

Daratumumab in the Treatment of Multiple Myeloma

Aryan Marri¹ and Jothsna Kethar^{1#}

¹Gifted Gabber

#Advisor

ABSTRACT

A monoclonal antibody called Daratumumab (trade name: Darzalex) was created by Janssen Biotech, a division of Johnson & Johnson. The U.S. Food and Drug Administration originally approved it in November 2015 as a treatment for multiple myeloma in patients who had already tried at least three other lines of treatment. Daratumumab has transformed multiple myeloma treatment since it was approved, and it has now acquired further approvals for a number of applications, reaffirming its place as a prominent therapeutic choice in the management of this challenging condition. It has been very effective in combating multiple myeloma. Although certain symptoms are present, its efficacy is still quite good. Daratumumab's ability to provide positive results in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation has been further supported by the Maia trial, a crucial study in this area. Daratumumab works by targeting CD38, a cell surface glycoprotein that is abundantly expressed in malignant plasma cells. This causes antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and direct activation of death. Daratumumab is becoming more and more important as a good therapeutic choice for people with multiple myeloma as a result of a thorough understanding of its effectiveness, symptoms, and mechanism of action.

Introduction

Multiple myeloma has caused a profuse amount of deaths, 12,590 in 2023 alone. Although this disease is quite infrequent (compared to other cancers), it has affected roughly 35,000 people this year alone. Multiple myeloma is seen as a deadly disease due to its mortality rate, ranging from 45 to 23 percent (depending on the stage the cancer is discovered). Many see this diagnosis of this disease as a death sentence, as it has limited treatment plans. Countless deaths and infections met with groundbreaking research have eventually led to an efficient solution: Daratumumab, an anti-cancer monoclonal antibody. This drug, first introduced by Genmab in 2013, is now widely sold by Johnson & Johnson under the brand name Darzalex. Variants of this drug include Darzalex, the original solution created, and Darzalex Faspro. Although there were previous treatments for Multiple Myeloma (corticosteroids, chemotherapy, stem cell transplants), Darzalex was the first antibody used. After the approval of this drug by the FDA, it has become widely available in various pharmacies across the world. Scientists continue to research the success of this drug, as it has managed to treat a previously untreatable disease. Its influence continues to grow in this modern age, as further advancements can unlock new possibilities for this drug.

History of Daratumumab

Multiple myeloma is a type of cancer that affects plasma cells, and daratumumab is a monoclonal antibody used to treat it. It was first created by Genmab, and in 2015, the FDA gave its clearance. Daratumumab was created in the early 2000s as a result of efforts to target CD38, a protein that is overexpressed on the surface of multiple myeloma cells. A completely human monoclonal antibody was developed after several years of study; it specifically binds to CD38 and causes cell death. Daratumumab had good results in early clinical studies, earning the FDA's fast-track

designation. Daratumumab became the first CD38-targeted treatment to earn FDA clearance in 2015 after subsequent trials supported its effectiveness in treating multiple myeloma. Daratumumab has since been authorized for use in patients with multiple myeloma who have already had at least one previous treatment.

Daratumumab Mechanism of Action

Daratumumab is a vital monoclonal immunoglobulin G1 Kappa-type antibody. It interacts with CD38-transmembrane glycoproteins found on multiple myeloma patients' surfaces through two significant phases. Secondly, interactions made between Daratumumab and natural killer cells equipped with Fc receptors lead up to stimulating such activities-ultimately making use of perforin and granzymes that trigger antibody-dependent cellular cytotoxicity responsible for killing multiple myeloma cells. Furthermore, stage three of the Daratumumab mode of action leads to complement-dependent cytotoxicity production, causing such interactions with complement protein C1q resulting in membrane attack complex production increasing cell destruction scientifically. Another important way in which this monoclonal antibody proves effective for treating cancer patients involves improving macrophages' phagocytic capabilities through detecting CD38 on surfaces making the identification process more manageable and treatments efficient. In conclusion, Daratumumab's overall significant aspect lies in detecting CD38-recognized on surfaces and making use of-independent mechanisms or establishing well-known immune effector pathways(antibody-dependent cellular cytotoxicity), microbe-mediated mechanisms such as complement-dependent cytotoxicity production. All these can lead up to eventually destroying multiple myeloma cancerous cells while maintaining relatively higher success rates. Daratumumab's Fc component is able to trigger phagocytosis by binding to macrophage's Fc receptors, thus enabling engulfment and bringing about cancer cell destruction.

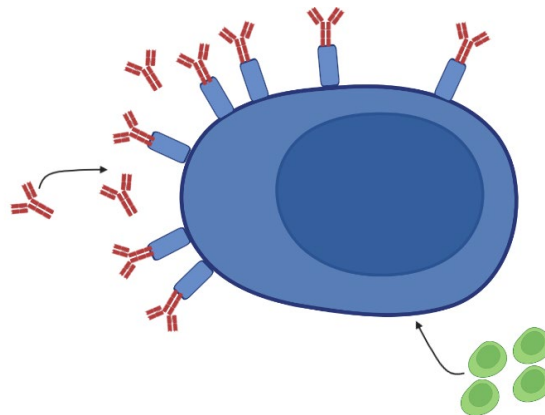


Figure 1 shows the mechanism of action of Daratumumab. The drug's antigens are flagging the CD38 glycoprotein on the large myeloma cell. The green cells shown are T cells.

Multiple Myeloma (Risk Factors, Diagnosis and, Symptoms)

Malignant plasma cell overgrowth characterizes multiple myeloma –a hematologic condition– inhibiting bone marrow from performing its classical function. As such aberrant cells hijack essential resources required for synthesizing good blood-forming counterparts such as red and white blood cells and platelets whose severely reduced levels result from this intrusion with visible implications on health variety. A notable example is anemia which manifests as weakening fatigue-yielding breath difficulties exemplified by pale skin. Reduced red blood cell creation disables efficient oxygenation and causes body tissues and organs to lack adequate resistance against infections. Individuals diagnosed with Multiple Myeloma may encounter recurrent or intense bacterial infections involving areas such as the skin and urinary tract fostering dangerous complications due to insufficient immunity. Calcium imbalance appears frequently known

as hypercalcemia causing calcium level surge in the bloodstream due to the secretion of malignant plasma cell substances promoting bone resorption contributing towards symptoms like confusion, thirstiness, constipation even progressing towards cardiac arrhythmia or coma. Broadly defined multi-symptomatic scenarios arise from Myelomas affecting specific areas under-expression; however, bone pain remains a frequently reported symptom area hip ribs back's aggravations worsened due to physical activity underlying osteoporosis developed from lytic lesions making bones weaker and more vulnerable towards fractures injuries apart from other common skeletal-related issues prompting healthcare interventions. Malignant plasma cells jeopardize normal bone marrow function leading to Anemia resulting in fatigue, lightheadedness weakened immune system contributing to multiple severe complications like cardiac arrest or acute respiratory disease. Hypercalcemia observed frequently among multiple myeloma patients leads to frequent thirst, nausea, and constipation requiring immediate medical intervention to avoid severe complications such as disorientation. Abnormal protein production damaging kidney functions results from malignant plasma cell expression causing fluid retention leading to frequent urination accumulation of renal dysfunction; early detection is crucial in maintaining kidney functionality. Multiple risk factors interact with age being a substantial determinant factor of Multiple Myeloma prevalence, incidence increases steadily with a rise in age affecting mostly people aged 65 years and above. Multiple risk factors contribute towards predisposition to multiple myeloma with genetic and environmental factors taking center stage. Individuals with a familial history of the condition are more likely to experience this disease due to hereditary traits. Evidence further associates conditions like translocations of the immunoglobulin heavy chain gene with multiple myeloma while linking it to environmental factors such as exposure to radiation, various chemicals, and heavy metals. The origination of multiple myeloma is from different plasma cell conditions that set in earlier like monoclonal gammopathy of uncertain significance arising from anomalies within one's protein bill of health. Multiple myeloma's pathogenesis starts when malignant plasma cells grow unchecked within the bone marrow, producing antibodies that help the immune system in battling infections until they become cancerous and create unnatural proteins known as monoclonal paraproteins or M proteins. However, accumulation of these M proteins impairs regular bone marrow operation by reducing healthy blood cell creation causing skeletal symptoms alongside breakdowns in bone tissues like common fractures. Extensive investigations through laboratory testing, and imaging examinations alongside performing bone marrow biopsies typify procedures for identifying multiple myeloma occurrences accurately among patients seeking treatment or diagnosis. Vital signs for diagnosis include indicators like M proteins detected through blood tests and beta-2 microglobulin serum-free light chains highlighting abnormalities using X-ray scans, computed tomography (CT) scans, MRI scans, or PET scans detecting extramedullary involvement often present in advanced stages before a specific diagnosis is made. Subsequent biopsy procedures analyzing percentages of plasma cells around one's bone marrow are necessary for determining accurate diagnoses corroborating findings related to suspected results discovered by doctors during routine checkups throughout examination periods focused on symptomatology hindering one's lifestyle.

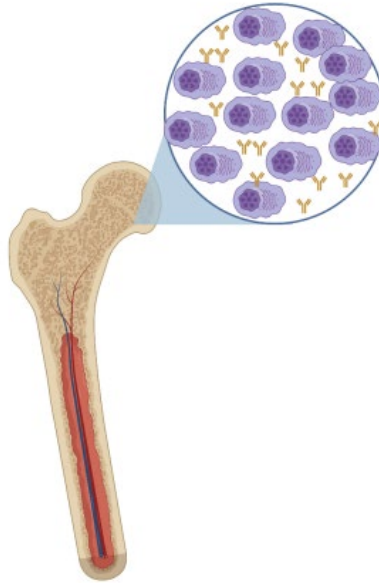


Figure 2 is a Microscopic Image of a Bone with Multiple Myeloma. The Plasma cells and antibodies are shown in the zoomed in portion.

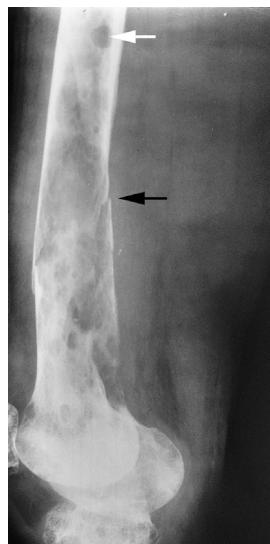


Figure 3 is an X-ray Image of a Femur that Contracted Multiple Myeloma. The white arrow points to the “punched out hole” (AAOS 2004)

Prognosis of Multiple Myeloma

The prognosis for multiple myeloma varies depending on several variables, including the stage of diagnosis, hereditary abnormalities, and response to treatment. The prognosis for multiple myeloma has generally improved in recent years as a result of developments in therapeutic options and supportive care practices. The prognosis might differ greatly from patient to patient, and multiple myeloma is still an incurable illness. In general, several variables, such as the patient's age, general health status, and the existence of specific genetic abnormalities, affect the prognosis for multiple

myeloma. Patients who are younger and who are in good performance status typically have a better prognosis. Additionally, individuals may have a better prognosis if they have favorable cytogenetic anomalies, such as the absence of specific genetic mutations or translocations. The prognosis for multiple myeloma is greatly influenced by the stage at which it is identified. The prognosis is typically better for early-stage or smoldering multiple myeloma, which is characterized by the presence of aberrant plasma cells in the bone marrow but without obvious symptoms or organ damage. However, the prognosis gets more difficult as the disease advances to symptomatic multiple myeloma, with the involvement of organs and the appearance of symptoms such as bone pain, anemia, and renal impairment. Multiple myeloma treatment choices have increased recently, improving results for many people. Proteasome inhibitors, immunomodulatory medicines, and monoclonal antibodies are only a few examples of innovative medications that have been developed recently, which have greatly increased response rates and overall survival. Additionally, greater results have been linked to the utilization of autologous stem cell transplantation in suitable patients. The prognosis for people with multiple myeloma has been considerably improved by the availability of targeted medications and individualized therapy modalities. Despite these developments, multiple myeloma is still an incurable condition, and after initial therapy, relapses or progression are frequent. Patients with relapses or those who are resistant to initial therapy may face more difficult prognoses. However, new targeted medicines and immunotherapies are constantly being developed, giving promise to better outcomes in these challenging situations. The overall prognosis of multiple myeloma patients is greatly improved by supportive care practices such as pain management, managing bone damage, and preventing and treating infections.

Genetics in Multiple Myeloma

Multiple myeloma is driven by genetic disorders caused by unusual alteration or rearrangement within chromosomes in these cells resulting in abnormalities such as chromosome alterations, mutated genes, or gene expression patterns. One remarkable factor behind this cancer is the role played by genetic influences. The t(4;14) translocation results in overexpression of fibroblast growth factor receptor 3 (FGFR3), which promotes cell growth and survival whereas t(11;14) translocation leads to an overexpression of cyclin D1 that enhances cell cycle progression. Chromosomal abnormalities like deletions or amplifications can also significantly impact multiple myeloma. Furthermore, the mutations present within the genes responsible for performing vital cellular body functions add weight to developing multiple myeloma. Gene mutations can dysregulate crucial cellular activities such as those involved in NF- κ B signaling pathways comprising CYLD, TRAF3, and NFKBIZ ultimately resulting in extending cell survivals hence inhibiting them from undergoing apoptosis. Additionally, different molecular subtypes discovered via gene expression research studies alongside tumor suppressor gene mutations like TP53 and RB1 contribute wholly towards abnormality during normal cell cycle regulations causing eventual genomic instability and demanding a closer look. These molecular subtypes provide valuable information about the biology of multiple myeloma that may benefit therapy selection.

Multiple Myeloma in Animals

Although humans are more likely diagnosed with it, multiple myeloma is also found in various animal species, for example, dogs, cats, and cows. Plasma cells that generate antibodies within a body often result from abnormal growth called for its development. There's still no fully identified culprit for multiple myeloma. The impact of genetic factors and environmental factors has, however, been reported to elevate its spread concern. When different animal species are affected by certain organ systems, symptoms vary. The most noticeable clinical signs seen in dogs suffering from this medical condition include weight loss, inappetence, high frequency of urination, increased thirst, long recovery time from exercise, bone pain, and other possibilities such as kidney dysfunction and anemia. Cat-related symptoms may be vague with reports of anorexia, weight loss, and occasional high-thirst patterns. Diagnosis is made possible by veterinary medical experts determining the extent through clinical evaluation while also performing imaging tests

and laboratory tests to confirm multiple myeloma. Treatment options available for multiple myeloma in animals share similarities with human care. A range of drugs can target cancerous elements like melphalan cyclophosphamide or vincristine. Careful consideration needs to be shown toward species selection, the animal's overall health status, as well as disease severity. The treatment may also involve bisphosphonates which contribute towards strengthening bones and managing bone lesions via supporting hydration, nutrition, and pain management. The chances of recovery for animals diagnosed with multiple myeloma hinge on different elements such as when it got diagnosed, and the effectiveness exhibited by any treatment approach adopted along dealing with concurrent illnesses. Regrettably, this type of cancer has a bleak outlook when found in these creatures; and is usually not treatable; only supportive measures aimed at controlling symptoms and slowing down its advancement remain helpful.

Symptoms of Darzalex

While Darzalex has demonstrated efficacy in improving outcomes for multiple myeloma patients, it should be acknowledged that there are possible symptoms prompted by its usage. Infusion-related responses represent one such symptom frequently linked with taking Darzalex. Ordinarily spanning across mild to severe discomforts such as fever chills vomiting headache cough itchiness rashes; these signs occur either during or immediately after an infusion session. This symptom often requires prompt medical consultation or even potentially lowering the infusion rate. Darzalex use can also cause thrombocytopenia, a reduction of platelets within the blood. When this happens, patients perceive heightened susceptibility towards bleeding bruises forming easily on their skin. Additionally, Darzalex is known to induce neutropenia which constitutes a decrease in white blood cell activities, especially neutrophils. The symptoms of neutropenia include fever plus sore throat or coughing which makes the risk of contracting infections significantly higher. Weakness and weariness are other known adverse effects experienced by some Darzalex users.

Physician opinion on Darzalex

Darzalex has a good reputation among doctors due to its extraordinary effectiveness in creating positive outcomes for patients with multiple myeloma. Darzalex, when combined with other medicines, can considerably prolong progression-free survival and overall survival in patients with newly diagnosed multiple myeloma, according to clinical studies and real-world experience. Doctors appreciate the versatility of Darzalex. It has been effective for individuals who have previously had several prior treatments as well as a frontline therapy when combined with other medications like lenalidomide and dexamethasone. Because of this adaptability, doctors may customize treatment plans depending on the unique patient features and illness state. Darzalex's outstanding safety profile is another feature that physicians strongly respect. No medication is without adverse effects, but patients have typically accepted Darzalex well. The most often reported side effects include upper respiratory infections, tiredness, and responses to infusions. These effects, nevertheless, are frequently controllable, and doctors have devised methods to lessen their influence through pre-medication and cautious administration techniques. Darzalex is delivered intravenously once weekly for the first eight weeks, then every two weeks for the following cycles, which is convenient for doctors. The treatment burden for patients is lessened by this dose regimen, enabling them to lead largely normal lives even while receiving medication. Darzalex has also been included in many treatment plans and combination medicines as multiple myeloma therapy has improved, further highlighting its significance in the field. In order to optimize Darzalex's effectiveness, doctors continue to research the best techniques for using this drug.

Why is Darzalex an Ideal Drug for Treating Myeloma

Daratumumab has established itself as a cutting-edge medication for multiple myeloma by becoming the treatment of choice. The exceptional efficacy of Daratumumab is one of the main justifications for picking it. Numerous clinical

investigations have repeatedly shown that it is superior in a range of therapy contexts. Daratumumab has demonstrated exceptional response rates when used as a monotherapy, with a sizable percentage of patients seeing profound and long-lasting improvements. Daratumumab has shown to be considerably more successful when coupled with conventional therapy like lenalidomide and dexamethasone, resulting in noticeably better progression-free survival and overall survival compared to conventional treatments alone. Daratumumab is a crucial tool in the battle against multiple myeloma because of the significant and long-lasting responses seen with it. Daratumumab differs from other medications used to treat multiple myeloma due to its distinct mechanism of action. Daratumumab is a monoclonal antibody that targets the cell surface glycoprotein CD38, which is abundantly expressed in malignant plasma cells. Daratumumab directs the production of apoptosis, antibody-dependent cellular cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC) via interacting with CD38. This multifaceted strategy makes use of the patient's own immune system to destroy cancer cells, providing a strong and efficient technique for treating the condition. One strong justification for Daratumumab's usage in the management of multiple myeloma is its capacity to activate the immune system and produce various mechanisms of action. Daratumumab's superior safety profile is another important benefit. Daratumumab has been shown in clinical studies to have a generally well-tolerated profile, despite the fact that all drugs have possible adverse effects. Although there have been reports of infusion-related responses, these can be successfully treated using premedications and slower infusion rates. Serious adverse effects are rare, and Daratumumab has advantages over competing medications in terms of response rates and survival outcomes. Daratumumab is a desirable option for patients and healthcare professionals due to its high efficacy and maintainable safety profile. Daratumumab administration's convenience only increases its allure. Daratumumab may be delivered as a subcutaneous injection, which greatly lessens the burden on patients and healthcare systems compared to chemotherapy regimens that frequently call for extended hospital stays or frequent trips to infusion centers. In terms of effectiveness and safety, the subcutaneous formulation has been shown to be comparable to intravenous administration. Additionally, it has the benefit of faster infusion times, which frees up patients' time to focus on their everyday activities rather than on therapy. Daratumumab is a popular option among patients and medical professionals alike because of its simplicity of administration and reduced stress on patients. The expanded indications for Daratumumab further add to its persuasive value. It was first authorized for use in patients with relapsed or resistant multiple myeloma, but it is now also authorized for use as frontline treatment. The drug's excellent effectiveness and the advantages it provides to patients early in their treatment journey are recognized by this enlarged indication. Daratumumab has become a crucial component of the first treatment plan by giving patients the chance to have more profound and long-lasting reactions, which pave the way for better long-term results.

Trials

MAIA Phase 3 Trial

In 2019, the phase 3 MAIA study was performed. It was a randomized trial meant to evaluate the effectiveness and safety of daratumumab in combination with lenalidomide and dexamethasone for newly diagnosed multiple myeloma patients. The study examined the data of 952 patients who were initially assessed for eligibility. Out of these 737 patients met the criteria and were arbitrarily assigned into one of two groups: the daratumumab group (n=368) or the control group (n=369). Participants included individuals aged 18 years or older with newly diagnosed multiple myeloma and disqualified from high-dose chemotherapy with autologous stem cell transplantation because they were either above age 65 or had comorbidities. The study's primary measure was progression-free survival (PFS), which records how long during and after treatment the disease does not worsen. Secondary measurements were overall survival (OS) assessing the duration between treatment initiation until death from any cause. Patient progress was monitored over a median period of 56.2 months. The analysis of data in MAIA showed substantial improvement in both PFS and OS for subjects in the daratumumab group compared to subjects in the control group. There was no median

PFS in the daratumumab arm indicating an extended period without disease progression; whereas those treated through traditional means had a median PFS lasting up to only around 34 months on average. This finding suggests that adding daratumumab to traditional treatment plans increased PFS rates significantly by serving as an effective therapy supplement minimizing symptoms or even boosting immunity if left unsupplemented. Moreover, when hazard ratio (HR) values were measured we found them to be at a favorable rate: HR for PFS displayed a value of .53 which is rare indicating results that are difficult to come by implying that Daratumab enhances antitumor efficiency. It also implied a startling 47% reduction in the risk of disease progression or death in the daratumumab group compared with those who were part of the control group ($p < 0.0001$). Hence from this research's outcomes, it is reasonable to draw a confident conclusion that adding daratumumab certainly led to significant improvements in PFS rates and also increased OS rates. The data obtained from this study indicate that newly diagnosed multiple myeloma patients who received daratumumab experienced a substantial decrease in the risk of death compared to those who didn't receive it ($p = 0.0013$). In fact, based on HR measurements it suggests around one-third (32%) less risk. As is often expected when involving new strategies in cancer treatment regimens such as immunotherapy; understanding potential drawbacks lies at the forefront when considering overall patient health outcomes (Facon, et al 2021).

Conclusion

Daratumumab has shown great success in the treatment of multiple myeloma, and it has considerably improved patient outcomes. It has been shown to be effective when combined with other treatments for multiple myeloma patients who are ineligible for stem cell transplantation, according to clinical trials like the crucial Maia study. Daratumumab has been approved by regulatory bodies all around the world as a consequence of the outstanding outcomes from these trials, which have completely changed the field of multiple myeloma therapy options. Daratumumab appears to have a bright future in the management of multiple myeloma. Its usage in conjunction with other medications, such as immunomodulatory medicines and chemotherapy, is still being investigated in clinical studies in an effort to increase its efficacy and expand its applicability to various patient subgroups. It is also being studied for the treatment of various hematologic cancers, including lymphoma and acute myeloid leukemia. Daratumumab subcutaneous formulations are also being developed, which should make administration easier and perhaps lower the frequency of adverse responses associated with infusions. Daratumumab has drawbacks despite its effectiveness, including a hefty price tag for therapy and the possibility of side effects like neutropenia, thrombocytopenia, and infections. However, addressing the safety and tolerability concerns of this treatment remains crucial, and ongoing efforts to optimize dosing and provide adequate support may prove beneficial. Daratumumab is a promising new cancer drug that has made great progress in the treatment of multiple myeloma.

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9. Author links open overlay panelProf Thierry Facon MD a, a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, ...
SummaryBackgroundIn the primary analysis of the phase 3 MAIA trial (median follow-up 28·0 months). (2021, October 13). *Daratumumab, Lenalidomide, and dexamethasone versus Lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): Overall survival results from a randomised, open-label, phase 3 trial*. *The Lancet Oncology*. <https://www.sciencedirect.com/science/article/abs/pii/S1470204521004666>