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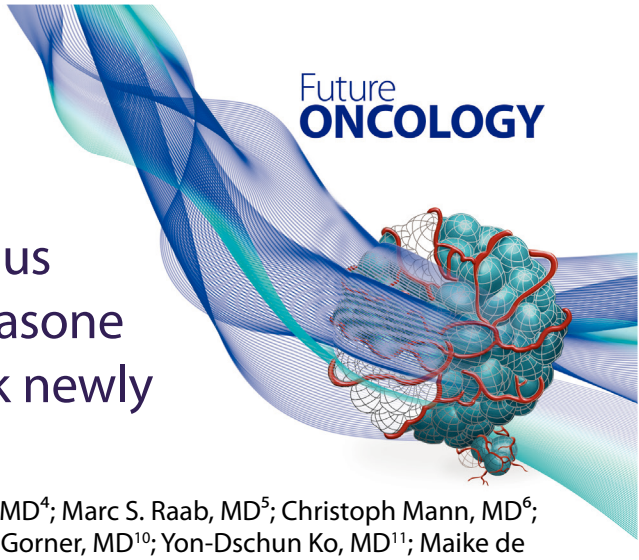
Plain Language Summary of Publication



Plain language summary of isatuximab plus carfilzomib, lenalidomide, and dexamethasone for the treatment of people with high-risk newly diagnosed multiple myeloma

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Where can I find the original article on which this summary is based?

The original article of this study is titled 'Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma'. You can read the full article, which is free to access at: https://ascopubs.org/doi/full/10.1200/JCO.23.01696

Summary

What is this summary about?

This is a summary of a publication about the GMMG-CONCEPT study that was published in the *Journal of Clinical Oncology* in September 2023. The study tested if a combination of cancer drugs (isatuximab plus carfilzomib, lenalidomide, and dexamethasone, or Isa-KRd for short) was a safe treatment for people with high-risk newly diagnosed **multiple myeloma**. The GMMG-CONCEPT study included participants who had not been treated before and were eligible to receive a procedure called autologous stem cell transplant, as well as participants who were not eligible to receive transplants.

How was the study in this summary conducted?

This report looked at a total of 125 participants; 99 were transplant-eligible and 26 were transplant-non-eligible. All participants were treated with Isa-KRd. The researchers measured the proportion of people who had 'no detectable levels' of myeloma cells in their body left while on treatment (called minimal residual disease negativity, or **MRD negativity** for short). The researchers measured the progression-free survival, or the average length of time it took between the participants joining the study until their cancer got worse or they died. The researchers also measured overall survival, which is the total amount of time people lived during the study, even if their cancer got worse. The researchers also monitored for **side effects** of Isa-KRd in all participants that received at least one treatment.

How to say (double click sound icon to play sound)...

- **Autologous:** aw-TOL-uh-guhs
- **Carfilzomib:** kar-FIL-zoh-mib
- **Dexamethasone:** DEK-suh-MEH-thuh-sown
- **Isatuximab:** I-suh-TUK-sih-mab
- **Lenalidomide:** leh-nuh-LI-duh-mide
- **Myeloma:** mai-UH-low-muh

Multiple myeloma: This is a form of blood cancer that occurs in a type of white blood cell known as a plasma cell. Abnormal plasma cells grow uncontrollably in multiple myeloma, and build up in the bone marrow.

MRD negativity: No detectable levels of myeloma cells are left while on treatment. This means a person has too few myeloma cells (less than 1 myeloma cell for every 100,000 cells) in their bone marrow to show up in this test. People with MRD negativity tend to live longer, as well as have longer periods of time without worsening disease.

Side effect: An effect of a medicine that is beyond its desired effect. Side effects can be harmful.

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What were the results of the study?
At the end of the consolidation therapy (intensified therapy that happens after initial therapy), MRD negativity was observed in the majority of transplant-eligible and transplant non-eligible patients. For many patients, this effect lasted 6 or more months. After more than 3 years in transplant eligible participants and 2 years and 9 months for transplant non-eligible participants, most participants were alive and their disease did not get worse. In both groups, the most common side effects of Isa-KRd treatment were low blood cell counts and infections. Overall, most of the side effects did not last long or were easily treated.

What were the main conclusions reported by the researchers?
In the GMMG-CONCEPT study, Isa-KRd treatment reduced the number of myeloma cells to no detectable levels in more than two thirds of the participants with high-risk newly diagnosed multiple myeloma.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research. This summary reports the results of a planned interim analysis of the study. This means that the study has not yet been completed.

Who is this article for?

This summary may help people with newly diagnosed multiple myeloma, their caregivers, patient advocates, **payors**, and healthcare professionals.

Payor: A person or organization that pays for the care services administered by a healthcare provider. This could be an insurance company.

Who sponsored this study?

This study was **sponsored** by University Medical Center Hamburg-Eppendorf.

Sponsor: A sponsor is a company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that was generated during the study.

What is multiple myeloma?

Multiple myeloma is a form of blood cancer that occurs in a type of white blood cell known as a plasma cell. Plasma cells are found in the bone marrow, the spongy tissue that makes blood cells, and is found in the center of most bones. Plasma cells make a type of protein called an antibody. Antibodies help fight infections in the body.

In people with multiple myeloma, abnormal plasma cells grow uncontrollably and build up in the bone marrow, reducing the space for healthy plasma cells to grow and function. The myeloma plasma cells make abnormal antibodies called M proteins, that build up in the blood. Unlike normal antibodies, M proteins do not fight off infections. Although multiple myeloma starts in the bone marrow, it can spread to the rest of the body through the blood. This can cause bone and organ damage.

In the early stages of multiple myeloma, people often have no symptoms. Often the only sign of the condition is a high level of M protein in the blood. In later stages of myeloma, patients may have symptoms throughout their whole body.

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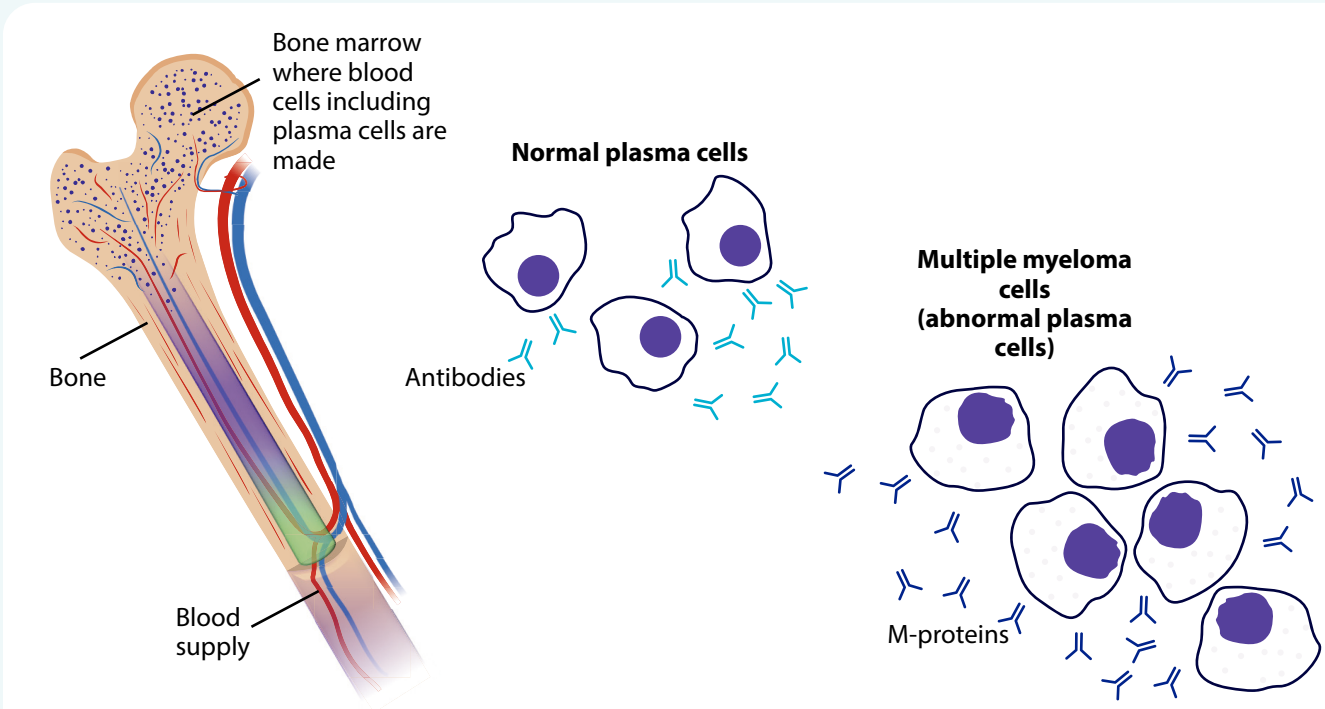
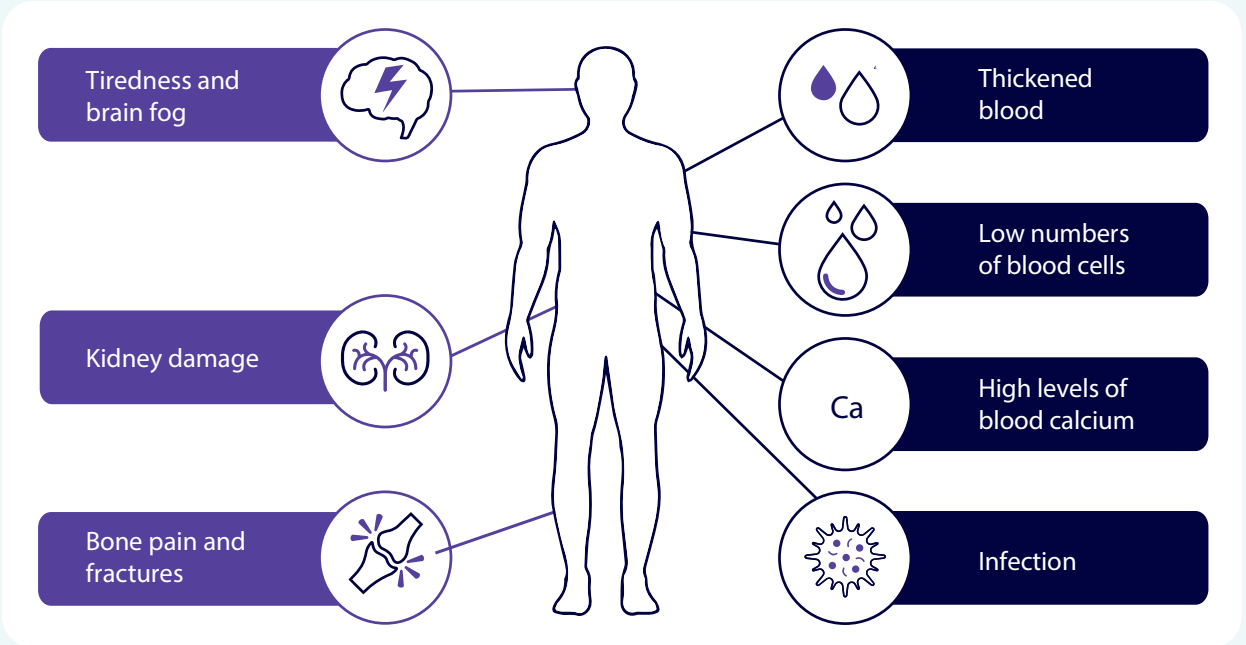

Bone marrow where blood cells including plasma cells are made
Bone
Blood supply
Normal plasma cells
Antibodies
Multiple myeloma cells (abnormal plasma cells)
M-proteins


Tiredness and brain fog
Kidney damage
Bone pain and fractures
Thickened blood
Low numbers of blood cells
Ca
High levels of blood calcium
Infection

What are the treatment options for multiple myeloma?

Patients with C.R.A.B. symptoms of active multiple myeloma are treated. This acronym stands for high levels of **c**alcium in the blood, kidneys not working properly (or **r**enal insufficiency that may cause symptoms such as swelling, extreme tiredness, or changes in urine production), low red blood cells (**a**nemia), and **b**one lesions.

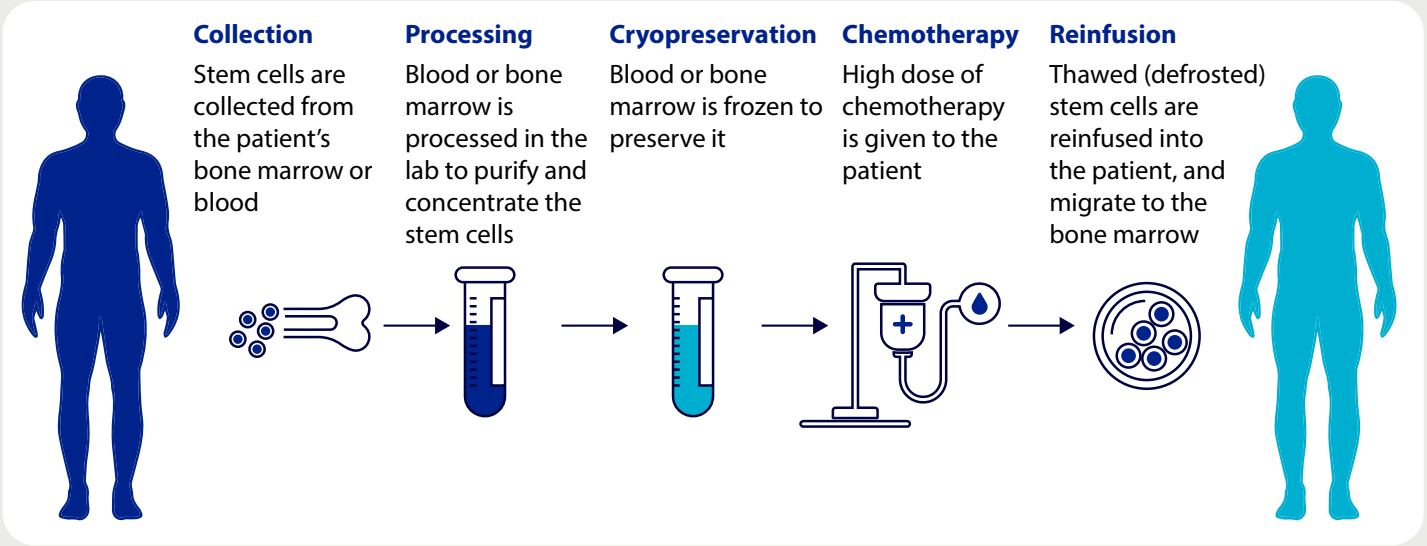
There are many different medicines available for people with multiple myeloma. These medicines kill the myeloma cells and are often given in combinations of between 2 to 5 drugs at a time.

The treatment of newly diagnosed multiple myeloma can be divided into three parts, and each has a different purpose:

- Initial therapy (induction): the goal is to get the active myeloma under control by reducing the levels of myeloma cells. It is the first phase of treatment.
- Consolidation therapy: the goal is to kill any remaining myeloma cells left behind after induction therapy.
- Maintenance therapy: the goal is to prevent the myeloma cells from coming back.

Doctors suggest the most appropriate treatments for an individual based on several factors including their age, how frail they are, how serious their myeloma is and if patients are fit enough for a stem cell transplant (a procedure called autologous stem cell transplantation) after induction therapy.

Autologous stem cell transplantation (also known as **ASCT**) is where people receive a high dose of chemotherapy to kill off as many myeloma cells in the bone marrow as possible. The dead myeloma bone marrow cells are then replaced with healthy bone marrow cells. These healthy cells are the patient's own bone marrow cells that were collected before they had the autologous stem cell transplantation procedure. Not all people with myeloma are able to have autologous stem cell transplantation. Generally only patients who are relatively young or fit are well enough to have this treatment.



Although there are many treatment options available, some people's multiple myeloma may get worse after a time of **controlled disease status** (relapse) or may stop responding to treatment (refractory). There are other treatments available for those patients, however, the focus in this study is treatment of newly diagnosed multiple myeloma.

ASCT: Autologous stem cell transplantation, which is when people receive a high dose of chemotherapy to kill off as many myeloma cells in the bone marrow as possible. The dead myeloma bone marrow cells are then replaced with healthy bone marrow cells.
Controlled disease status: When there is no sign of active disease in the body or bone marrow, and if there are myeloma cells, they remain at a very low level.

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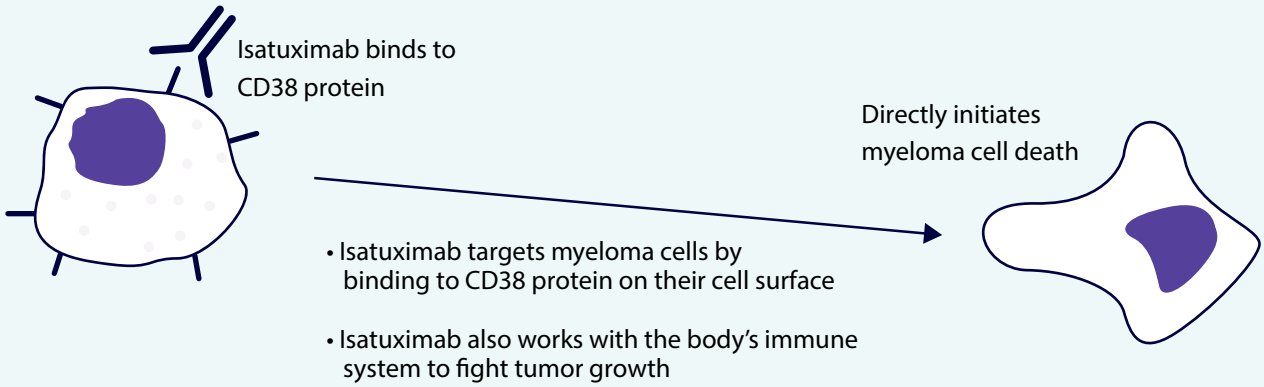
What is isatuximab?

Isatuximab (Isa) is a treatment for multiple myeloma. It is a protein, called a monoclonal antibody, that binds to the CD38 protein that is almost always present on the surface of myeloma cells.

Once Isatuximab has bound to the CD38 protein, it kills the myeloma cells by:

- Signaling to the body's immune system to kill the multiple myeloma cells.
- Triggering a chemical process in the myeloma cells, causing the myeloma cells to die.



What is carfilzomib, lenalidomide, and dexamethasone (KRd) treatment?

There is a combination of 3 drugs that is commonly used to treat multiple myeloma. These drugs are called carfilzomib (K), lenalidomide (R), and dexamethasone (d), and this combination is collectively known as KRd.

As this is a commonly used treatment combination, it is called a backbone therapy. Several studies are looking at how well adding other treatments, such as isatuximab, to backbone therapies like KRd works to treat multiple myeloma. The combination of isatuximab and KRd used in this study is called Isa-KRd.

What did this study look at?

In the GMMG-CONCEPT study, researchers looked at how well the Isa-KRd combination works as a treatment for people with high-risk, newly diagnosed multiple myeloma and to find out whether this treatment is feasible/safe.

What is high-risk, newly diagnosed multiple myeloma? Why was this study done in solely high-risk newly diagnosed multiple myeloma patients?

Some people with multiple myeloma have high-risk multiple myeloma. High-risk newly diagnosed multiple myeloma often comes back sooner after treatment and is more aggressive than multiple myeloma that is not high-risk (called standard-risk). Therefore, treatments that work well in patients with standard-risk myeloma may not work as well in high-risk newly diagnosed multiple myeloma.

There are differing definitions of high-risk newly diagnosed multiple myeloma in current practice because of specific features not everyone might have, like extramedullary disease which is when myeloma cells form tumors in soft tissues or organs (such as the lungs), or a condition called plasma cell leukemia. Plasma cell leukemia is a rare type of multiple myeloma where the cancerous plasma cells spread to the blood.

In this study, researchers considered a patients' multiple myeloma to be high-risk if it was stage 2 or 3 as measured by the International Staging System and the myeloma cells had certain pre-defined genetic changes (as shown in the figure). Patients with plasma cell leukemia in addition to the above high-risk definition were also included in the study.

International Staging System

- The International Staging System, or ISS for short, uses blood test results to classify patients' multiple myeloma as stages 1, 2, or 3:
  - Stage 1 is the least severe stage of multiple myeloma
  - Stage 2 is the intermediate stage of multiple myeloma
  - Stage 3 is the most severe stage of multiple myeloma

Genetic changes linked to high-risk newly diagnosed multiple myeloma

- Cancer cells often have changes in their genes and DNA
- There are 4 genetic changes that are often seen in the myeloma cells of people with high-risk multiple myeloma:
  - **del(17p)**: this is when part of **chromosome** 17 has been deleted
  - **t(4;14)**: this is when specific parts of chromosomes 4 and 14 have swapped places
  - **t(14;16)**: this is when specific parts of chromosomes 14 and 16 have swapped places
  - **amp(1q21)**: this is when there are extra copies of part of chromosome 1

People with high-risk newly diagnosed multiple myeloma may or may not be able to have stem cell transplant (called: transplant-ineligible or transplant non-eligible), depending on their fitness and age. Few studies have been carried out that focus on finding new treatments for people with high-risk newly diagnosed multiple myeloma. So very little is known about the best way to treat these patients.

The GMMG-CONCEPT study aimed to find a new effective treatment option for these patients.

Chromosome: Package of DNA containing genetic material.
Teaching hospital: A hospital that provides training for doctors and other medical professionals.

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Who took part in the study?

- In total, 153 people with multiple myeloma from 17 different **teaching hospitals** across Germany took part in the GMMG-CONCEPT study
- All of the participants had high-risk newly diagnosed multiple myeloma that had not been treated before

153 participants with high-risk newly diagnosed multiple myeloma

TE group (transplant eligible)
127 participants who were:
- eligible for **ASCT** and
- up to 70 years old

TNE group (transplant-non-eligible)
26 participants who were:
- not eligible for ASCT or
- over 70 years old

	TE Group 127 participants	TNE Group 26 participants
Median age	58 years	74 years
Sex of participants	53% were women; 47% were men	54% were women; 46% were men
ISS stage	54% had stage 2 myeloma; 46% had stage 3 myeloma	50% had stage 2 myeloma; 50% had stage 3 myeloma
Genetic changes	44% had del(17p); 42% had t(4;14); 17% had t(14;16); 31% had amp(1q21)	42% had del(17p); 23% had t(4;14); 8% had t(14;16); 54% had amp(1q21)
	Around 31% of participants had more than 1 genetic change	Around 27% of participants had more than 1 genetic change

What happened in the GMMG-CONCEPT study?

The GMMG-CONCEPT study investigating the Isa-KRd combination started in August 2017 and is still ongoing. The study tested if the combination of Isa-KRd was a safe treatment for people with high-risk newly diagnosed multiple myeloma. This article summarizes the findings of the study based on data collected up to December 1, 2022.

Isa-KRd treatment cycles

- Cancer treatment often happens in "cycles" where treatments are taken on specific days, and then each cycle is repeated a certain number of times
- In this study, each treatment cycle was 4 weeks long and was repeated a set number of times in each part of the study

	Isatuximab (Isa)	**Carfilzomib (K)**	**Lenalidomide (R)**	**Dexamethasone (d)**
How was the treatment given?	As an injection into a vein, also called an infusion		As a pill by mouth	
When was the treatment taken (induction and consolidation)?	On the 1st day of each week for 4 weeks. After that, on the 1st day of every other week	On the 1st and 2nd day of each week for 3 weeks	Every day for 3 weeks	On the 1st day of each week
When was the treatment taken (maintenance)?	On Days 1 and 15	On Days 1 and 15	Every day for 3 weeks	–
How many times was the treatment taken in each 4-week cycle?	4 times for the first cycle of therapy; 2 times for all cycles after the first cycle	6	21	4

	Part 1 Induction therapy (8 months)	**Part 2 Consolidation therapy (4 months)**	**Part 3 Maintenance therapy (up to 2 years)**
TE Group (transplant eligible) 127 participants	6 cycles of Isa-KRd treatment followed by ASCT procedure	4 cycles of Isa-KRd treatment	Up to 26 cycles of Isa-KR treatment
TNE Group (transplant non-eligible) 26 participants	8 cycles of Isa-KRd treatment	4 cycles of Isa-KRd treatment	Up to 26 cycles of Isa-KR treatment

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The GMMG-CONCEPT study took place in 3 parts:

1 Part 1: Initial therapy (induction)

- In the induction therapy part, participants in the transplant eligible group had 6 cycles of treatment with Isa-KRd. They then received high dose of chemotherapy followed by autologous stem cell transplantation to kill the myeloma cells in their bone marrow and introduce healthy bone marrow cells.
- Participants in the transplant non-eligible group did not have the autologous stem cell transplantation procedure. Instead, after completing the 6 cycles of Isa-KRd treatment, they were given 2 more cycles of Isa-KRd.

2 Part 2: Consolidation therapy

- In the consolidation therapy part of the study, all participants received 4 cycles of Isa-KRd (Isa was given every other week starting in cycle 2).
- Participants in the transplant eligible group could start this part of the study when they had recovered from the autologous stem cell transplantation procedure.

3 Part 3: Maintenance

- During the maintenance part of the study, the participants did not take dexamethasone. They continued to take all the other treatments as they had in earlier parts of the study for up to 26 cycles, but at lower doses.
- The participants stopped taking treatments when they completed the study or left the study early due to:
  - » side effects
  - » worsening of their myeloma
  - » if they or their doctor felt they should stop the study, or
  - » death

How did investigators determine which patients did well in the study?

Although 127 participants were enrolled in the transplant eligible cohort, and 26 were enrolled in the transplant non-eligible cohort, researchers had determined beforehand that only 99 participants in the transplant eligible cohort were needed for statistical purposes to show that Isa-KRd was effective.

The researchers measured the proportion of people who had 'no detectable levels' of myeloma cells left while on treatment. This means that a person has too few myeloma cells (less than 1 myeloma cell every 100,000 cells) in their bone marrow to show up in this test. This is also called MRD negativity. It has been shown that in general, people who have minimal residual disease negativity tend to live longer as well as go for longer periods of time without worsening disease.

- Minimal residual disease, or MRD for short, is used to measure how effective a treatment has been.
- Doctors measure MRD by taking a sample of bone marrow and measuring the number of cancer cells compared with healthy cells in the sample.
- MRD positivity means that there are still some cancer cells left after treatment.
- MRD negativity means that there are so few cancer cells (1 myeloma cell every 100,000 cells) left after treatment that the test cannot detect them.

Minimal residual disease results

- MRD was measured at the end of Part 2 of the study (consolidation therapy) and then every 6 months during Part 3 (maintenance therapy)
- MRD was measured earlier during Part 1 or 2 if a participant's blood tests showed they had a very good partial response to treatment or better

TE Group
(transplant eligible)
99 participants

68% had no myeloma cells in their bone marrow at the end of Part 2 of the study

82% had no myeloma cells in their bone marrow at some point during the study

Of these patients:

73% still had no myeloma cells in their bone marrow after 6 months

63% still had no myeloma cells in their bone marrow after 12 months

TNE Group
(transplant non-eligible)
26 participants

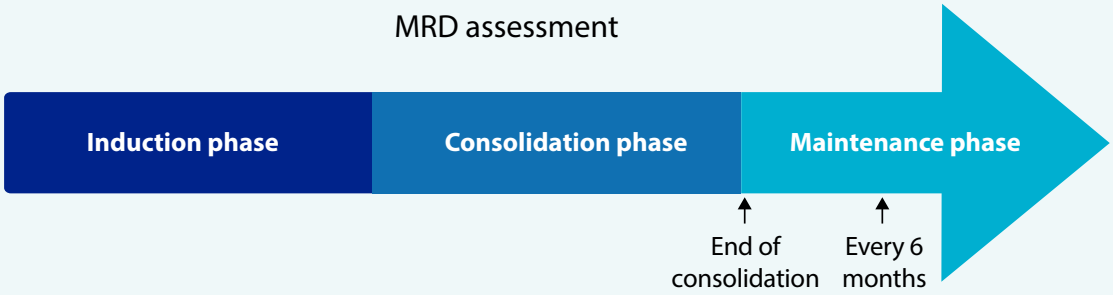
54% had no myeloma cells in their bone marrow at the end of Part 2 of the study

69% had no myeloma cells in their bone marrow at some point during the study

Of these patients:

54% still had no myeloma cells in their bone marrow after 6 months

46% still had no myeloma cells in their bone marrow after 12 months



The researchers determined the response to treatment, which is measured by comparing the following before and after treatment:

- the amount of myeloma protein in the blood and/or urine
- the percentage of myeloma cells in the bone marrow

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Treatment response	Signs of myeloma in blood and urine tests	Signs of myeloma in bone marrow
Stringent complete response	Complete response plus normal amounts of proteins called "light chains" that may be found in urine and in blood	No cancer cells in bone marrow
Complete response	No signs of myeloma in blood or urine tests	Less than 5% cancer cells in bone marrow
Very good partial response	Decrease of signs of myeloma in blood of 90% or more. Less than 100mg of signs of myeloma in urine	No change in bone marrow cancer cells
Partial response	Decrease of signs of myeloma in blood of 50% or more. Decrease of signs of myeloma to less than 200mg in urine or decrease of 90% or more	No change in bone marrow cancer cells

Response to treatment results

- Response rates were assessed at several times during the study. Response rates improved the longer that participants took the study treatment. The results below are the best response rates until the end of Part 2 (consolidation therapy) of the study
- These findings mean that an overall 94.9% of TE group participants and 88.5% of TNE group participants showed a response to treatment

TE Group (transplant eligible) 99 participants

- 17% had a stringent complete response
- 56% had a complete response
- 18% had a very good partial response
- 4% had a partial response

TNE Group (transplant non-eligible) 26 participants

- 31% had a stringent complete response
- 27% had a complete response
- 31% had a very good partial response
- 0% had a partial response

- Another way that researchers measure how well a treatment works is to measure the average length of time it took between the participants joining the study until their cancer got worse or they died. This is called progression-free survival.
- **Median progression-free survival** is the middle value in the time it takes for half the participants to either die, or for their disease to get worse, from the time they joined the study. For the median to be calculated, the times are listed from shortest to longest, and the middle value is found.
- **Median overall survival** is the middle value in the total amount of time people lived during the study, even if their cancer got worse. For the median to be calculated, the times are listed from shortest to longest, and the middle value is found.

Median: For the median to be calculated, data are listed from shortest to longest, and the middle value is found.

Progression-free survival results

- The researchers have not been able to find the median progression-free survival for the TE or TNE groups, because most of the patients in both groups are alive and their disease did not get worse
- The median time the participants have been in the study is:

3 years, 8 months in the TE group

2 years, 9 months in the TNE group

Overall survival results

- The researchers have not been able to find the median overall survival for the transplant eligible or transplant non-eligible groups, because most of the patients in both groups are alive.

What were the most common side effects of Isa-KRd?

The researchers monitored for side effects of Isa-KRd in all participants that received at least one treatment. In both groups, the most common side effects were low blood cell counts and infections, which is as expected from the disease and myeloma treatments of similar drug combinations.

Overall, most of the side effects of Isa-KRd treatment did not last long or were easily treated. The table below shows the proportion of participants in each group who had severe side effects.

Side effects involving the blood

	TE Group (transplant eligible) 97 participants	TNE Group (transplant non-eligible) 25 participants
Low levels of a type of white blood cell called neutrophils	51%	28%
Low levels of blood cells called platelets, which help with blood clotting and to stop or slow bleeding	31%	20%
Low levels of white blood cells, also called leukocytes	26%	4%
Low levels of red blood cells or a protein called hemoglobin	16%	12%

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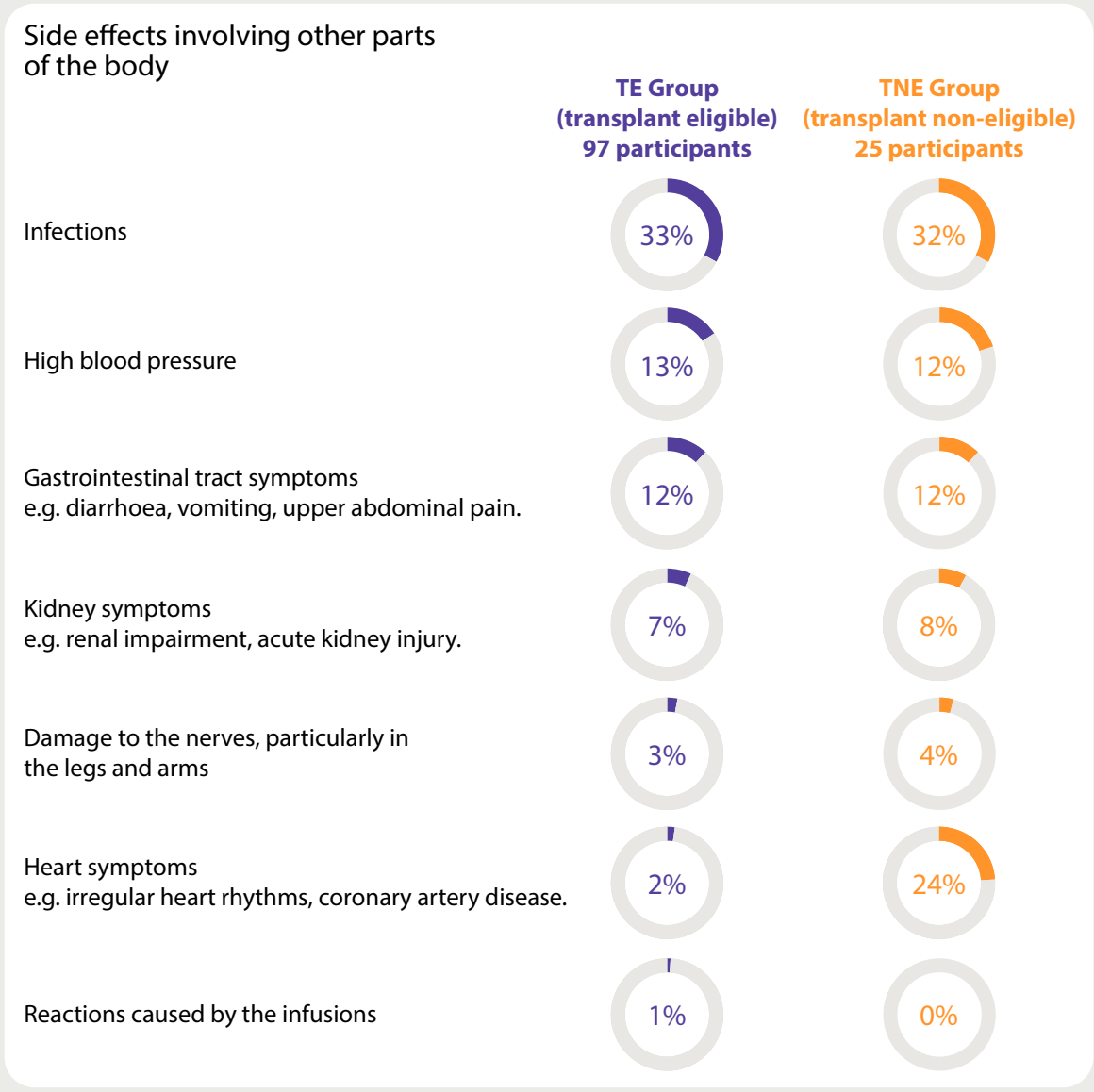

What do these results mean?

For many patients, Isa-KRd treatment reduces the number of myeloma cells in patients with high-risk newly diagnosed multiple myeloma. The majority of participants had no detectable myeloma cells left in their bone marrow while on treatment. For many patients, this effect lasted for 12 months or more. This treatment effect was seen in both participants who were eligible for an autologous stem cell transplantation, and in those who were not eligible.

In both groups, more than half of the participants had a complete or stringent complete response to treatment. Researchers have not been able to calculate the median progression-free survival of patients in the study because most are still alive and their myeloma has not progressed. Researchers have not been able to calculate the median overall survival of patients in the study because most are still alive.

Most of the side effects the participants had were either easily treated or went away quickly. The most common severe side effects in both groups were low blood counts and infections.

Where can I find more information on this study?

- The full title of this article is: Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma
- The full citation for the article is: Leypoldt et al. *J Clin Oncol.* 2023 Sep 27:JCO2301696. doi: 10.1200/JCO.23.01696. Epub ahead of print.
- You can access the full article for free here: https://ascopubs.org/doi/full/10.1200/JCO.23.01696
- More information about this study can be found here: https://clinicaltrials.gov/study/NCT03104842
- The start date of this study was 15 August 2017, and the last patient was included in November 2022. The study is currently ongoing.

Further information and educational resources

- International Myeloma Foundation: https://www.myeloma.org/
- Myeloma UK: https://www.myeloma.org.uk/
- Mayo Clinic: https://www.mayoclinic.org/diseases-conditions/multiple-myeloma
- MacMillan Cancer Support: https://www.macmillan.org.uk/
- Myeloma Patients Europe: https://www.mpeurope.org/

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Declaration of interest

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Author contributions

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