRd as the new SOC for TI patients by comparing Isa-VRd to Isa-Rd. By adding Velcade (bortezomib), complete response and MRD-negativity rates were higher as compared to the Isa-Rd group.



|                                           | Isa-VRd | VRd |
|-------------------------------------------|---------|-----|
| <b>PFS (24 months estimated*)</b>         | 85.2%   | 80% |
| <b>CR or better (18 months)</b>           | 58%     | 33% |
| <b>MRDneg (10<sup>-5</sup>) 18 months</b> | 53%     | 26% |

Source: [Leleu X, Hulin C, Lambert J, et al. Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial. Nat Med. 2024;30\(8\):2235-2241. doi:10.1038/s41591-024-03050-2](#) (<https://pubmed.ncbi.nlm.nih.gov/38830994/>)

The BENEFIT clinical trial of Isa-VRd vs. Isa-Rd demonstrated that at all time points in this study, patients receiving Isa-VRd achieved better response rates, with superior rates of MRD and sustained MRD (sMRD), which demonstrated better correlation to survival times than a one-time measurement of the be rate). Data was presented at the 2025 ASH annual meeting.

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Also, sarclisa (isatuximab) in combination with VRd is included in the National Comprehensive Cancer Network (NCCN) guidelines for primary treatment of multiple myeloma for transplant and non-transplant candidates.

Additional combination options include:

Revlimid and dexamethasone (Rd)

Velcade and dexamethasone (Vd)

VRd Lite, which means the patient will take a VRd regimen with lighter doses of each drug to improve tolerance

DRd, the [MAIA \(/node/5303\)](/node/5303) regimen: [Darzalex® \(daratumumab\) \(/darzalex-daratumumab\)](#), Revlimid, and dexamethasone

## Resources on Four-Drug Combinations for Transplant-Ineligible Patients

Here are some valuable resources for transplant-ineligible patients:



[Tip Card: Sarclisa® \(/resource-library/tip-card-sarclisa\)](/resource-library/tip-card-sarclisa)

[Understanding the VRd Regimen for Newly Diagnosed Myeloma \(/resource-library/understanding-vrd-regimen\)](/resource-library/understanding-vrd-regimen)

[Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma \(https://www.nejm.org/doi/10.1056/NEJMoa2400712\)](https://www.nejm.org/doi/10.1056/NEJMoa2400712) (Facon, et al. NEJM, 2024)

[Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial \(https://www.nature.com/articles/s41591-024-03050-2\)](https://www.nature.com/articles/s41591-024-03050-2) (Leleu, et al. Nat Med, 2024)

## What Are the Expectations of Frontline Treatment?

Most patients will experience an excellent response to induction therapy that occurs within the first 2-3 months of treatment. This response is tracked by measuring the myeloma protein levels (free light chains, M-spike, or M-protein)

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protein or free light chains are no longer detectable by traditional methods (SPEP or IFE tests), then it is known as complete response or CR.

The expectation of frontline therapy is that response will last, on average, 4-5 years, especially for patients with “standard risk” myeloma. For people with “high risk” features, in whom remission has lasted less than one year, adjustment to frontline therapy should be made to improve response. For example, your doctor may substitute Kyprolis® (carfilzomib) in DVRd to make DKRd with plans for ongoing therapy for myeloma control.

## Improvement in Myeloma Symptoms

Typically, myeloma symptoms improve with response to treatment. For example, CRAB features (Calcium levels, Renal/Kidney function, Anemia, and Bone disease) correct during the first months of treatment leading to improvement in symptoms. It may be helpful for you to keep a symptom diary to track changes (improvement or worsening) to inform your healthcare team. Your healthcare team will repeat blood tests to monitor calcium, creatinine (kidney function), and hemoglobin levels (anemia), as well as monitor response to treatment. Your doctor may also recommend additional imaging studies such as X-rays, MRIs, or CT scans.

If significant bone damage has occurred, associated pain and other issues may take longer to resolve. Use of radiation therapy, interventional procedures (i.e. vertebroplasty, kyphoplasty, surgery) and pain medication may be needed to manage acute and long-term pain. Bone strengthening medications are used to quickly reduce high calcium levels and reduce the risk of future bone loss and fracture.

## Resources for Managing Myeloma Symptoms and Complications

Below are some resources to help you better understand your symptoms and complications:

[Understanding Your Test Results \(/resource-library/understanding-your-test-results\)](/resource-library/understanding-your-test-results)

[Understanding Fatigue \(/resource-library/understanding-fatigue\)](/resource-library/understanding-fatigue)

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## What Are Side Effects of Myeloma Treatments?

Typically, D-VRd or alternate combinations are very well tolerated. Close monitoring for any signs or symptoms of infection is of greatest importance, especially in the first few weeks of therapy. During this time, the immune system is compromised because of both myeloma and the treatment. As the treatment begins to destroy the myeloma cells, the immune system becomes more effective. Yet, the treatment has a continued immunocompromising effect. Changes in appetite (increase and decrease), bowel function (constipation and diarrhea), and nerve damage (neuropathy) are possible and can increase over time. As mentioned, maintain a symptom diary and report side effects to your healthcare team.

## Gain a Better Understanding of Myeloma Drugs

Explore the FDA-approved myeloma medications:



[FDA-Approved Drugs for Myeloma page \(/multiple-myeloma-drugs\)](/multiple-myeloma-drugs)

[Tip Card: Myeloma and the Immune System \(/resource-library/tip-card-myeloma-immune-system\)](/resource-library/tip-card-myeloma-immune-system)

## Myeloma and Treatment Decision-Making

A diagnosis of multiple myeloma and starting treatment is overwhelming for you and your loved ones. Understanding your treatment options, how they may affect your quality of life, and what matters most to you are key to participating in shared decision-making with your doctor and healthcare team. Together, you will consider the treatment options, including benefits and side effects.

Be sure to discuss [expectations for quality of life \(/node/12890/\)](/node/12890/), the impact on your career if you are still working, and the impact of treatment on other life activities. The cost of care may also be a consideration for you.

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[Tip Card: Myeloma Treatment Discussion Tool \(/resource-library/tip-card-myeloma-treatment-discussion-tool\)](/resource-library/tip-card-myeloma-treatment-discussion-tool)

[Tip Card: Ask Your Doctor These Important Questions \(/resource-library/tip-card-ask-your-doctor\)](/resource-library/tip-card-ask-your-doctor)

[Comprehensive Glossary \(/publications-videos/terms-definitions-multiple-myeloma\)](/publications-videos/terms-definitions-multiple-myeloma)

## Need More Information? Chat to Myelo!

Have questions about myeloma? Get instant answers with Myelo®, our 24/7 generative AI chatbot. Myelo can provide personalized information, explain complex topics, and guide you to relevant resources.



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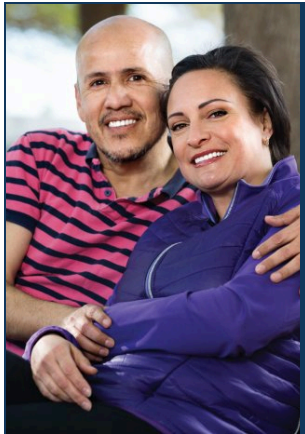
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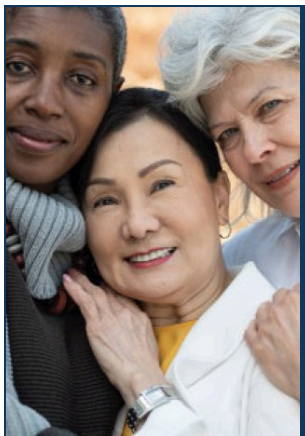
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## Understanding the Isa-VRd Regimen for Newly Diagnosed Myeloma ([/resource-library/understanding-isa-vrd-regimen](#))

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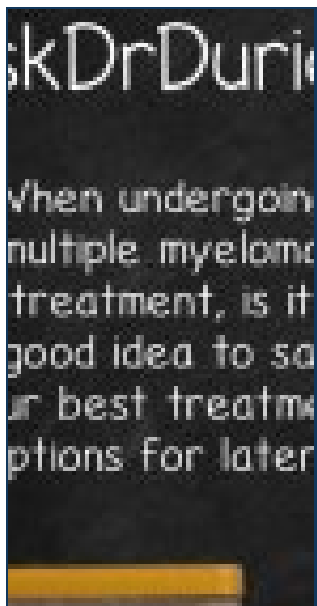


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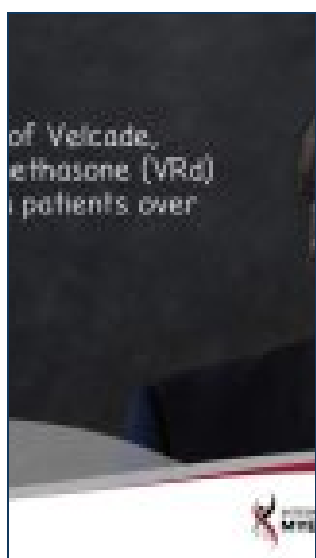
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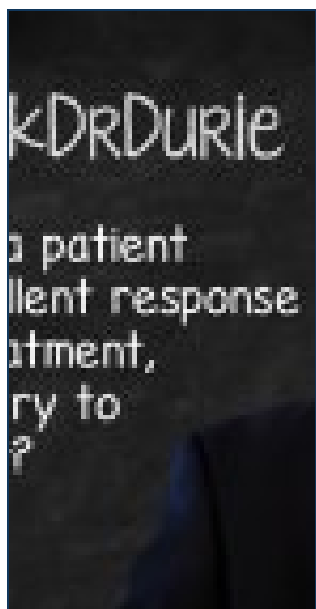
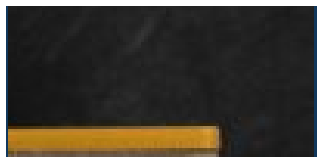


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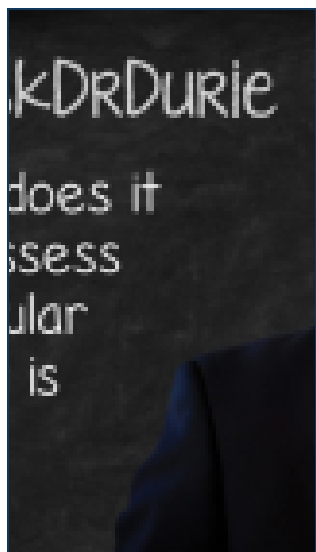


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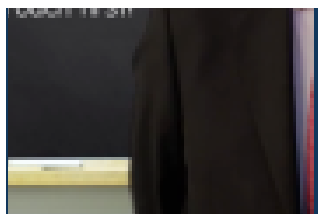
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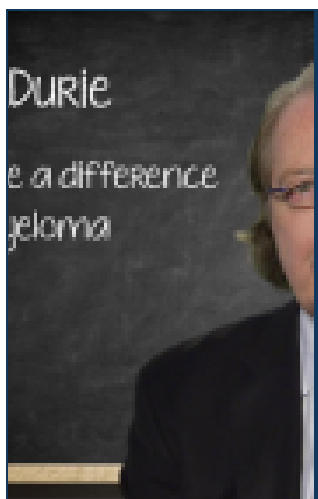
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## Foundation medical and editorial content team

Comprised of leading medical researchers, hematologists, oncologists, oncology-certified nurses, medical editors, and medical journalists, our team has extensive knowledge of the multiple myeloma treatment and care landscape.

Additionally, the content on this page is medically reviewed by myeloma physicians and healthcare professionals.

Last Medical Content Review: June 9, 2025



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