Aus dem Institut für Öffentliches Gesundheitswesen

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Daratumumab mit antineoplastischer Therapie verglichen mit alleiniger antineoplastischer Therapie bei Menschen mit neu diagnostiziertem Multiplen Myelom, die nicht für eine Hochdosistherapie mit autologer Stammzelltransplantation geeignet sind – eine Cochrane Übersichtsarbeit

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Abkürzungsverzeichnis

Abkürzung	Definition
CD	Cluster of Differentiation. Oberflächenmarkermoleküle von Zellen
CRAB	Hypercalcaemia, renal insufficiency, anaemia, bone lesions. Hyperkalzämie, Niereninsuffizienz, Anämie, Osteolyse(n)
CTCAE	Common Terminology Criteria for Adverse Events. Allgemeine Terminologiekriterien von unerwünschten Ereignissen
EORTC-QLQ C30	European Organisation for Research and Treatment of Cancer-Quality of life questionnaire, containing 30 questions. Ein Fragebogen zur Erfassung der Lebensqualität, bestehend aus 30 Fragen
GRADE	Grading of Recommendations, Assessment, Development and Evaluation. Bewertung von Empfehlungen, Entwicklung und Auswertung.
IgG	Immunglobulin G (Hauptbestandteil der Gammaglobulin-Fraktion der Serumelektrophorese)
IMWG	International Myeloma Working Group. Internationale Myelom Arbeitsgruppe
ISS	International Staging System. Internationales System der Stadieneinteilung
kDa	Kilodalton
M-Protein	Paraprotein = monoklonales Protein
MGUS	Monoklonale Gammopathie unklarer Signifikanz
PRISMA	Preferred reporting items for systematic reviews and meta-analyses. Bevorzugte Berichtselemente für systematische Übersichten und Meta-Analysen
SLiM	S wie sixty: ≥ 60% klonale Plasmazellen im Knochenmark; Li wie Light Chains: freie Leichtketten-Ratio (betroffen/ nicht-betroffen) ≥ 100; M wie MRT: > 1 fokale Läsion in einer Magnetresonanztomographie-Bildgebung
WHO	World Health Organization. Weltgesundheitsorganisation

1. Zusammenfassung

Als maligne hämatologische Erkrankung ist das Multiple Myelom durch die Vermehrung von bösartigen Plasmazellen im Knochenmark gekennzeichnet. Erwachsene Teilnehmer, die für eine hochdosierte Chemotherapie und eine autologe Stammzelltransplantation nicht geeignet sind, erhalten als Erstlinientherapie in der Regel Kombinationen aus alkylierenden Substanzen, immunmodulatorischen Medikamenten und Proteasom-Inhibitoren. Daratumumab, ein humaner monoklonaler IgG1κ-Antikörper, richtet sich gezielt gegen das Oberflächenmolekül CD38, das von Myelomzellen überexprimiert wird. Es wurde speziell für die Behandlung des Multiplen Myeloms entwickelt und zugelassen. Bei der Behandlung eines rezidivierten oder refraktären Multiplen Myeloms wurden bereits signifikante Vorteile nachgewiesen.[1-3]

Auf Grundlage der bisher erlangten Erkenntnisse sollte mit dieser Übersichtsarbeit herausgefunden werden, ob für Studienteilnehmer mit einem neu diagnostizierten Multiplen Myelom, die nicht für eine Hochdosistherapie mit Stammzelltransplantation geeignet sind, durch die additive Gabe von Daratumumab zur bisherigen antineoplastischen Therapie Vor- oder Nachteile entstehen. Hierzu erfolgte eine Metaanalyse, die als Cochrane Übersichtsarbeit veröffentlicht wurde. Insgesamt wurden vier Studien mit insgesamt 1783 Teilnehmern eingeschlossen.[3]

In den Analysen wurden klinisch relevante Endpunkte wie das Gesamtüberleben, das progressionsfreie Überleben, die Lebensqualität, die studienbegleitende Mortalität als auch unerwünschte Ereignisse hervorgehoben.

Nach dem internationalen GRADE Schema war die Vertrauenswürdigkeit in die Evidenz für die Endpunkte Gesamtüberleben und progressionsfreies Überleben moderat – hier zeigte sich eine wahrscheinliche Verbesserung in der Daratumumab-basierten Teilnehmergruppe. Bei niedriger Vertrauenswürdigkeit in die Evidenz konnte für die Lebensqualität zwischen den Teilnehmergruppen ein sehr leichter Vorteil in der Daratumumab-basierten Therapiegruppe berichtet werden. Für den Endpunkt studienbegleitende Mortalität konnte bei moderater Vertrauenswürdigkeit in die Evidenz eine wahrscheinliche Reduzierung in der Therapie mit Daratumumab verzeichnet werden. Schwerwiegende unerwünschte Ereignisse traten bei moderater Vertrauenswürdigkeit in die Evidenz in der Behandlung mit Daratumumab wahrscheinlich häufiger auf. Für den Endpunkt unerwünschte Ereignisse (CTCAE Grad ≥ 3) stellte sich bei moderater Vertrauenswürdigkeit in die Evidenz kaum ein Unterschied zwischen den Therapiegruppen dar. Ein wahrscheinlich erhöhtes Risiko bei moderater Vertrauenswürdigkeit in die Evidenz trat hingegen für Infektionen (CTCAE Grad ≥ 3) in der Therapie mit Daratumumab auf.[3]

Obwohl die mediane Gesamtüberlebenszeit noch nicht erreicht ist, deutet das Hazard Ratio auf einen klaren Vorteil für die Daratumumab Therapie hin. Vor Beginn einer Therapie sollte

vom Kliniker gemeinsam mit dem Patienten das Risiko von Infektionen individuell besprochen werden. Sechs weitere derzeit laufende Studien können in Zukunft die Aussagekraft dieser Übersichtsarbeit erhöhen.[3]

2. Einleitung

2.1. Das Multiple Myelom

Das Multiple Myelom ist eine bösartige hämatologische Erkrankung, die durch die Proliferation maligner Plasmazellen im Knochenmark charakterisiert ist. Asymptomatische Vorstufen sind die Monoklonale Gammopathie unklarer Signifikanz (MGUS) wie auch das sich hieraus entwickelnde schwelende (smouldering) Multiple Myelom.[4] Pathophysiologisch kommt es beim Multiplen Myelom zu einer vermehrten Produktion abnormaler (monoklonaler) Immunglobuline.[1] Als klonal vermehrte freie Leichtketten können sie im Blut und im Urin nachgewiesen werden. Blut- und Urintests sind daher eine Methode zur Erkennung und Überwachung des Multiplen Myeloms. Durch die Verdrängung der normalen Hämatopoese zeichnet sich die Erkrankung symptomatisch durch Anämie, Leukopenie, einem damit einhergehenden Antikörpermangelsyndrom und assoziierten sekundären Immundefekten aus. Daraus resultiert ein erhöhtes Risiko für Infektionen.[5] Hinzu kommen frakturgefährdete Osteolysen mit Osteopenie und infolgedessen eine Hyperkalzämie.[6] Durch die glomeruläre Filtration der übermäßig produzierten Immunglobulin-Leichtketten und damit einhergehenden Ablagerung in den Nierentubuli, kann es zu einer Myelomniere (Cast-Nephropathie) und somit zu einer schweren Niereninsuffizienz kommen.[7,8] Die Diagnosekriterien für das Multiple Myelom wurden von der International Myeloma Working Group (IMWG) definiert und im Jahr 2014 überarbeitet.[3]

2.2. Epidemiologie

Aus epidemiologischer Sicht ist hervorzuheben, dass die Inzidenz des Multiplen Myeloms auf globaler Ebene von 1990 bis 2016 um 126% und die Zahl der auf das Multiple Myelom zurückzuführenden Todesfälle um 94% zugenommen hat. Der Anstieg der Inzidenzfälle um 126% ist mit 40,4% auf das Bevölkerungswachstum, mit 52,9% auf die Alterung der Weltbevölkerung und mit 32,6% auf den Anstieg der altersspezifischen Inzidenzraten zurückzuführen.[9] Die höchste globale Inzidenz des Multiplen Myeloms findet sich in den Regionen mit einem hohen Einkommen, hier mit einer altersstandardisierten Inzidenz von 4.3 pro 100.000 Personen, während in den einkommensschwachen Regionen eine altersstandardisierte Inzidenz von 1.2 pro 100.000 Personen zu verzeichnen ist.[9] Die 5-Jahres-Überlebensrate liegt bei unter 50%. Daten aus dem Vereinigten Königreich belegen, dass sich die 10-Jahres Überlebensrate in den letzten 40 Jahren von 6% auf 33% vervierfacht hat.[10]

2.3. Therapieoptionen

Die Behandlung von Menschen mit neu diagnostiziertem Multiplen Myelom richtet sich nach den SLiM-CRAB-Kriterien der IMWG, dem Grad der Fitness und den persönlichen

Wünschen des Betroffenen. Ist die Person gesundheitlich dazu in der Lage, besteht die empfohlene Erstlinientherapie aus einer Induktions-Chemotherapie, gefolgt von einer Hochdosis-Chemotherapie mit autologer Stammzelltransplantation.[11] Aufgrund von Komorbiditäten oder Gebrechlichkeit sind einige Menschen mit Multiplem Myelom für eine Hochdosis-Chemotherapie mit anschließender autologer Stammzelltransplantation nicht geeignet.[9] Für diese Menschen wird eine Therapie empfohlen, die aus zwei, drei oder mehr Wirkstoffkombinationen besteht. Eine empfohlene Erstlinientherapie umfasst Thalidomid, ein immunmodulatorisches Medikament, kombiniert mit einem Alkylierungsmittel, wie Melphalan oder Cyclophosphamid, und einem Kortikosteroid, wie Prednisolon oder Dexamethason.[12] Bei Kontraindikationen gegen Thalidomid kann die Person stattdessen Bortezomib erhalten.[13] Eine weitere Erstlinientherapie ist Lenalidomid als immunmodulatorisches Medikament in Kombination mit Dexamethason.[14] Ziel der Behandlung ist es, die Krankheit so lange wie möglich zu stabilisieren, was als Plateauphase bezeichnet wird.

2.4. Daratumumab

Daratumumab ist ein Medikament, das sich gegen das Protein CD-38 auf Zelloberflächen richtet. Myelomzellen überexprimieren einheitlich CD-38, ein 46-kDa-Typ-II-Transmembranglykoprotein, was diese maligne entartete Zellen zu einem spezifischen Ziel für Daratumumab macht.[15] Daratumumab als humaner monoklonaler IgG1κ-Antikörper zeigt hierüber vielversprechende Wirkmechanismen zur Bekämpfung der Myelomzellen. Neben der direkten Induktion einer Apoptose führt Daratumumab zu einer Zytotoxizität durch die Aktivierung des Komplementsystems wie auch zu einer Antikörper-abhängigen zellulären Phagozytose.[16] Daratumumab löst darüber hinaus die Aktivierung und klonale Expansion zytotoxischer T-Zellen aus, was eine unterstützende Wirkung gegen die Erkrankungen zeigen kann.[17] Für die Behandlung von Patienten mit rezidiviertem oder refraktärem Multiplen Myelom wurde Daratumumab bereits zugelassen.[18] In diversen unterschiedlichen Studien konnten positive Effekte zugunsten der Kohorten, die Daratumumab erhalten haben, nachgewiesen werden. Definierte Endpunkte wie das Gesamtüberleben, das progressionsfreie Überleben und die Ansprechraten zeigten Vorteile in den Daratumumab-behandelten Kohorten.[1,2,19]

2.5. Ziel und Fragestellung der Arbeit

Das Ziel der Arbeit bestand darin, eine klinisch relevante Übersichtsarbeit zu erstellen, die wichtige Erkenntnisse für die klinische Praxis und die Gesundheitsversorgung beim Multiplen Myelom liefert. Daratumumab konnte in der Behandlung eines rezidivierten oder refraktären Multiplen Myeloms bemerkenswerte Vorteile erzielen.[1-3] Es galt herauszufinden, inwieweit erwachsene Personen mit einem neu diagnostizierten Multiplen Myelom, die nicht

für eine Hochdosistherapie mit Stammzelltransplantation in Frage kommen, durch eine ergänzende Therapie mit Daratumumab profitieren. Darüber hinaus erfolgte eine Beurteilung der potenziellen Nebenwirkungen, die für eine klinische Entscheidungsfindung einer Therapie entscheidend sind.

3. Material und Methoden

Wie in der folgenden Publikation dargestellt, wurde zur Beantwortung der Fragestellung eine systematische Übersichtsarbeit mit Metaanalyse ausgewählt. Diese orientierte sich an den internationalen PRISMA Kriterien. Die Arbeit wurde in der Cochrane Library veröffentlicht.[3]

3.1. Studientypen

In diese Übersichtsarbeit wurden ausschließlich randomisiert kontrollierte Studien eingeschlossen. Erfasst wurden Volltexte, Kurzfassungen von Veröffentlichungen und Studien, die in Studienregistern gemeldet wurden, sofern ausreichende Informationen zum Studiendesign, zu den Merkmalen der Teilnehmer und zu den Behandlungsmethoden zur Verfügung standen.[3]

3.2. Studienteilnehmer

Studienteilnehmer waren erwachsene Personen mit einem neu diagnostizierten Multiplen Myelom, die nicht für eine Hochdosistherapie mit Stammzelltransplantation geeignet waren. Es gab keine Einschränkungen hinsichtlich des Geschlechts oder der ethnischen Zugehörigkeit. Studien mit weniger als 80% erwachsenen Teilnehmern wurden ausgeschlossen, es sei denn, es gab Subgruppenanalysen von Erwachsenen mit Multiplem Myelom.[3]

3.3. Behandlungsmethoden

Eine Gruppe der Teilnehmer erhielt eine Kombination der bisher empfohlenen antineoplastischen Therapie, während die andere Gruppe zu der gleichen Therapie zusätzlich Daratumumab erhielt. Die Teilnehmer beider Studienarme sollten dieselbe antineoplastische Therapie erhalten haben, wie z.B. denselben Alkylierungswirkstoff (z.B. Cyclophosphamid, Melphalan), Proteasominhibitor (z.B. Bortezomib), immunmodulatorischen Wirkstoff (z.B. Lenalidomid, Thalidomid) oder Glukokortikoide (z.B. Dexamethason, Prednison), in derselben Wirkstoffkombination, Dosis und Anzahl der Zyklen.[3]

3.4. Studienendpunkte

Zu den hervorgehobenen Endpunkten gehörten das Gesamtüberleben, das progressionsfreie Überleben, die Lebensqualität, die studienbegleitende Mortalität sowie unerwünschte Ereignisse. Hinsichtlich der unerwünschten Ereignisse wurde sich auf die Auswertung von schwerwiegenden unerwünschten Ereignissen sowie von häufigen unerwünschten Ereignissen dritten Grades oder höher beschränkt. Anhand von Kriterien wurde für jede Studie das potenzielle Maß einer Verzerrung bewertet. Für den primären

Endpunkt des Gesamtüberlebens wurden verschiedene Subgruppen verglichen. Dabei wurden zwei Subgruppen basierend auf zytogenetischem Risiko gebildet: eine mit hohem Risiko und eine mit Standardrisiko. Zusätzlich wurden drei Subgruppen nach dem International Staging System (ISS) gebildet: ISS I, ISS II und ISS III.[3]

3.5. Suchmethoden zur Identifizierung von Studien

Es wurden unterschiedliche Quellen wie die Datenbanken für medizinische Literatur, mehrere Studienregister, Konferenzberichte von verschiedenen Jahrestagungen und andere Quellen elektronisch und manuell durchsucht. Eine weitere Autorin und ich prüften unabhängig voneinander die Ergebnisse auf ihre Eignung für diese Übersichtsarbeit.

4. Publikation als Cochrane Übersichtsarbeit

Cochrane Library

Cochrane Database of Systematic Reviews

Daratumumab and antineoplastic therapy versus antineoplastic therapy only for adults with newly diagnosed multiple myeloma ineligible for transplant (Review)

Langer P, John L, Monsef I, Scheid C, Piechotta V, Skoetz N

Langer P, John L, Monsef I, Scheid C, Piechotta V, Skoetz N.
Daratumumab and antineoplastic therapy versus antineoplastic therapy only for adults with newly diagnosed multiple myeloma ineligible for transplant.
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[Intervention Review]

Daratumumab and antineoplastic therapy versus antineoplastic therapy only for adults with newly diagnosed multiple myeloma ineligible for transplant

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ABSTRACT

Background

Multiple myeloma (MM) is a haematological malignancy that is characterised by proliferation of malignant plasma cells in the bone marrow. For adults ineligible to receive high-dose chemotherapy and autologous stem cell transplant, the recommended treatment combinations in first-line therapy generally consist of combinations of alkylating agents, immunomodulatory drugs, and proteasome inhibitors. Daratumumab is a CD38-targeting, human IgG1k monoclonal antibody recently developed and approved for the treatment of people diagnosed with MM. Multiple myeloma cells uniformly over-express CD-38, a 46-kDa type II transmembrane glycoprotein, making myeloma cells a specific target for daratumumab.

Objectives

To determine the benefits and harms of daratumumab in addition to antineoplastic therapy compared to antineoplastic therapy only for adults with newly diagnosed MM who are ineligible for transplant.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, EU Clinical Trials Register, ClinicalTrials.gov, WHO ICTRP, and conference proceedings from 2010 to September 2023.

Selection criteria

We included randomised controlled trials that compared treatment with daratumumab added to antineoplastic therapy versus the same antineoplastic therapy alone in adult participants with a confirmed diagnosis of MM. We excluded quasi-randomised trials and trials with less than 80% adult participants, unless there were subgroup analyses of adults with MM.

Data collection and analysis

Two review authors independently screened the results of the search strategies for eligibility. We documented the process of study selection in a flowchart as recommended by the PRISMA statement. We evaluated the risk of bias in included studies with RoB 1 and assessed the certainty of the evidence using GRADE. We followed standard Cochrane methodological procedures.

Main results

We included four open-label, two-armed randomised controlled trials (34 publications) involving a total of 1783 participants. The ALCYONE, MAIA, and OCTANS trials were multicentre trials conducted worldwide in middle- and high-income countries. The AMaRC 03-16 trial was conducted in one high-income country, Australia. The mean age of participants was 69 to 74 years, and the proportion of female participants was between 40% and 54%.

All trials evaluated antineoplastic therapies with or without daratumumab. In the ALCYONE and OCTANS trials, daratumumab was combined with bortezomib and melphalan-prednisone. In the AMaRC 03-16 study, it was combined with bortezomib, cyclophosphamide, and dexamethasone, and in the MAIA study, it was combined with lenalidomide and dexamethasone.

None of the included studies was blinded (high risk of performance and detection bias). One study was published as abstract only, therefore the risk of bias for most criteria was unclear. The other three studies were published as full texts. Apart from blinding, the risk of bias was low for these studies.

Overall survival

Treatment with daratumumab probably increases overall survival when compared to the same treatment without daratumumab (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.53 to 0.76, 2 studies, 1443 participants, moderate-certainty evidence). After a follow-up period of 36 months, 695 per 1000 participants survived in the control group, whereas 792 per 1000 participants survived in the daratumumab group (95% CI 758 to 825).

Progression-free survival

Treatment with daratumumab probably increases progression-free survival when compared to treatment without daratumumab (HR 0.48, 95% CI 0.39 to 0.58, 3 studies, 1663 participants, moderate-certainty evidence). After a follow-up period of 24 months, progression-free survival was reached in 494 per 1000 participants in the control group versus 713 per 1000 participants in the daratumumab group (95% CI 664 to 760).

Quality of life

Treatment with daratumumab may result in a very small increase in quality of life after 12 months, evaluated on the EORTC QLQ-C30 global health status scale (GHS), when compared to treatment without daratumumab (mean difference 2.19, 95% CI −0.13 to 4.51, 3 studies, 1096 participants, low-certainty evidence). The scale is from 0 to 100, with a higher value indicating a better quality of life.

On-study mortality

Treatment with daratumumab probably decreases on-study mortality when compared to treatment without daratumumab (risk ratio (RR) 0.72, 95% CI 0.62 to 0.83, 3 studies, 1644 participants, moderate-certainty evidence). After the longest follow-up available (12 to 72 months), 366 per 1000 participants in the control group and 264 per 1000 participants in the daratumumab group died (95% CI 227 to 304).

Serious adverse events

Treatment with daratumumab probably increases serious adverse events when compared to treatment without daratumumab (RR 1.18, 95% CI 1.02 to 1.37, 3 studies, 1644 participants, moderate-certainty evidence). After the longest follow-up available (12 to 72 months), 505 per 1000 participants in the control group versus 596 per 1000 participants in the daratumumab group experienced serious adverse events (95% CI 515 to 692).

Adverse events (Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3)

Treatment with daratumumab probably results in little to no difference in adverse events (CTCAE grade ≥ 3) when compared to treatment without daratumumab (RR 1.01, 95% CI 0.99 to 1.02, 3 studies, 1644 participants, moderate-certainty evidence). After the longest follow-up available (12 to 72 months), 953 per 1000 participants in the control group versus 963 per 1000 participants in the daratumumab group experienced adverse events (CTCAE grade ≥ 3) (95% CI 943 to 972).

Treatment with daratumumab probably increases the risk of infections (CTCAE grade ≥ 3) when compared to treatment without daratumumab (RR 1.52, 95% CI 1.30 to 1.78, 3 studies, 1644 participants, moderate-certainty evidence). After the longest follow-up available (12 to 72 months), 224 per 1000 participants in the control group versus 340 per 1000 participants in the daratumumab group experienced infections (CTCAE grade ≥ 3) (95% CI 291 to 399).

Authors' conclusions

Overall analysis of four studies showed a potential benefit for daratumumab in terms of overall survival and progression-free survival and a slight potential benefit in quality of life. Participants treated with daratumumab probably experience increased serious adverse events. There were likely no differences between groups in adverse events (CTCAE grade ≥ 3); however, there are probably more infections (CTCAE grade ≥ 3) in participants treated with daratumumab.

We identified six ongoing studies which might strengthen the certainty of evidence in a future update of this review.

PLAIN LANGUAGE SUMMARY

What are the benefits and harms of daratumumab in addition to antimyeloma medicines compared to antimyeloma medicines only for adults with newly diagnosed multiple myeloma who aren't suited for stem cell transplant?

Key messages

• Research shows that in adults with multiple myeloma, adding a newer medicine called daratumumab to standard antimyeloma treatments probably helps people live longer than treatment with standard antimyeloma treatments alone.

• Adding daratumumab probably increases the chance of serious adverse events, but probably not the chance of overall adverse events defined as Common Terminology Criteria for Adverse Events (CTCAE) of grade ≥ 3.

• Treatment with daratumumab probably increases the chance of infections.

What is multiple myeloma?

Multiple myeloma is a type of blood cancer. The disease is caused when abnormal plasma cells, a type of white blood cell in the bone marrow, multiply uncontrollably. Multiple myeloma is a life-threatening condition.

How is multiple myeloma treated in adults with newly diagnosed disease who cannot have a stem cell transplant?

Adults with newly diagnosed multiple myeloma who aren't suited for a stem cell transplant (a procedure where damaged blood cells are replaced with healthy ones) receive treatment consisting of multiple-drug combinations of medicines.

What did we want to find out?

Daratumumab is a newly developed medicine that causes the death of myeloma cells. The addition of daratumumab has been approved for people who have already tried other treatments for multiple myeloma but whose disease returned or never got any better. We wanted to find out if daratumumab added to antimyeloma medicines shows advantages or disadvantages in adults with newly diagnosed multiple myeloma who aren't suited for a stem cell transplant when compared to antimyeloma medicines alone.

What did we do?

We searched for studies that compared the benefits and harms of daratumumab plus antimyeloma medicines with the same antimyeloma medicines alone in adults with a newly confirmed diagnosis of multiple myeloma who were not suitable for high-dose chemotherapy with stem cell transplantation. We compared and summarised the results, and rated our confidence in the evidence.

What did we find?

We found four studies involving a total of 1783 adults (females and males) with confirmed newly diagnosed multiple myeloma who were unsuitable for stem cell transplantation. The average age of participants in three studies was 69 to 74 years.

Treatment with daratumumab probably increases how long people live. At 36 months after treatment, 695 of 1000 people who received antimyeloma treatment alone and 792 of 1000 people who received the same treatment plus daratumumab were still alive.

Treatment with daratumumab probably increases the length of time that multiple myeloma does not get any worse. At 24 months after treatment, 494 of 1000 people who received antimyeloma treatment alone and 713 of 1000 people who received the same treatment plus daratumumab had disease that did not get worse.

Treatment with daratumumab may slightly improve quality of life at 12 months, but we have little confidence in this result. The daratumumab group was 2.19 higher on a 0-to-100 scoring system than the antimyeloma treatment-alone group.

Treatment with daratumumab probably increases the chance of serious adverse events (treatment-related health problems that result in hospitalisation or that are life-threatening). After the longest follow-up available (12 to 72 months), 505 of 1000 people in the antimyeloma treatment-alone group and 596 of 1000 people in the daratumumab group experienced serious adverse events.

There is likely little or no difference between groups in overall adverse events (CTCAE grade ≥ 3). After the longest follow-up available (12 to 72 months), 953 of 1000 people in the antimyeloma treatment-alone group and 963 of 1000 people in the daratumumab group experienced adverse effects (CTCAE grade ≥ 3).

Treatment with daratumumab probably increases the risk of infections (CTCAE grade ≥ 3). After the longest follow-up available (12 to 72 months), 224 of 1000 people in the antimyeloma treatment-alone group and 340 of 1000 people in the daratumumab group had infections (CTCAE grade ≥ 3).

What are the limitations of the evidence?

We are moderately confident in the evidence about how long people live because of incomplete data in one trial.

We are moderately confident in the evidence about the length of time after treatment that multiple myeloma doesn't get worse, serious adverse events, adverse events (CTCAE grade ≥ 3), and infections (CTCAE grade ≥ 3). This was due to the possibility that participants and personnel in the studies were aware of the treatment given, which could have influenced the results, and because the findings for serious adverse events were very different across the included studies.

We have little confidence in the evidence about quality of life due to the possibility that participants and personnel in the studies were aware of the treatment given, which could have influenced the results, and because of the small study sizes.

How up-to-date is this evidence?

The evidence is current to September 2023. Several new studies of daratumumab are ongoing that may provide more information about the possible benefits and harms of daratumumab for multiple myeloma. We will update this review when those studies are finished.

Summary of findings 1. Summary of findings table - Daratumumab plus standard therapy compared to standard therapy for people with newly diagnosed multiple myeloma ineligible for transplant

Daratumumab plus standard therapy compared to standard therapy for people with newly diagnosed multiple myeloma ineligible for transplant

Patient or population: people with newly diagnosed multiple myeloma ineligible for transplant
Setting: mostly inpatient; mostly multicentre studies across Europe, Asia, North and South America, Australia and the Pacific region
Intervention: daratumumab plus standard therapy
Comparison: standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard therapy	Risk with daratumumab plus standard therapy				
Overall survival (at 36 months)	Study population		**HR 0.64** (0.53 to 0.76) []	1443 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	Control risk calculated out of both studies (ALCYONE; MAIA) at 36 months.
	695 per 1000	**792 per 1000** (758 to 825)				
Progression-free survival (at 24 months)	Study population		**HR 0.48** (0.39 to 0.58) []	1663 (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	Control risk calculated out of 3 studies (ALCYONE; MAIA; OCTANS) at 24 months.
	494 per 1000	**713 per 1000** (664 to 760)				
Quality of life: EORTC 12 month Scale from: 0 to 100	The mean quality of life: EORTC 12 month was **58**	MD **2.19 higher** (0.13 lower to 4.51 higher)	-	1096 (3 RCTs)	⊕⊕⊖⊖ Low[b,c]	A higher value means a better quality of life. Risk with standard treatment is 58 at 12 months. The risk with daratumumab plus standard treatment may show a very small increase (2.19 higher) compared to control group.
On-study mortality (longest available follow-up)	Study population		**Risk Ratio 0.72** (0.62 to 0.83)	1644 (3 RCTs)	⊕⊕⊕⊖ Moderate[d]	In ALCYONE length of follow-up: 66 months (24 June 2019); in MAIA length of follow-up: 72 months (19 February 2021); in OCTANS length of follow-up: 12.3 months (2 July 2020). Mean follow-up: 50.1 months.
	366 per 1000	**264 per 1000** (227 to 304)				
Serious adverse events (longest	Study population		**Risk Ratio 1.18** (1.02 to 1.37)	1644 (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	In ALCYONE length of follow-up: 54.5 months (24 June 2019); in MAIA length of follow-up: 72 months (2 February 2021); in OCTANS length of follow-up:
	505 per 1000	**596 per 1000**				

available follow-up)		(515 to 692)				12.3 months (2 July 2020). Mean follow-up: about 46 months.
Adverse events (CTCAE grade ≥ 3) (longest available follow-up)	Study population		**Risk Ratio 1.01** (0.99 to 1.02)	1644 (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	In ALCYONE length of follow-up: unknown; in MAIA length of follow-up: 72 months (19 February 2021); in OCTANS length of follow-up: 12.3 months (2 July 2020).
	953 per 1000	**963 per 1000** (943 to 972)				
Adverse events: infections (CTCAE grade ≥ 3) (longest available follow-up)	Study population		**Risk Ratio 1.52** (1.30 to 1.78)	1644 (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	In ALCYONE length of follow-up: 42 months (12 June 2018); in MAIA length of follow-up: 72 months (19 February 2021); in OCTANS length of follow-up: 12.3 months (2 July 2020). Mean follow-up: about 42 months.
	224 per 1000	**340 per 1000** (291 to 399)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_419380816263797880.

[a] Downgraded one level due to study limitations: incomplete survival data in one trial.
[b] Downgraded one level due to study limitations: participants, staff, and outcome assessor not blinded.
[c] Downgraded one level due to imprecision: wide CI.
[d] Downgraded one level due to study limitations: unclear allocation concealment, no blinding of participants and personnel (performance bias): all outcomes, and incomplete survival data (attrition bias) in MAIA.

BACKGROUND

Description of the condition

Multiple myeloma is a haematological malignancy that originates in the bone marrow. In contrast to other haematological malignancies, multiple myeloma is usually preceded by an age-progressive benign condition called monoclonal gammopathy of undetermined significance (MGUS), which can progress to smouldering (asymptomatic) myeloma and finally to symptomatic myeloma (Palumbo 2011). The disease is caused when abnormal plasma cells, a type of white blood cell, multiply uncontrollably. Multiple myeloma cells produce an abnormal (monoclonal) immunoglobulin, also called a paraprotein (Palumbo 2011). This immunoglobulin can be found in the blood and urine. One part of these abnormal immunoglobulins is called the light chain; this can also be detected in excessive amounts in the blood and urine (Bence Jones protein) (Corso 1999). Blood and urine tests are therefore a way of diagnosing and monitoring myeloma.

Myeloma cells in the bone marrow fill the space where normal blood cell production (haematopoiesis) occurs. People with multiple myeloma are therefore affected by symptoms caused by a reduction in the production of normal red cells (anaemia) and white cells (leukopenia), with an associated antibody deficiency disorder, resulting in an increased risk of infections (Blimark 2015). Furthermore, the disease destroys bone tissue (a process called osteolysis), resulting in bone pain and spontaneous fractures. It also increases the release of calcium into the blood (Panaroni 2017). This hypercalcaemia can cause symptoms including abdominal and bone pain, nausea, and confusion.

Myeloma cast nephropathy (light chain cast nephropathy) is the formation of plugs (urinary casts) in the renal tubules caused by large amounts of free light chains passing through the kidney into the urine. This can lead to renal failure, and is the most common cause of kidney injury in myeloma (Gerecke 2016; Röllig 2015).

The revised International Myeloma Working Group (IMWG) diagnostic criteria for multiple myeloma define myeloma based on the following characteristics (Rajkumar 2014).

- At least 10% of cells in the bone marrow are plasma cells, or there is a biopsy-proven plasmacytoma and one or more of the following myeloma-defining events.
  - End organ damage caused by the myeloma, specifically:
    - hypercalcaemia;
    - renal insufficiency;
    - anaemia;
    - bone lesions: one or more osteolytic lesions.
  - Any one or more of the following biomarkers of malignancy:
    - at least 60% of bone marrow plasma cells are clonal;
    - involved:uninvolved serum free light chain ratio ≥ 100;
    - > 1 focal lesions on magnetic resonance imaging (MRI) studies.

Multiple myeloma is a life-threatening condition. In 2018 there were 160,000 new cases worldwide (accounting for 0.9% of all cancers), with about 106,000 deaths caused by multiple myeloma (Bray 2018). Five-year survival of people with myeloma is less than 50%. Ten-year myeloma survival in the UK has quadrupled in the last 40 years, from 6% to 33% (Cancer Research UK 2018). From 1990 to 2016, the incidence of myeloma has increased by 126%, and the number of deaths caused by multiple myeloma has increased by 94% (Cowan 2018). The global incidence and death rates of multiple myeloma are highest in regions with high incomes like Australasia, North America, and Western Europe (age-standardised incidence rate of 4.3 per 100,000 persons). Populations with the lowest incidence of multiple myeloma are located in low-income regions of Asia, Oceania, and sub-Saharan Africa (age-standardised incidence rate of 1.2 per 100,000 persons) (Cowan 2018).

Multiple myeloma is divided into three different prognostic subgroups according to the International Staging System (ISS) (Greipp 2005) (Appendix 1).

As multiple myeloma is a genetically complex and heterogeneous disease, the IMWG recommends risk stratification by combining the ISS stage (serum beta-2 microglobulin, serum albumin) and genetic abnormalities (t(4;14), 17p13 and 1q21) detected by fluorescence in situ hybridisation (FISH) (Chng 2014). Cytogenetic and molecular genetic aberrations characterise people with multiple myeloma into two prognostic groups: a high-risk group, with poorer overall survival (hypodiploid group) associated with t(4;14)(p16;q32) or t(14;16)(q32;q23), and a group with better overall survival (hyperdiploid group) associated with t(11;14)(q13;q32).

Tumour progression of multiple myeloma can lead to four main secondary chromosomal abnormalities: translocations of MYC(8q24); loss or deletion of chromosome 13; deletion of chromosome 17p13; and deletions or amplifications of chromosome 1 (Sawyer 2011). MYC(8q24) mutations occur in up to 45% of people who are affected by multiple myeloma, and can cause shorter overall survival (Merz 2018). Chromosome 13 abnormalities occur in approximately 50% of cases: 85% of these are monosomy 13, while 15% are deletions of part of chromosome 13. Although chromosome 13 abnormalities in isolation are not a negative prognostic factor, when they are associated with other high-risk factors like t(4;14), del(17p) or high serum level of β2–microglobulin, they show an unfavourable prognosis (Paszekova 2014). In addition, deletions of chromosome 13 are co-responsible for the clonal expansion of multiple myeloma (Sawyer 2011). In approximately 10% of people with multiple myeloma, the deletion of 17p13 is a rare late event, which probably leads to an inactivation of TP53. TP53 is a tumour suppressor gene that transcriptionally controls cell-cycle progression and apoptosis. In conclusion, the deletion of 17p13 indicates a very poor prognosis with a more aggressive disease, a higher prevalence of extramedullary disease, and shorter overall survival (Sawyer 2011). Chromosome 1 abnormalities frequently occur in multiple myeloma; these usually comprise deletions of 1p and amplifications of 1q27. People with multiple myeloma and deletions of 1p or a gain or amplification of 1q21 are also associated with poor prognosis (Paszekova 2014).

Description of the intervention

Antineoplastic therapy is a generic term with subdivisions of different modalities, which include chemotherapy as a traditional form as well as newer techniques including hormonal drugs and immunotherapy. Depended on different criteria, modalities can be combined to create a treatment programme that is appropriate. A high-dose chemotherapy contains cytotoxic drugs that destroy cancer cells, but also normal cells as well as the bone marrow, and can cause severe adverse events. It is usually followed by stem cell transplantation to rebuild the bone marrow (Gale 2018; NCI 2020).

The treatment of people with newly diagnosed multiple myeloma depends on the SLiM-CRAB criteria of the IMWG, levels of fitness, and the personal wishes of the individual who is affected. With a good level of fitness, the individual is eligible to receive intensive treatment with high-dose chemotherapy followed by a stem cell transplant (Röllig 2015). The worldwide availability of stem cell transplantation for all indications, not only with respect to multiple myeloma, differs greatly. In 2010, the highest rates of stem cell transplantations per 10 million people took place in Israel (814), Italy (671), Germany (665), Sweden (625), and the Netherlands (614) (Cowan 2018).

People with newly diagnosed multiple myeloma who are not eligible for transplant, due to health problems or poor performance status, receive treatment consisting of multiple-drug combinations. A recommended first-line therapy is thalidomide, an immunomodulatory drug, combined with an alkylating agent, such as melphalan or cyclophosphamide, and a corticosteroid, such as prednisolone or dexamethasone (Kumar 2019). If there are contraindications to thalidomide, the individual can receive bortezomib instead (NICE 2018). The combination of bortezomib, melphalan, and prednisone shows a median overall survival of 53.1 months and a median progression-free survival of 17.3 months (Niesvizky 2015). The combination of bortezomib, cyclophosphamide, and dexamethasone has a median overall survival of 41.4 months and a median progression-free survival of 16.7 months (Venner 2015). Another first-line therapy is lenalidomide as an immunomodulatory drug combined with dexamethasone (Moreau 2017).

In high-income countries, people with multiple myeloma who are not eligible for transplant receive thalidomide- or bortezomib-based therapies combined with melphalan and prednisone, or cyclophosphamide and dexamethasone, or lenalidomide and dexamethasone (Moreau 2017; NICE 2018; Piechotta 2019). In low- and middle-income countries, people with multiple myeloma are treated with melphalan and prednisone, or if it is available with melphalan, prednisone, and thalidomide, or bortezomib, melphalan, and prednisone (Nwabuko 2017). The aim of the treatment is to achieve a period of stable disease (known as the plateau phase) for as long as possible.

Daratumumab is a newly developed drug that targets CD-38, a human IgG1k monoclonal antibody. Multiple myeloma cells uniformly over-express CD-38, a 46-kDa type II transmembrane glycoprotein, making myeloma cells a specific target for daratumumab (de Weers 2011).

How the intervention might work

Daratumumab induces the death of myeloma cells via multiple mechanisms, including direct induction of apoptosis (cell death), complement- and antibody-mediated cytotoxicity, and antibody-dependent cellular phagocytosis (Krejcik 2016). Daratumumab also triggers the activation and clonal expansion of cytotoxic T-cells, which may provide additional antimyeloma effects (Usmani 2016).

Daratumumab has been approved for the treatment of people with relapsed or refractory multiple myeloma (McKeage 2016). People with relapsed or refractory multiple myeloma who are heavily pretreated before and therefore refractory to standard treatments can receive daratumumab monotherapy (Usmani 2016a). People with relapsed or refractory multiple myeloma who have had at least one previous treatment can receive daratumumab in addition to chemotherapy (Blair 2017). Daratumumab in addition to a proteasome-inhibitor such as bortezomib induces a significantly lengthened progression-free survival at 12 months compared to standard treatment without daratumumab (60.7% versus 26.9%). Additionally, the same combination shows a higher rate of overall response (82.9% versus 63.2%), very good partial response (59.2% versus 29.1%), and complete response (19.2% versus 9.0%) (Palumbo 2016).

A combination of daratumumab with an immunomodulatory drug such as lenalidomide in people with relapsed or refractory multiple myeloma shows comparable results. This combination significantly lengthened progression-free survival at 12 months (83.2% versus 60.1%) and overall response (92.9% versus 76.4%) compared to lenalidomide only (Dimopoulos 2016). Daratumumab is also effective in triple-relapsed/refractory myeloma patients, with a median overall survival of 16.7 months (Boyle 2019).

The most frequent adverse event is an infusion reaction, with a prevalence of approximately 50%; 92% of these reactions arise with the first dose of therapy. Mostly, these infusion reactions are grade 1 or 2, whereas grade 3 shows an incidence of 5% to 10% (McCullough 2018). Besides infusion reactions, the most commonly (> 20%) reported adverse events include fatigue, nausea, anaemia, back pain, cough, upper respiratory tract infection, thrombocytopenia, and neutropenia (Usmani 2016a).

It is important to note that switching the administration of daratumumab from intravenous to subcutaneous may improve health-related quality of life and increases the role of flexible care (Cook 2023).

Why it is important to do this review

As mentioned above, daratumumab has shown remarkable benefits for people with relapsed disease. It is now important to understand whether there is also an advantage for individuals with newly diagnosed myeloma who are ineligible for a stem cell transplant. An assessment of potential harms is also essential to guide clinical decision-making. By combining results of randomised controlled trials, we will overcome the limitations of individual studies, such as small sample sizes and a lack of statistical power.

OBJECTIVES

To determine the benefits and harms of daratumumab in addition to antineoplastic therapy compared to antineoplastic therapy only for adults with newly diagnosed multiple myeloma who are ineligible for transplant.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials (RCTs). We excluded quasi-randomised trials (e.g. treatment allocation alternate or by date of birth), as randomisation is the best way to prevent systematic differences between baseline characteristics of participants in different intervention groups in terms of both known and unknown (or unmeasured) confounders. In the case of cross-

over trials, we included only the first period to avoid carry-over effects.

We included full texts, abstract publications, and studies reported in trial registries if sufficient information was available on study design and characteristics of participants and interventions. We did not exclude trials if they were eligible for inclusion but did not report our pre-planned outcomes. There was no limitation on length of follow-up.

Types of participants

We included trials on adult (≥ 18 years) participants with a confirmed diagnosis of multiple myeloma. We applied no gender or ethnicity restrictions. We considered only people with newly diagnosed multiple myeloma who were not candidates for high-dose chemotherapy with stem cell transplantation. We excluded trials with less than 80% adult participants, unless there were subgroup analyses of adults with multiple myeloma.

Types of interventions

The intervention consisted of daratumumab as a monoclonal antibody added to antineoplastic therapy versus the same antineoplastic therapy alone. Participants in both study arms should have received the same antineoplastic therapy, such as the same alkylating agent (e.g. cyclophosphamide, melphalan), proteasome inhibitor (e.g. bortezomib), immunomodulatory drug (e.g. lenalidomide, thalidomide), or glucocorticoids (e.g. dexamethasone, prednisone), in the same combination of agents, dose, and number of cycles.

We included all daratumumab dosages used in RCTs.

Types of outcome measures

We included all studies meeting our inclusion criteria irrespective of whether they reported our outcomes of interest or not.

Primary outcomes

- Overall survival, defined as time from random treatment assignment within a study to death from any cause or to last follow-up

For this outcome, measured as a hazard ratio (HR), we evaluated the longest follow-up available within each study. We performed subgroup analyses for different lengths of follow-up.

Secondary outcomes

We analysed the following as secondary outcomes.

- Progression-free survival (we used the longest follow-up available)
- Quality of life, if validated tools were used (e.g. EORTC QLG Core Questionnaire (EORTC QLQ-C30) or 5-level EQ-5D version (EQ-5D-5L)):
  - We considered the EORTC QLQ-C30 Global Health Status to be the most representative of quality of life.
  - All questionnaires were measured at certain periods:
    - short (one to three months after start of treatment);
    - medium (six to nine months after start of treatment);
    - long (12 months and longer after start of treatment).
- On-study mortality (we used the longest follow-up available)
- Serious adverse events (we used the longest follow-up available)
- Adverse events (Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3) (we used the longest follow-up available)
- Adverse events: infections (CTCAE grade ≥ 3) (we used the longest follow-up available)

Additional outcomes

- Adverse events
  - Neutropenia (we used the longest follow-up available)
  - Thrombocytopenia (we used the longest follow-up available)
  - Anaemia (we used the longest follow-up available)
  - Leukopenia (we used the longest follow-up available)
  - Lymphopenia (we used the longest follow-up available)
  - Infections (we used the longest follow-up available)
  - Diarrhoea (we used the longest follow-up available)
  - Pneumonia (we used the longest follow-up available)
  - Nausea (we used the longest follow-up available)
- Complete response (we used the longest follow-up available)
- Minimal residual disease negativity (we used the longest follow-up available)

Search methods for identification of studies

Electronic searches

We adapted our search strategies as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019). We did not apply any language restrictions to reduce the risk of language bias. We started the search in 2010, as daratumumab was mentioned for the first time in 2011 (de Weers 2011). We searched the following databases.

- Databases of medical literature
  - Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library; Issue 7, 2022) (until 20 September 2023) (Appendix 2)
  - MEDLINE (Ovid) (until 20 September 2023) (Appendix 3)
  - Embase (Ovid) (until 20 September 2023) (Appendix 4)
- Study registries (until 20 September 2023)
  - EU Clinical Trials Register (www.clinicaltrialsregister.eu) (Appendix 5)
  - World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch) (Appendix 6)
  - ClinicalTrials.gov (clinicaltrials.gov) (Appendix 7)
  - ISRCTN registry (www.isrctn.com) (Appendix 8)
- Conference proceedings of annual meetings of the following societies for abstracts, if not included in CENTRAL (2010 until 20 September 2023)
  - American Society of Hematology
  - American Society of Clinical Oncology
  - European Hematology Association

Searching other resources

- Handsearching of references
  - References to all identified trials and relevant review articles; current treatment guidelines; Institute for Quality and Efficiency in Healthcare (IQWiG) reports

Data collection and analysis

Selection of studies

Two review authors (PL, NS) independently screened the results of the search strategies for eligibility by reading the abstracts using EndNote software (EndNote X9). We coded the abstracts as either 'include' or 'exclude.' In the case of disagreement, or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Two review authors (PL, NS) assessed the full-text articles of selected studies. In the case of disagreement, a third review author was consulted to reach a final decision (Lefebvre 2019; Li 2019).

We documented the study selection process in a flowchart as recommended by the PRISMA statement (Moher 2009), showing the total numbers of retrieved references and numbers of included and excluded studies.

Data extraction and management

We conducted data extraction according to the guidelines proposed by Cochrane (Lefebvre 2019; Li 2019). Two review authors (PL, NS) extracted data from eligible studies independently and in duplicate. We resolved disagreements by discussion. If there was no agreement, a third review author resolved the disagreement. We used a customised data extraction form that was piloted and developed in Microsoft Excel containing the following items.

- General information
  - Author, title, source, publication date, country, language, duplicate publications
- Quality assessment
  - Allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias
- Study characteristics
  - Trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, subgroup analysis, treatment cross-overs, compliance with assigned treatment, length of follow-up
- Participant characteristics
  - Newly diagnosed individuals, ineligible for transplant, cytogenetic subtype, additional diagnoses, age, gender, ethnicity, number of participants recruited/allocated/evaluated, participants lost to follow-up, type of treatment (multiple-agent standard treatment (intensity of regimen, number of cycles))
- Interventions
  - Dose and cycles of daratumumab; type, dose, and cycles of standard treatment; duration of follow-up
- Outcomes
  - Overall survival, progression-free survival, quality of life, on-study mortality, serious adverse events, adverse events (CTCAE grade ≥ 3), complete response, minimal residual disease negativity

We extracted data from all available sources, that is study publications as well as other sources like clinical study registries and IQWiG reports.

Assessment of risk of bias in included studies

Two review authors (PL, NS) independently assessed the risk of bias in each study using the following criteria, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. To analyse the risk of bias in the underlying study results, we used the RoB 1 tool (Higgins 2011). Any discrepancies were resolved by discussion or by involving a third review author if necessary. We assessed the following risk of bias domains.

- Sequence generation
- Allocation concealment
- Blinding (participants, personnel; blinding of outcome assessment was judged at the outcome level)
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias

We made a judgement for each domain, using one of the following categories.

- 'Low risk': if the domain is adequately fulfilled in the study (i.e. the study is at low risk of bias for the given domain).
- 'High risk': if the domain is not fulfilled in the study (i.e. the study is at high risk of bias for the given domain).
- 'Unclear': if the study report does not provide sufficient information to allow a clear judgement, or if the risk of bias is unknown for the domain.

Measures of treatment effect

We used intention-to-treat data. For binary outcomes, we extracted the number of participants and number of events per arm and calculated risk ratios (RRs) with 95% confidence intervals (CIs) for each trial. For time-to-event outcomes, we extracted hazard ratios (HRs) and 95% CIs from published data according to Parmar 1998 and Tierney 2007. We calculated continuous outcomes as mean differences (MDs) with standard deviations (SD) when the outcome was assessed with the same instrument; otherwise, we calculated standardised mean differences (SMDs) with SD.

Unit of analysis issues

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022), we combined arms of studies with multiple treatment groups as long as they could be regarded as subtypes of the same intervention. When arms could not be pooled this way, we compared each arm with the common comparator separately. For pairwise meta-analysis, we split the 'shared' group into two or more groups with a smaller sample size, and included two or more (reasonably independent) comparisons. For this purpose, both the number of events and the total number of participants were divided up for dichotomous outcomes, and the total number of participants was divided up with unchanged means and SDs for continuous outcomes.

Dealing with missing data

As suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022), many potential sources of missing data must be taken into account: at the study, outcome, and summary data levels. Firstly, it was important to distinguish between 'missing at random' and 'not missing at random'. In cases of study results that were not reported or missing data, we consulted the study

authors to request the missing data. If data were still missing, we made explicit assumptions regarding any methods used, for example that the data were assumed to be missing at random, or that missing values were assumed to have a particular value, such as a poor outcome. We imputed missing data for participants lost to follow-up after randomisation (dichotomous data) by assuming poor outcomes (worst-case scenario) for missing individuals. We performed sensitivity analysis to assess how sensitive results were to reasonable changes in assumptions made. We addressed the potential impact of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

We assessed the heterogeneity of treatment effects between trials using the Chi^2 test with a significance level of $P < 0.1$. We used the I^2 statistic to quantify possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity) (Deeks 2022). We explored possible causes of heterogeneity by performing sensitivity and subgroup analyses.

Assessment of reporting biases

In meta-analyses with 10 or more trials, we planned to investigate potential publication bias by generating a funnel plot and testing statistics by using a linear regression test (Page 2019). We considered a P value less than 0.1 as significant for this test. However, as we did not identify at least 10 studies, we did not generate a funnel plot.

We screened databases of clinical studies to identify completed but not published studies.

Data synthesis

If we considered the data sufficiently similar to be combined, we pooled results by applying meta-analyses using the random-effects model, and used the fixed-effect model as a sensitivity analysis for the primary outcome. When trials were clinically too heterogeneous to be combined (e.g. various types of diseases), we performed only subgroup analyses without calculating an overall estimate. When different tools were used to evaluate quality of life, we calculated SMDs to perform a meta-analysis. We performed analyses according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022), using Cochrane statistical software RevMan for analysis (RevMan 2024).

Subgroup analysis and investigation of heterogeneity

We analysed subgroup data for the primary outcome of overall survival.

- Cytogenetic risk (high risk versus standard risk)
  - Cytogenetic high-risk subgroup is defined by the presence of del(17p), t(4;14), t(14;16), del(13q) by conventional karyotype and hypodiploidy (Jimenez-Zepeda 2016).
  - *We chose this subgroup due to a high-risk group with poorer overall survival in general (hypodiploid group) associated with t(4;14)(p16;q32) or t(14;16)(q32;q23), and a group with better overall survival in general (hyperdiploid group) associated with t(11;14)(q13;q32)* (Sawyer 2011).
- International Staging System (I versus II versus III)
  - *We chose this subgroup due to potential prognostic factors for overall survival depending on the stage of the International Staging System.*

If data are available in future updates of this review, we will also perform the following subgroup analyses for the primary outcome of overall survival.

- Antineoplastic therapy consisting of two drugs versus antineoplastic therapy consisting of three drugs
  - *We chose this subgroup as a two-drug regimen might have fewer benefits and harms compared to a three-drug regimen.*
- Follow-up (short term (< 1 year) versus long term (≥ 1 year))
  - *We chose this subgroup to evaluate whether there are differences in short- and long-term outcomes.*

Sensitivity analysis

We performed the following sensitivity analyses.

- Trials at low or unclear risk of bias for all domains for the primary outcome of overall survival
- Random-effects modelling for the primary outcome of overall survival

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table on absolute risks in each group according to the GRADE system (GRADEpro GDT; Schünemann 2019), in which we summarised the evidence on overall survival, progression-free survival, quality of life (EORTC at 12 months), on-study mortality, serious adverse events, adverse events (CTCAE grade ≥ 3), and infections (CTCAE grade ≥ 3).

RESULTS

Description of studies

Results of the search

The database searches identified 3486 potentially relevant records, which were screened independently by two review authors. At the initial screening stage, we removed 464 duplicate records and excluded 2970 records based on title or abstract. We retrieved the remaining 52 publications as full-text or abstract publications, excluding a total of 10 studies (11 records), eight due to incorrect study design and two due to wrong comparison.

We also identified two references from the Institute for Quality and Efficiency in Healthcare (IQWiG). Both references were health technology assessment reports. IQWiG has access to clinical study reports, therefore we mainly used it as a source of information for this systematic review.

The initial screening of each database (CENTRAL and MEDLINE) was conducted till August 2019. The second electronic search (CENTRAL, MEDLINE, and Embase) was conducted till May 2020, the third screening (CENTRAL, MEDLINE, Embase, EU Clinical Trials Register, ClinicalTrials.gov, WHO ICTRP, and ISRCTN registry) was conducted till July 2022, and the fourth screening (CENTRAL, MEDLINE, Embase, EU Clinical Trials Register, ClinicalTrials.gov, WHO ICTRP, and ISRCTN registry) was conducted till September 2023.

Four studies (34 records) involving a total of 1783 participants were eligible for inclusion in the review (ALCYONE; AMaRC 03-16; MAIA; OCTANS). Six trials (seven records) are ongoing and are expected to be reported (CEPHEUS; NCT03217812; NCT03710603; NCT03742297; NCT03993912; NCT04268498).

The process and results of study identification are documented in the PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram.

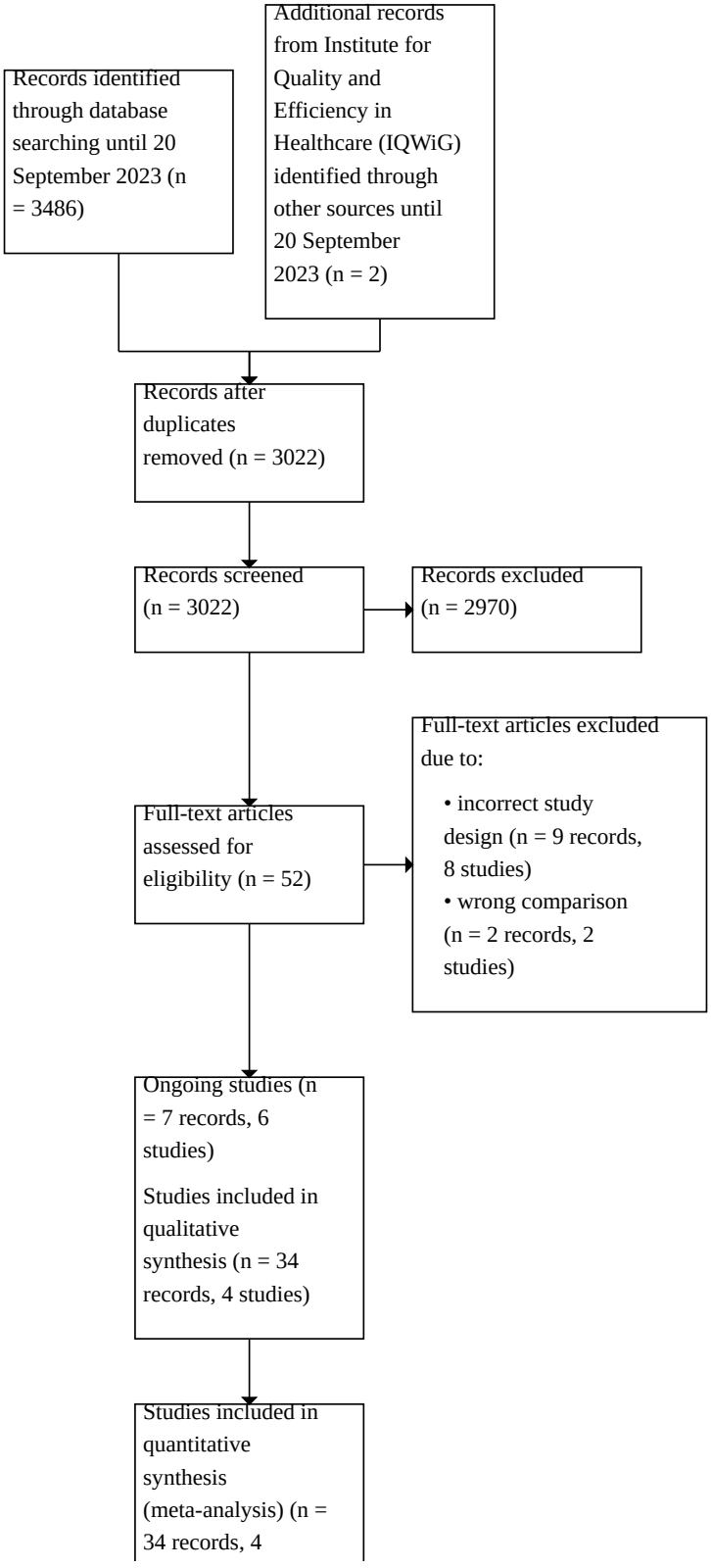


Figure 1. (Continued)

(meta-analysis) (n = 34 records, 4 studies)

Included studies

Four studies (34 records) involving a total of 1783 participants were eligible for inclusion in the review. All studies were conducted in high- and middle-income countries. We contacted the authors of AMaRC 03-16 for missing data, but they could not offer us any further information.

In ALCYONE, the mean age of participants was 71.4 years; the proportion of female participants was 53.7%. AMaRC 03-16 did not report mean age or proportion of male and female participants. In MAIA, the mean age of participants was 74.1 years; the percentage of female participants was 47.9%. In OCTANS, the mean age of participants was 69 years; the percentage of female participants was 40.5%.

All trials evaluated antineoplastic therapies, either with daratumumab or without daratumumab. Daratumumab was combined with bortezomib and melphalan-prednisone in ALCYONE; with bortezomib, cyclophosphamide, and dexamethasone in AMaRC 03-16; with lenalidomide and dexamethasone in MAIA; and with bortezomib and melphalan-prednisone in OCTANS.

Design

All four included trials were open-label, two-armed RCTs.

Sample size

Sample sizes were as follows: ALCYONE, 706 participants; AMaRC 03-16, 120 participants; MAIA, 737 participants; and OCTANS, 220 participants.

Setting

Three trials were multicentre trials conducted in several countries (ALCYONE; MAIA; OCTANS). One study was conducted in only one country (AMaRC 03-16).

Participants

All trials included male and female participants with a diagnosis of multiple myeloma who were at least 18 years of age. All trials included only participants with newly diagnosed multiple myeloma who were not candidates for high-dose chemotherapy with stem cell transplantation.

Interventions

Interventions in the ALCYONE and the OCTANS studies included daratumumab as a monoclonal antibody in combination with bortezomib as a proteasome inhibitor, melphalan as a chemotherapy drug, and prednisone as a corticosteroid. In the AMaRC 03-16 study, interventions were daratumumab combined with bortezomib, dexamethasone, and cyclophosphamide, with the latter two agents acting as alkylating agents. Interventions in the MAIA study included daratumumab in combination with lenalidomide as an immunomodulatory agent and dexamethasone as a corticosteroid. Daratumumab is given as an intravenous infusion or a subcutaneous injection; bortezomib as a subcutaneous injection; melphalan, prednisone, lenalidomide, and cyclophosphamide orally; and dexamethasone orally or as an intravenous infusion.

Doses

Daratumumab is given as an intravenous infusion of 16 mg/kg on single days of each cycle and thereafter once every four weeks until documented progression, unacceptable toxicity, or study end (ALCYONE; AMaRC 03-16; MAIA; OCTANS). Bortezomib is dosed in 1.3 mg/m^2 as a subcutaneous injection on different days of each cycle (ALCYONE; AMaRC 03-16; OCTANS). Lenalidomide is given in a 25-milligram capsule orally on several days of each cycle (MAIA). Dexamethasone dosed in 20 or 40 mg is given as an intravenous infusion or orally on different days of each cycle (ALCYONE; AMaRC 03-16; MAIA). Melphalan is given orally at 9 mg/m^2 on several days of each cycle (ALCYONE; OCTANS). Prednisone is dosed at 60 mg/m^2 and given orally on several days of each cycle (ALCYONE; OCTANS).

Outcomes

The studies ALCYONE, MAIA, and OCTANS reported overall survival, progression-free survival, quality of life, complete response, on-study mortality, serious adverse events, adverse events, and minimal residual disease negativity as relevant outcomes for this review. The AMaRC 03-16 study reported overall survival, progression-free survival, quality of life, and minimal residual disease negativity as relevant outcomes for this review.

In all studies, minimal residual disease negativity was measured with the same sensitivity threshold of 10^{-5}.

We prioritised the extraction and analysis of serious adverse events as well as common grade 3 adverse events such as neutropenia, thrombocytopenia, anaemia, leukopenia, lymphopenia, infections, diarrhoea, pneumonia, and nausea.

Reported outcomes not relevant for this review were: overall response rate, very good partial response, progression-free survival on next line of therapy, stringent complete response, time to disease progression, time to response, duration of response, time to next treatment, best m-protein response, patient-reported outcomes, immunogenicity, and pharmacokinetics of daratumumab.

For further details, see Characteristics of included studies and Table 1.

Excluded studies

We excluded 10 studies at full-text stage (Characteristics of excluded studies): six meta-analyses (Facon 2019; Gil-Sierra 2020; Manier 2019; San-Miguel 2018; Sekine 2019; van Beekhuizen 2019), two non-randomised studies (Syed 2019; Thein 2019), one study with propensity score matching method (Cavo 2018), and one study with matching-adjusted indirect treatment comparison (Dimopoulos 2020).

Ongoing studies

All six ongoing studies are RCTs (CEPHEUS; NCT03217812; NCT03710603; NCT03742297; NCT03993912; NCT04268498), one in phase II and five in phase III.

- One study is expected to be completed in 2023 and plans to evaluate 220 participants (NCT03217812).
- One study is planned to be completed in 2025 (CEPHEUS), randomising 395 participants.
- Two studies have an estimated study completion date of 2027 (NCT03993912; NCT04268498), randomising 294 and 306 participants, respectively.
- One study is expected to be completed in 2029 and plans to evaluate 294 participants (NCT03710603).
- One study is planned to be completed in 2031 (NCT03742297), randomising 300 participants.

For further details, see Characteristics of ongoing studies.

Studies awaiting classification

There are no studies awaiting classification.

Risk of bias in included studies

The AMaRC 03-16 study was published as abstract only, therefore bias for most domains remains unclear. None of the four studies was blinded (high risk of performance and detection bias). The two larger studies, ALCYONE and MAIA, and the OCTANS study were published as full texts. Apart from blinding, the risk of bias was low for these studies.

Further details on the risk of bias assessment are presented as risk of bias summaries in Figure 2 and Figure 3 and in the risk of bias table in Characteristics of included studies.

Figure 2. Risk of bias - summary chart.

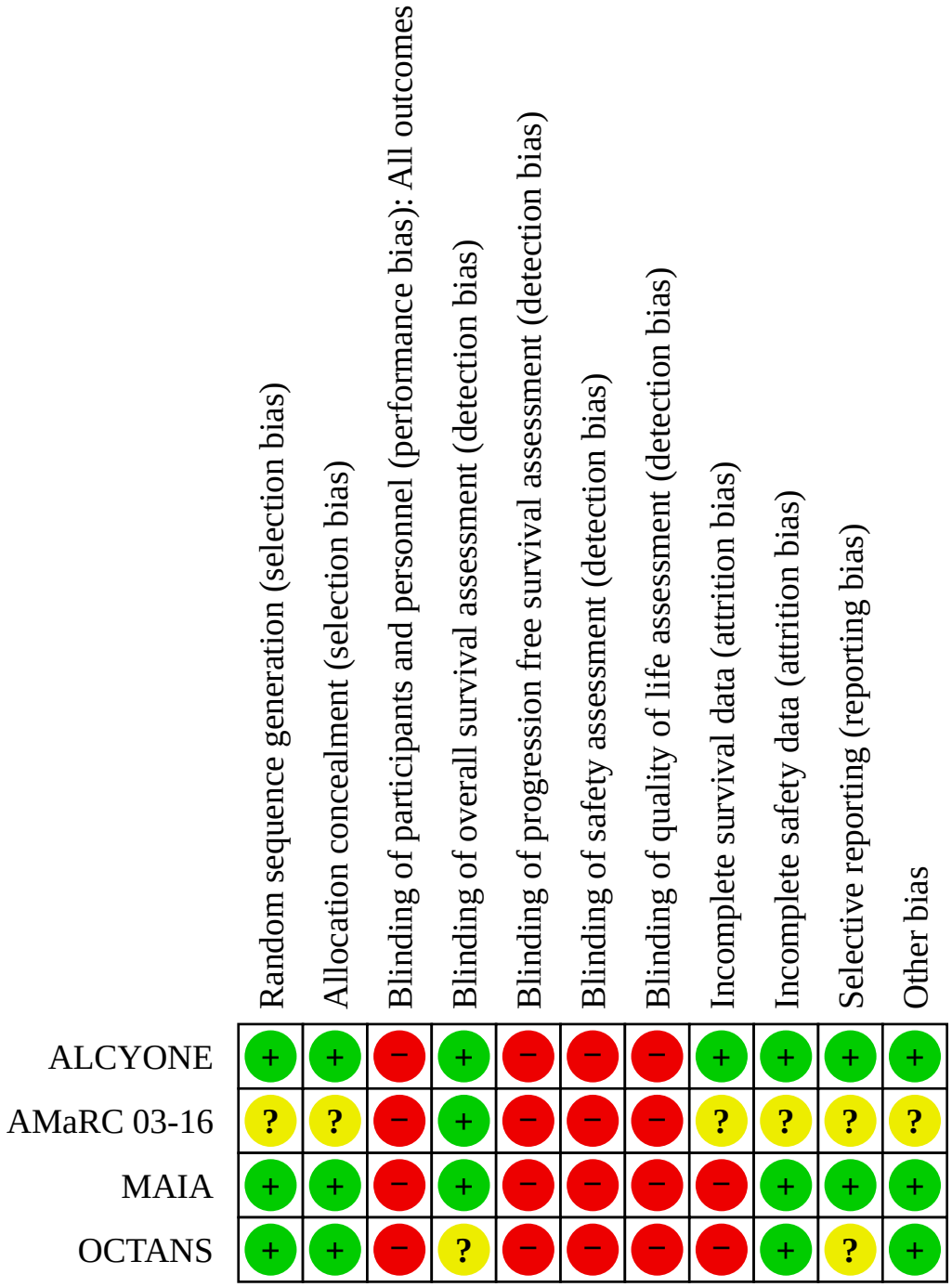
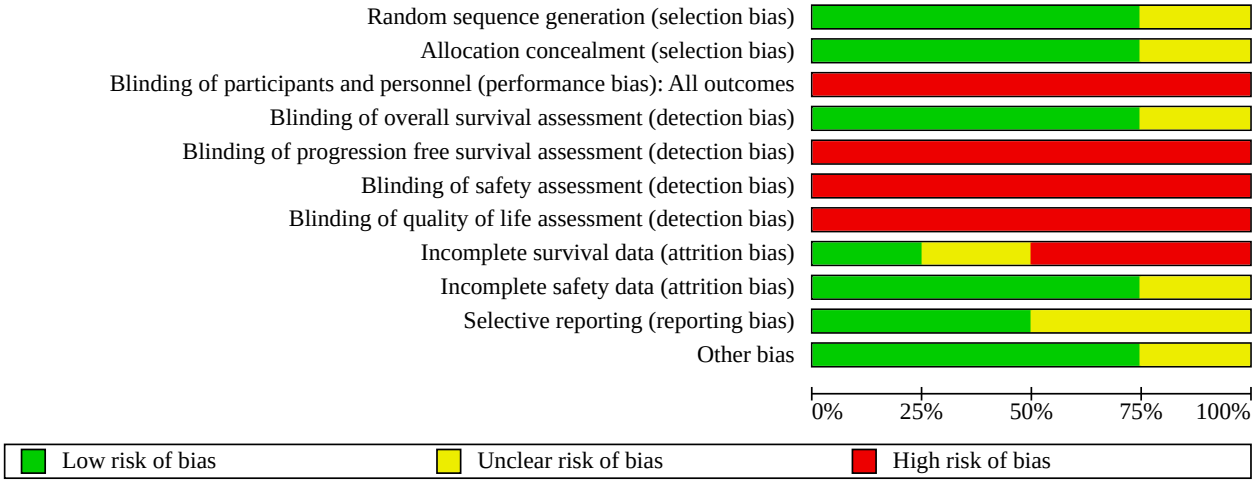


Figure 3. Risk of bias - summary plot.



Allocation

ALCYONE and MAIA used a method of randomisation by randomly permuted blocks and an interactive web-based randomisation system and were therefore judged as at low risk of bias for allocation concealment. Participants in the OCTANS study were randomised by computer- generated randomisation; we also considered this study as at low risk for allocation concealment.

We judged allocation concealment as unclear for AMaRC 03-16 due to insufficient information.

Blinding

All trials were open-label studies, so there was no blinding. We rated the risk of performance bias for blinding of participants and personnel to be high.

We assessed blinding of outcome assessment in three outcome categories: overall survival, progression-free survival, and safety (adverse events/serious adverse events) outcomes. For overall survival, we judged the risk of detection bias to be low in three studies (ALCYONE; AMaRC 03-16; MAIA). The determination of the endpoint cannot be influenced by the knowledge of group allocation. We assessed one study as at unclear risk of detection bias due to insufficient information (OCTANS).

Progression-free survival and safety outcomes can be dependent on the outcome assessor. All studies were considered to be unblinded for outcome assessment and were therefore judged to be at high risk of detection bias.

Incomplete outcome data

We judged the risk of attrition bias as low for ALCYONE.

In MAIA, we considered the risk of incomplete safety data as low, but the risk of incomplete survival data as high, reasoned by the unclear status of participants in both groups after discontinuing the study. In MAIA, around 325 of 729 participants discontinued treatment in September 2018.

In OCTANS, at the time of clinical cut-off (2 July 2020), 31 participants in the daratumumab group and 26 participants in the control group had discontinued treatment. We therefore considered the risk of incomplete safety data as low, but the risk of incomplete survival data as high.

We judged the risk of attrition bias for AMaRC 03-16 as unclear due to insufficient information.

Selective reporting

We judged the risk of reporting bias as low in two trials (ALCYONE; MAIA), as the results for all prespecified primary and secondary outcomes were available. Reporting was very precise in journal publications, and results were available in study registers. We extracted outcome data from the dossier evaluations of IQWiG, because of their access to the clinical study reports.

There is no information on the outcome overall survival in the OCTANS study. All other prespecified primary and secondary outcomes were available, so we considered the risk of reporting bias as unclear.

We judged the risk of reporting bias for AMaRC 03-16 as unclear due to insufficient information.

As we included fewer than 10 studies, we did not conduct a funnel plot.

Other potential sources of bias

There was no information in ALCYONE, MAIA, and OCTANS to suggest other sources of bias, therefore we rated the risk of other bias as low.
We judged the risk of other bias for AMaRC 03-16 as unclear due to insufficient information.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Daratumumab plus standard therapy compared to standard therapy for people with newly diagnosed multiple myeloma ineligible for transplant

Primary outcome

Overall survival

Two studies reported overall survival for 1443 participants (ALCYONE; MAIA). Median survival was not reached in either group of both studies. Treatment with daratumumab probably increases overall survival when compared to treatment without daratumumab. We downgraded the certainty of evidence one level due to incomplete survival data in one trial (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.53 to 0.76, I^2 = 0%, moderate-certainty evidence, see Analysis 1.1). After a follow-up period of 36 months, 695 per 1000 participants survived in the control group, whereas 792 per 1000 participants survived in the daratumumab group (95% CI 758 to 825). See Summary of findings 1.

AMaRC 03-16 and OCTANS reported no information about overall survival.

Subgroup analyses

We evaluated two subgroup analyses for the primary outcome. However, only one study reported subgroup results (MAIA).

We did not identify any subgroup differences for the cytogenetic risk (high risk versus standard risk) (see Analysis 1.2) or for the International Staging System (I versus II versus III) (see Analysis 1.3).

Secondary outcomes

Progression-free survival

Three studies reported progression-free survival for 1663 participants (ALCYONE; MAIA; OCTANS). Treatment with daratumumab probably increases progression-free survival when compared to treatment without daratumumab. We downgraded the certainty of evidence one level due to no blinding (HR 0.48, 95% CI 0.39 to 0.58, I^2 = 44%, moderate-certainty evidence, see Analysis 2.1). After a follow-up period of 24 months, progression-free survival was reached in 494 per 1000 participants in the control group versus 713 per 1000 participants in the daratumumab group (95% CI 664 to 760). See Summary of findings 1.

AMaRC 03-16 reported no information about progression-free survival.

Quality of life

Three studies reported quality of life (ALCYONE; MAIA; OCTANS). All trials used the validated EORTC QLQ-C30 to evaluate quality of life. In addition, ALCYONE and MAIA used the EQ-5D-5L questionnaire.

The EORTC QLQ-C30 is a 30-item self-reporting questionnaire that includes five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), one global health status scale (GHS), three symptom scales (fatigue, nausea and vomiting, and pain) and six single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) (Knop 2021). The scale for all EORTC QLQ-C30 scores ranges from 0 to 100, with higher scores representing greater global health status, better functioning, and worse symptoms.

All three trials reported quality of life based on the EORTC QLQ-C30 GHS: after three months for 1302 participants (see Analysis 3.1), after nine months for 1119 participants (see Analysis 3.2), and after 12 months for 1096 participants (see Analysis 3.3).

In ALCYONE, both the control group and the daratumumab group showed an improvement of more than 10 points from baseline. In OCTANS, only the daratumumab group showed an improvement of more than 10 points from baseline. Treatment with daratumumab may result in a very small increase in quality of life after 12 months evaluated with the EORTC QLQ-C30 when compared to treatment without daratumumab. We downgraded the certainty of the evidence one level due to no blinding and one level due to a wide CI (mean difference 2.19, 95% CI −0.13 to 4.51, I^2 = 0%, low-certainty evidence, see Analysis 3.3). See Summary of findings 1.

Two studies reported baseline data for the EORTC QLQ-C30 GHS (ALCYONE; MAIA), with a mean between 50 and 60 (Knop 2021; Perrot 2020). No baseline data were reported in OCTANS.

The EQ-5D-5L, a general measurement tool to assess health status, evaluates five aspects such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) to measure "today's health" (Knop 2021). Higher EQ-5D-5L VAS scores represent better health.

ALCYONE and MAIA reported quality of life based on the EQ-5D-5L VAS after three months for 1051 participants (see Analysis 3.4), after nine months for 874 participants (see Analysis 3.5), and after 12 months for 848 participants (see Analysis 3.6).

AMaRC 03-16 reported no information about quality of life.

On-study mortality

Three studies reported on-study mortality for 1644 participants (ALCYONE; MAIA; OCTANS). Treatment with daratumumab probably decreases on-study mortality when compared to treatment without daratumumab. We downgraded the certainty of evidence one level due to unclear allocation concealment and no blinding of participants and personnel (risk ratio (RR) 0.72, 95% CI 0.62 to 0.83, I^2 = 0%, moderate-certainty evidence, see Analysis 4.1). After the longest follow-up available (12 to 72 months), 366 per 1000 participants in the control group died, whereas 264 per 1000 participants in the daratumumab group died (95% CI 227 to 304). See Summary of findings 1.

AMaRC 03-16 reported no information about on-study mortality.

Serious adverse events

Three studies reported serious adverse events for 1644 participants (ALCYONE; MAIA; OCTANS). Treatment with daratumumab probably increases serious adverse events when compared to treatment without daratumumab. We downgraded the certainty of evidence one level due to no blinding of participants and personnel (RR 1.18, 95% CI 1.02 to 1.37, I^2 = 48%, moderate-certainty evidence, see Analysis 5.1). After the longest follow-up available (12 to 72 months), 505 per 1000 participants in the control group experienced serious adverse events versus 596 per 1000 participants in the daratumumab group (95% CI 515 to 692). See Summary of findings 1.

AMaRC 03-16 reported no information about serious adverse events.

Adverse events (CTCAE grade ≥ 3)

Three studies reported adverse events (CTCAE grade ≥ 3) for 1644 participants (ALCYONE; MAIA; OCTANS). There was probably little to no difference in adverse events (CTCAE grade ≥ 3) between treatment with and without daratumumab. We downgraded the certainty of evidence one level due to no blinding of participants and personnel (RR 1.01, 95% CI 0.99 to 1.02, I^2 = 5%, moderate-certainty evidence, see Analysis 6.1). After the longest follow-up available (12 to 72 months), 953 per 1000 participants in the control group versus 963 per 1000 participants in the daratumumab group experienced adverse events (CTCAE grade ≥ 3) (95% CI 943 to 972). See Summary of findings 1.

AMaRC 03-16 reported no information about adverse events (CTCAE grade ≥ 3).

Adverse events: infections (CTCAE grade ≥ 3)

Three studies reported infections (CTCAE grade ≥ 3) for 1644 participants (ALCYONE; MAIA; OCTANS). Treatment with daratumumab probably increases infections (CTCAE grade ≥ 3) when compared to treatment without daratumumab. We downgraded the certainty of evidence one level due to no blinding of participants and personnel (RR 1.52, 95% CI 1.30 to 1.78, I^2 = 0%, moderate-certainty evidence, see Analysis 6.2). After the longest follow-up available (12 to 72 months), 224 per 1000 participants in the control group versus 340 per 1000 participants in the daratumumab group experienced infections (CTCAE grade ≥ 3) (95% CI 291 to 399). See Summary of findings 1.

AMaRC 03-16 reported no information about infections (CTCAE grade ≥ 3).

Additional outcomes

Adverse events

Neutropenia

Three studies reported neutropenia for 1644 participants (ALCYONE; MAIA; OCTANS). Considering the reported event rates (RR 1.02, 95% CI 0.75 to 1.39, I^2 = 89%, see Analysis 6.3), 490 per 1000 participants in the control group experienced neutropenia, which corresponds to 38 more per 1000 participants in the daratumumab group experiencing neutropenia.

AMaRC 03-16 reported no information about neutropenia.

Thrombocytopenia

Three studies reported thrombocytopenia for 1644 participants (ALCYONE; MAIA; OCTANS). Considering the reported event rates (RR 0.95, 95% CI 0.84 to 1.07, I^2 = 0%, see Analysis 6.4), 377 per 1000 participants in the control group experienced thrombocytopenia, which corresponds to 9 fewer per 1000 participants in the daratumumab group experiencing thrombocytopenia.

AMaRC 03-16 reported no information about thrombocytopenia.

Anaemia

Three studies reported anaemia for 1644 participants (ALCYONE; MAIA; OCTANS). Considering the reported event rates (RR 0.88, 95% CI 0.69 to 1.14, I^2 = 65%, see Analysis 6.5), 380 per 1000 participants in the control group experienced anaemia, which corresponds to 49 fewer per 1000 participants in the daratumumab group experiencing anaemia.

AMaRC 03-16 reported no information about anaemia.

Leukopenia

Three studies reported leukopenia for 1644 participants (ALCYONE; MAIA; OCTANS). Considering the reported event rates (RR 1.11, 95% CI 0.69 to 1.80, I^2 = 80%, see Analysis 6.6), 152 per 1000 participants in the control group experienced leukopenia, which corresponds to 40 more per 1000 participants in the daratumumab group experiencing leukopenia.

AMaRC 03-16 reported no information about leukopenia.

Lymphopenia

Three studies reported lymphopenia for 1644 participants (ALCYONE; MAIA; OCTANS). Considering the reported event rates (RR 1.32, 95% CI 1.05 to 1.67, I^2 = 0%, see Analysis 6.7), 127 per 1000 participants in the control group experienced lymphopenia, which corresponds to 52 more per 1000 participants in the daratumumab group experiencing lymphopenia.

AMaRC 03-16 reported no information about lymphopenia.

Diarrhoea

Three studies reported diarrhoea for 1644 participants (ALCYONE; MAIA; OCTANS). Considering the reported event rates (RR 1.13, 95% CI 0.88 to 1.45, I^2 = 55%, see Analysis 6.8), 353 per 1000 participants in the control group experienced diarrhoea, which corresponds to 33 more per 1000 participants in the daratumumab group experiencing diarrhoea.

AMaRC 03-16 reported no information about diarrhoea.

Pneumonia

Three studies reported pneumonia for 1644 participants (ALCYONE; MAIA; OCTANS). Considering the reported event rates (RR 2.04, 95% CI 1.41 to 2.94, I^2 = 46%, see Analysis 6.9), 115 per 1000 participants in the control group experienced pneumonia, which corresponds to 113 more per 1000 participants in the daratumumab group experiencing pneumonia.

AMaRC 03-16 reported no information about pneumonia.

Nausea

Two studies reported nausea for 1429 participants (ALCYONE; MAIA). Considering the reported event rates (RR 1.22, 95% CI 0.79 to 1.87, I^2 = 82%, see Analysis 6.10), 228 per 1000 participants in the control group experienced nausea, which corresponds to 59 more per 1000 participants in the daratumumab group experiencing nausea.

AMaRC 03-16 and OCTANS reported no information about nausea.

Adverse events were reported in three studies as long as the participants received treatment and during the end-of-treatment visit (ALCYONE; MAIA; OCTANS). In the intervention group, treatment with daratumumab continues after the last cycle until documented progression, unacceptable toxicity, or until the end of study. We therefore cannot evaluate these safety results as a relative comparison between both treatment arms.

Complete response

Three studies reported complete response for 1663 participants (ALCYONE; MAIA; OCTANS). Considering the reported event rates (RR 1.78, 95% CI 1.56 to 2.04, I^2 = 0%, see Analysis 7.1), 268 per 1000 participants in the control group achieved a complete response, which corresponds to 208 more per 1000 participants in the daratumumab group achieving a complete response.

AMaRC 03-16 reported no information about a complete response.

Minimal residual disease negativity

Three studies reported minimal residual disease negativity for 1663 participants (ALCYONE; MAIA; OCTANS). Considering the reported event rates (RR 3.35, 95% CI 2.62 to 4.28, I^2 = 0%, see Analysis 8.1), 89 per 1000 participants in the control group experienced minimal residual disease negativity, which corresponds to 212 more per 1000 participants in the daratumumab group experiencing minimal residual disease negativity.

Additionally, three studies reported adverse events considered not to be relevant for this review: vascular disorders, peripheral sensory neuropathy, pyrexia, upper respiratory tract infection, bronchitis, lower respiratory tract infection, respiratory, thoracic, and mediastinal disorders, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, nervous system disorders, gastrointestinal disorders, urinary tract infections, hypokalaemia, constipation, hypocalcaemia, hyperglycaemia, increased alanine aminotransferase, hypertension, increased aspartate transaminase, hypoalbuminaemia, general disorders, investigations, skin and subcutaneous tissue disorders (ALCYONE; MAIA; OCTANS).

Sensitivity analysis

Two studies indicated robust estimations, as both studies were at high risk of bias (ALCYONE; MAIA). Fixed-effect and random-effects models for the primary outcome of overall survival led to the same results (HR 0.64, 95% CI 0.53 to 0.76).

DISCUSSION

Summary of main results

The aim of this systematic review was to assess and compare the effectiveness and safety (adverse events/serious adverse events) of daratumumab in addition to antineoplastic therapy compared to antineoplastic therapy only for adults with multiple myeloma in non-transplant settings. We identified four eligible RCTs (34 records) involving a total of 1783 participants. We identified a further seven ongoing studies which are expected to be reported.

All studies were open-label. One study was published as abstract only, therefore the risk of bias for most criteria was unclear. The other three studies were published as full texts. Apart from blinding, the risk of bias was low for these studies.

Overall survival

Treatment with daratumumab probably increases overall survival when compared to treatment without daratumumab.

Progression-free survival

Treatment with daratumumab probably increases progression-free survival when compared to treatment without daratumumab.

Quality of life: EORTC QLQ-C30 GHS

Based on the EORTC QLQ-C30, treatment with daratumumab may result in a very small increase in quality of life after 12 months when compared to treatment without daratumumab.

On-study mortality

Treatment with daratumumab probably decreases on-study mortality when compared to treatment without daratumumab.

Serious adverse events

Treatment with daratumumab probably increases serious adverse events when compared to treatment without daratumumab.

Adverse events (CTCAE grade ≥ 3)

There is probably little to no difference in adverse events (CTCAE grade ≥ 3) between treatment with and without daratumumab.

Adverse events: infections (CTCAE grade ≥ 3)

Treatment with daratumumab probably increases infections (CTCAE grade ≥ 3) when compared to treatment without daratumumab.

Overall completeness and applicability of evidence

Since median overall survival has not yet been reached, we cannot predict the effect of daratumumab in this instance. However, at present, there is a clear trend in favour of the daratumumab group.

From a clinical perspective, it is difficult to assess long-term outcomes for a specific treatment when individuals receive multiple lines of therapy. Moreover, according to study protocols, participants from the control arm could switch to daratumumab in case of progress. Consequently, the overall survival effect seen in the review might be even bigger.

It is worth mentioning that the control arms of all studies had different treatment combinations (ALCYONE; AMaRC 03-16; MAIA; OCTANS). Regarding progression-free survival, the results suggest a favourable effect of therapy with lenalidomide and dexamethasone, MAIA, compared to bortezomib plus melphalan-prednisone (ALCYONE; OCTANS).

With major variations across all four study arms, the intervention arms with daratumumab as continuous therapy showed prolonged progression-free survival. It should be added that long-term therapy, as in the control arm in MAIA, showed much better results than limited therapy, as in the control arms in ALCYONE and OCTANS.

Regarding quality of life, very slight improvement was seen in the daratumumab group compared to the control group (ALCYONE; MAIA). Reported baseline data indicated not a very good, but also not necessarily poor, health status at baseline for all participants, so that we can say that there is room for improvement and deterioration. In addition, minimally important differences (MIDs) of ≥ 10 points were suggested as clinically relevant changes to the

EORTC QLQ-C30. With the wide CI in quality of life, we even see a possibility of a decrease in quality of life. See Analysis 3.3.

It would be important to know which causes of death are included in on-study mortality, and how they are distinguished from all-cause mortality. Depending on observation periods in each study arm, on-study mortality varies to the disadvantage of continuous therapy.

Safety (adverse events/serious adverse events) endpoints were reported for as long as participants received treatment. This implies a higher number of adverse events for participants with longer treatment time. We contrast a treated participant with an untreated participant, placing the treated participant at a disadvantage. The observation periods would need to be equal for all study arms to have the same risk of an event occurring. Of further interest would be at what time points the safety endpoints occurred (during or after treatment), and whether they were attributed to therapy. It should be noted that there is limited available information on the safety endpoints.

There were no major differences in outcomes for adverse events (CTCAE grade ≥ 3), highlighting that almost all participants experienced at least one event. Clinically, there is already a tendency for infections (CTCAE grade ≥ 3) to occur more frequently with daratumumab.

In addition, two studies included in the meta-analysis provided data on all primary and secondary outcomes (ALCYONE; MAIA). Two studies did not report all primary and secondary outcomes analysed in our review (AMaRC 03-16; OCTANS), therefore we expect further information; data for further subgroup analyses were not available.

An established first-line therapy consists of bortezomib, lenalidomide, and daratumumab. It would be interesting to know if this combination leads to better results compared to the same combination without daratumumab.

Of further note is that daratumumab, as a human immunoglobin G1-kappa monoclonal antibody, is similar in its molecular weight to that of M protein and cannot be distinguished from IgG-κ-M protein. The lack of differentiation between endogenous M protein and therapeutic antibodies may lead to false-positive interference, imprecision, and especially to downgrading of participant response (Kirchhoff 2021; van de Donk 2016).

Quality of the evidence

Risk of bias in included studies

Overall, apart from blinding, we judged the potential risk of bias in all included trials as low. All trials were reported as randomised and open-label studies. With regard to the study design, it is likely that there was no blinding of either participants or personnel. We therefore judged all studies to be at high risk of performance bias, except for the primary outcome of overall survival. As death is an endpoint that cannot be influenced by the knowledge of group allocation and is not susceptible to bias from the outcome assessor, we judged detection bias for overall survival as low. We judged detection bias in all studies for the outcomes progression-free survival, quality of life, and safety (adverse events/serious adverse events) as high risk, due to no blinding (ALCYONE; AMaRC 03-16; MAIA; OCTANS).

In ALCYONE and MAIA, the method of randomisation was randomly permuted blocks and an interactive web-based randomisation system, therefore we judged allocation concealment as low risk.

We judged the risk of attrition bias as low for ALCYONE. In MAIA, we considered the risk of incomplete safety data as low, but the risk of incomplete survival data as high, given the unclear status of participants in both groups after discontinuing the study. In MAIA, around 325 of 729 participants discontinued treatment in September 2018. In OCTANS, at the time of clinical cut-off (2 July 2020), 31 participants in the daratumumab group and 26 participants in the control group had discontinued treatment. We therefore considered the risk of incomplete safety data as low, but the risk of incomplete survival data as high. We judged the risk of attrition bias for AMaRC 03-16 as unclear due to insufficient information.

We judged the risk of reporting bias as low for ALCYONE and MAIA, as results for all prespecified primary and secondary outcomes were available. The OCTANS study did not provide any information on overall survival, therefore we judged the risk of reporting bias as unclear. In the AMaRC 03-16 study, we rated the risk of reporting bias as unclear due to insufficient information.

In ALCYONE, MAIA, and OCTANS there was no information to suggest other potential sources of bias, therefore we assessed these studies as at low risk of other bias. We rated the risk of other bias in AMaRC 03-16 as unclear due to insufficient information.

Certainty of the evidence

The certainty of evidence was moderate for overall survival. In two studies, median survival was not reached in either group (ALCYONE; MAIA). We downgraded this outcome by one level due to incomplete survival data in one trial. For progression-free survival, the certainty of evidence was moderate, downgraded one level due to no blinding. The certainty of evidence was low for quality of life after 12 months as evaluated with the EORTC QLQ-C30 GHS, downgraded two levels due to no blinding and wide CI. We downgraded the certainty of evidence for on-study mortality by one level due to unclear allocation concealment and no blinding of participants and personnel. The certainty of evidence was moderate for serious adverse events, adverse events (CTCAE grade ≥ 3), and the adverse event infections (CTCAE grade ≥ 3) due to no blinding.

We did not identify a risk of publication bias, as all registered trials were published or still ongoing.

Potential biases in the review process

To avoid potential bias in the review, every step including study selection, data extraction, risk of bias assessment, and GRADE assessment was performed independently by two review authors. With a peer-reviewed systematic search, we included only RCTs. We did not identify any publication bias and are confident that we identified all relevant studies. In fact, we could only identify four RCTs. To increase the informative value of our review, we are tracking all registered trials and will continually update this review as more evidence becomes available. We used the reports of IQWiG as the primary source of evidence for this review because of its completeness and the access to clinical study reports.

Any conflicts were discussed until consensus could be reached. Overall, we followed Cochrane guidelines and recommendations

at every stage of the review and are not aware of any deficiencies in our review process. However, the results are likely to be different and conclusions may change as soon as peer-reviewed high-certainty evidence becomes available. There is a potential limitation, because ranking of outcomes was done after the protocol was published. However, bias resulting from this is limited, as priorisation was performed by a participant representative.

Agreements and disagreements with other studies or reviews

We identified three systematic reviews and network meta-analyses which all demonstrated favourable efficacy results for daratumumab in addition to antineoplastic therapies versus the same antineoplastic therapies without daratumumab for participants with newly diagnosed multiple myeloma who are transplant ineligible and eligible.

Facon 2019 and Ahmed 2020 performed network meta-analyses comparing daratumumab-based treatments with standard-of-care treatments for participants with newly diagnosed multiple myeloma who were transplant ineligible. Two trials were included in each network meta-analysis (ALCYONE; MAIA), both of which were also included in our review. They demonstrated an additional benefit of daratumumab in antineoplastic therapy. In Facon 2019, only overall survival and progression-free survival were reported as relevant outcomes. In Ahmed 2020, progression-free survival, neutropenia, anaemia, pneumonia, minimal residual disease negative status, and overall response rate were reported.

Neupane 2020 is a systematic review reporting the efficacy and safety of daratumumab in a four-drug regimen in transplant eligible and ineligible participants with newly diagnosed multiple myeloma. Three trials were included in this review, of which one, ALCYONE, was also included in our review. Neupane 2020 showed favourable efficacy results for daratumumab in addition to four-drug regimens. Reported outcomes were progression-free survival, minimal residual disease negative status, and overall response rate.

In summary, all systematic reviews have in common an improved efficacy of daratumumab-based treatments compared with standard-of-care treatments without daratumumab. Treatment effects on adverse events as well as on quality of life were not studied and answered as thoroughly as in our review.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review focused on clinically relevant outcomes such as survival, quality of life, and adverse events. The results of our analyses demonstrate favourable efficacy results for daratumumab in addition to antineoplastic therapies versus the same antineoplastic therapies without daratumumab. The addition of daratumumab probably increases overall survival, as well as progression-free survival, and may result in a very small increase in quality of life after 12 months evaluated with the EORTC QLG Core Questionnaire (EORTC QLQ-C30). However, daratumumab probably increases serious adverse events when compared to treatment without daratumumab. Daratumumab-based treatments show little to no difference in reported adverse events (Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3) compared to standard-of-care treatments without daratumumab. Of note, there is an increased risk of infections (CTCAE grade ≥ 3) with daratumumab-based regimens.

We conclude that daratumumab might be considered as a treatment option for participants with newly diagnosed multiple myeloma who are transplant ineligible. However, clinicians in the field should always individually evaluate with their patients whether the increase in overall survival achieved with the novel drug combinations is outweighed by the potential increase in harms, including the increased risk of serious adverse events and infections (CTCAE grade ≥ 3).

Implications for research

Substantial clinical evidence from randomised controlled trials supports the effectiveness of daratumumab in addition to antineoplastic therapies versus the same antineoplastic therapies without daratumumab for people with newly diagnosed multiple myeloma who are transplant ineligible.

Our review demonstrates the need for further research to clarify the role of antineoplastic therapy with or without daratumumab. To find and verify the optimal treatment regimen for people with a confirmed diagnosis of multiple myeloma who are transplant ineligible, and the efficacy and toxicity of daratumumab, further randomised controlled trials are necessary. We have identified a further seven ongoing studies which are expected to be reported between December 2023 and October 2031. Special focus must be placed on more data on quality of life as well as on comparable data collection of adverse events.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ALCYONE

Study characteristics	
Methods	• Design: randomised, open-label, phase III multicentre trial • Sample size: n = 706 participants enrolled (actual); Arm A: daratumumab plus velcade (bortezomib) plus melphalan-prednisone n = 350, Arm B: velcade plus melphalan-prednisone n = 356 • Duration of treatment: 9 x 5-week cycles • Median follow-up: 40.1 months • Ongoing: yes • Estimated study completion date: 30 June 2023 • Trial registration numbers: NCT02195479; EuCTR2014-002272-88; 54767414MMY3007; CR104761

Participants	• Participants with newly diagnosed multiple myeloma ineligible for high-dose therapy plus stem cell transplantation
	• Inclusion criteria: newly diagnosed multiple myeloma and not considered candidate for high-dose chemotherapy with stem cell transplantation due to: age ≥ 65 years; or < 65 years and ineligible for high-dose chemotherapy; presence of CRAB criteria, bone marrow plasmacytosis with ≥ 10% plasma cells or biopsy-proven plasmacytoma, and measurable secretory disease in serum or urine; ECOG performance status 0 to 3; women of childbearing potential must have negative pregnancy test 14 days prior to randomisation and must abstain from sexual intercourse or use 2 methods of reliable birth control simultaneously
	• Exclusion criteria: primary amyloidosis, monoclonal gammopathy of undetermined significance, or smouldering multiple myeloma; Waldenström's disease, or similar conditions with presence of IgM M protein in the absence of a clonal plasma cell infiltration with lytic bone lesions; prior or current systemic therapy or stem cell transplantation for multiple myeloma, except an emergency use of a short course of corticosteroids before treatment; peripheral neuropathy or neuropathic pain > NCI criteria grade 2; malignancy within 3 years before the date of randomisation (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy with minimal risk of recurrence within 3 years); radiation therapy within 14 days of randomisation; plasmapheresis within 28 days of randomisation; chronic obstructive pulmonary disease; moderate or severe persistent asthma within the last 2 years or currently uncontrolled asthma; known or suspected COPD must have an FEV1 test; seropositive for HIV, hepatitis B or history of hepatitis C; concurrent medical or psychiatric condition or disease (hazard for participating in this study)
	• Baseline characteristics:
	  ○ Mean age: 71.4 years
	  ○ Male/female: 46.3% to 53.7%
	  ○ ISS: I, II, III
	  ○ ECOG performance status: 0 to 3
	  ○ Country: worldwide in high- and middle-income countries

ALCYONE *(Continued)*

Interventions	• Arm A: velcade (bortezomib) 1.3 mg/m^2 as subcutaneous injection, twice weekly at weeks 1, 2, 4, and 5 in cycle 1 followed by once weekly at weeks 1, 2, 4, and 5 in cycles 2 to 9, melphalan 9 mg/m^2, orally, once daily (on days 1 to 4) and prednisone 60 mg/m^2, orally, once daily, on days 1 to 4 of each cycle up to cycle 9. In addition, participants will also receive daratumumab 16 mg/kg as intravenous infusion, once weekly, for 6 weeks in cycle 1 and then every 3 weeks, in cycle 2 to 9 and thereafter, once every 4 weeks until documented progression, unacceptable toxicity, or study end. On days when daratumumab is given, dexamethasone 20 mg intravenous or orally is given 1 hour or less prior to daratumumab administration as pre-medication and prednisone substitute, and prednisone 60 mg/m^2 once daily will be given on days 2 to 4. Following amendment 7, participants will have the option to switch to daratumumab subcutaneous on day 1 of any cycle, at the discretion of the investigator. • Arm B: velcade (bortezomib) 1.3 mg/m^2 as subcutaneous injection, twice weekly at weeks 1, 2, 4, and 5 in cycle 1 followed by once weekly at weeks 1, 2, 4, and 5 in cycles 2 to 9, melphalan 9 mg/m^2, orally, once daily (on days 1 to 4) and prednisone 60 mg/m^2, orally, once daily, on days 1 to 4 of each cycle up to cycle 9

Outcomes	• Primary:
	  ○ Progression-free survival
	• Secondary:
	  ○ Overall response rate
	  ○ Very good partial response
	  ○ Complete response
	  ○ Minimal residual disease negativity
	  ○ Overall survival
	  ○ Progression-free survival on next line of therapy
	  ○ Stringent complete response
	  ○ Time to disease progression
	  ○ Time to response
	  ○ Duration of response
	  ○ Time to next treatment
	  ○ Best m-protein response
	  ○ Change from baseline in EORTC QLQ-C30: emotional functioning score: from day 1, in cycle 1: every 12 weeks for year 1; thereafter every 24 weeks until disease progression; after disease progression in week 8 and 16 with a window of ± 14 days
	  ○ Change from baseline in EQ-5D-5L: visual analogue scale: from day 1, in cycle 1: every 12 weeks for year 1; thereafter every 24 weeks until disease progression; after disease progression in week 8 and 16 with a window of ± 14 days
	  ○ Change from baseline in EQ-5D-5L: utility score: from day 1, in cycle 1: every 12 weeks for year 1; thereafter every 24 weeks until disease progression; after disease progression in week 8 and 16 with a window of ± 14 days
	  ○ On-study mortality
	  ○ Serious adverse events
	  ○ Adverse events
	  ■ Neutropenia
	  ■ Thrombocytopenia
	  ■ Anaemia
	  ■ Leukopenia
	  ■ Lymphopenia
	  ■ Infections and parasitic diseases
	  ■ Diarrhoea
	  ■ Pneumonia
	  ■ Nausea
	• Outcomes of interest (for the review):
	  ○ Overall survival: reported
	  ○ Progression-free survival: reported

ALCYONE *(Continued)*

- Quality of life: reported
- Complete response: reported
- On-study mortality: reported
- Serious adverse events: reported
- Adverse events (CTCAE grade ≥ 3): reported
  - Neutropenia: reported
  - Thrombocytopenia: reported
  - Anaemia: reported
  - Leukopenia: reported
  - Lymphopenia: reported
  - Infections: reported
  - Diarrhoea: reported
  - Pneumonia: reported
  - Nausea: reported
- Minimal residual disease negativity: reported

- Additional study outcomes:
  - Overall response rate
  - Very good partial response
  - Stringent complete response
  - Time to disease progression
  - Time to response
  - Duration of response
  - Time to next treatment
  - Best m-protein response

Notes	• Sponsor/Funding: Janssen Research & Development, LLC • Type of publication (full text or abstract only): full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "permuted block randomization by an interactive web based randomization system. Each subject was assigned a unique subject number"
Allocation concealment (selection bias)	Low risk	Quote: "permuted block randomization by an interactive web based randomization system. Each subject was assigned a unique subject number"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: not blinded, but awareness of intervention cannot bias detection of outcome; participants are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: "open-label" Comment: not blinded, awareness of intervention can bias detection of outcome
Blinding of safety assessment (detection bias)	High risk	Quote: "open-label"

ALCYONE *(Continued)*

		Comment: not blinded, awareness of intervention can bias detection of outcome
Blinding of quality of life assessment (detection bias)	High risk	Quote: "open label" Comment: not blinded, awareness of intervention can bias detection of outcome
Incomplete survival data (attrition bias)	Low risk	Comment: trial is still going; missing participants in both arms are reasoned; both arms are balanced
Incomplete safety data (attrition bias)	Low risk	Comment: all reported participants received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Comment: no information to suggest other sources of bias

AMaRC 03-16

Study characteristics	
Methods	• Design: randomised, open-label, phase II clinical trial • Sample size: n = 121 participants enrolled (actual); Arm A: bortezomib, cyclophosphamide, dexamethasone, and daratumumab n = 64, Arm B: bortezomib, cyclophosphamide, and dexamethasone n = 57 • Duration of treatment: 9 x 5-week cycles and beyond • Estimated median follow-up: 23.7 months • Ongoing: yes • Estimated study completion date: 30 April 2025 • Trial registration numbers: AMARC 03-16; ACTRN12617000202369; U1111-1192-2799
Participants	• Participants with newly diagnosed multiple myeloma ineligible for high-dose therapy plus stem cell transplantation • Inclusion criteria: age ≥ 18; untreated participants with symptomatic myeloma as per IMWG criteria, measurable disease, ineligible for high-dose chemotherapy with autologous stem cell transplantation; no contraindication to any of the study drugs; ECOG performance status of 0, 1, or 2; must meet certain clinical laboratory criteria; certain level of absolute neutrophil count, platelet count, bilirubin, ALT, and AST; must sign an informed consent form; women are postmenopausal or agree to use effective contraception; men who agree to use effective contraception; study site must be able to get correlative samples to the Alfred Hospital, Melbourne, Australia, within 24 hours of collection • Exclusion criteria: amyloid light-chain amyloidosis, monoclonal gammopathy of uncertain significance or smouldering multiple myeloma; women who are lactating or have a positive serum pregnancy test; peripheral neuropathy ≥ grade 3 or grade 2 with pain; significant airways disease according to certain definitions; known COPD with FEV1 < 50%; moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification; uncontrolled cardiovascular conditions; known ongoing or active systemic infection, active hepatitis B or C, or known seropositivity for HIV; active malignancy (except for adequately treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix; stage I cancer, currently in remission for 2 years; stage I prostate cancer, that does not require treatment) unless the participant has been free of the disease for ≥ 2 years; serious medical or psychiatric illness; allergies to any of the study medications, their analogues, or excipients; participation in other clinical trials for the treatment of multiple myeloma • Baseline characteristics: ◦ Country: Australia

AMaRC 03-16 *(Continued)*

Interventions	• Arm A: 9 x 5-week cycles of bortezomib 1.3 mg/m^2 as subcutaneous injection on days 1, 8, 15, and 22; cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 and dexamethasone 20 mg orally on days 1, 8, 15, and 22 plus daratumumab 16 mg/kg as intravenous infusion on days 1, 8, 15, and 22 in cycles 1 and 2, days 1 and 15 in cycles 3 to 6, and day 1 of cycles 7 to 9, followed by daratumumab maintenance 16 mg/kg as intravenous infusion every 4 weeks until progression • Arm B: 9 x 5-week cycles of bortezomib 1.3 mg/m^2 as subcutaneous injection on days 1, 8, 15, and 22; cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 and dexamethasone 20 mg orally on days 1, 8, 15, and 22

Outcomes	• Primary:
	  ◦ Progression-free survival
	• Secondary:
	  ◦ Overall response rate
	  ◦ Minimal residual disease negativity rates by Euroflow (lower limit of detection 10^{-5})
	  ◦ Overall survival
	  ◦ Toxicity
	  ◦ Quality of life
	• Outcomes of interest (for the review):
	  ◦ Overall survival: reported
	  ◦ Progression-free survival: reported
	  ◦ Quality of life: reported
	  ◦ Complete response: not reported
	  ◦ On-study mortality: not reported
	  ◦ Serious adverse events: not reported
	  ◦ Adverse events (CTCAE grade ≥ 3): not reported
	  ■ Neutropenia: not reported
	  ■ Thrombocytopenia: not reported
	  ■ Anaemia: not reported
	  ■ Leukopenia: not reported
	  ■ Lymphopenia: not reported
	  ■ Infections: not reported
	  ■ Diarrhoea: not reported
	  ■ Pneumonia: not reported
	  ■ Nausea: not reported
	  ◦ Minimal residual disease negativity: reported
	• Additional study outcomes:
	  ◦ Overall response rate
	  ◦ Toxicity

Notes	• Sponsor/Funding: Janssen Pharmaceuticals; Alfred Health • Contact: Prof Peter Mollee; Princess Alexandra Hospital, 199 Ipswich Road, Woolloongabba, QLD 4102, Australia; Tel: +61 7 3176 2111; Email: Peter.Mollee@health.qld.gov.au • We contacted the authors for missing data, but they were unable to provide further information. • Type of publication (full text or abstract only): abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available

AMaRC 03-16 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: not blinded, but awareness of intervention cannot bias detection of outcome; participants are dead or alive
Blinding of progression free survival assessment (detection bias)	High risk	Quote: "open-label" Comment: not blinded, awareness of intervention can bias detection of outcome
Blinding of safety assessment (detection bias)	High risk	Quote: "open-label" Comment: not blinded, awareness of intervention can bias detection of outcome
Blinding of quality of life assessment (detection bias)	High risk	Quote: "open label" Comment: not blinded, awareness of intervention can bias detection of outcome
Incomplete survival data (attrition bias)	Unclear risk	No information available
Incomplete safety data (attrition bias)	Unclear risk	No information available
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Unclear risk	No information available

MAIA

Study characteristics	
Methods	• Design: randomised, open-label, phase III multicentre trial • Sample size: n = 737 participants enrolled (actual); Arm A: daratumumab plus lenalidomide plus dexamethasone n = 368; Arm B: lenalidomide plus dexamethasone n = 369 • Duration of treatment: 7 x 28-day cycles and beyond • Median follow-up: 28 months • Ongoing: yes • Estimated study completion date: 31 January 2026 • Trial registration numbers: NCT02252172; EuCTR2014-002273-11; 54767414MMY3008; CR104762
Participants	• Participants with newly diagnosed multiple myeloma ineligible for high-dose therapy plus stem cell transplantation • Inclusion criteria: newly diagnosed multiple myeloma and not considered candidate for high-dose chemotherapy with stem cell transplantation; age ≥ 65 years, or < 65 years and ineligible for high-dose chemotherapy; presence of CRAB criteria; monoclonal plasma cells in bone marrow ≥ 10% or biopsy-proven plasmacytoma, and measurable secretory disease in serum or urine; ECOG performance

MAIA *(Continued)*

	status 0 to 2; women of childbearing potential must have negative pregnancy test 14 days prior to randomisation, and must abstain from sexual intercourse or use 2 methods of reliable birth control simultaneously; men must use an adequate contraception method and must agree to not donate sperm • Exclusion criteria: primary amyloidosis, monoclonal gammopathy of undetermined significance or smouldering multiple myeloma; Waldenström's disease, or similar conditions with presence of IgM M protein in the absence of a clonal plasma cell infiltration with lytic bone lesions; malignancy within 5 years before the date of randomisation (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy with minimal risk of recurrence within 5 years); prior or current systemic therapy or stem cell transplantation, except an emergency use of a short course of corticosteroids; radiation therapy within 14 days of randomisation; COPD; persistent or uncontrolled asthma; known or suspected COPD must have an FEV1 test; HIV, hepatitis B or history of hepatitis C • Baseline characteristics: ◦ Mean age: 74.1 ◦ Male/female: 52.1% to 47.9% ◦ ISS: I, II, III ◦ ECOG performance status: 0 to 2 ◦ Country: worldwide in high-income countries
Interventions	• Arm A: daratumumab 16 mg/kg by intravenous infusion, once a week for 8 weeks, then once every other week for 16 weeks, thereafter once every 4 weeks, lenalidomide 25-milligram capsule orally on day 1 through day 21 of each 28-day cycle, dexamethasone 40 mg orally or intravenously once a week. Study treatment continues until disease progression, unacceptable toxicity, or end of study. • Arm B: lenalidomide 25-milligram capsule orally on day 1 through day 21 of each 28-day cycle, dexamethasone 40 mg orally or intravenously once a week. Study treatment continues until disease progression, unacceptable toxicity, or end of study.
Outcomes	• Primary: ◦ Progression-free survival • Secondary: ◦ Complete response ◦ Very good partial response ◦ Minimal residual disease negativity ◦ Overall response rate ◦ Overall survival ◦ Time to disease progression ◦ Time to response ◦ Duration of response ◦ Time to subsequent antimyeloma treatment ◦ Progression-free survival on next line of therapy ◦ Change from baseline in EORTC QLQ-C30 Global Health Status score: day 1 of cycle 3, 6, 9, 12 for year 1; thereafter every 6th month ± 14 days until disease progression; after disease progression in week 8 and 16 ◦ Change from baseline in EQ-5D-5L visual analogue scale: day 1 of cycle 3, 6, 9, 12 for year 1; thereafter every 6th month ± 14 days until disease progression; after disease progression in week 8 and 16 ◦ Change from baseline in EQ-5D-5L utility score: day 1 of cycle 3, 6, 9, 12 for year 1; thereafter every 6th month ± 14 days until disease progression; after disease progression in week 8 and 16 ◦ On-study mortality ◦ Serious adverse events ◦ Adverse events ■ Neutropenia ■ Thrombocytopenia ■ Anaemia ■ Leukopenia

MAIA *(Continued)*

- Lymphopenia
- Infections and parasitic diseases
- Diarrhoea
- Pneumonia
- Nausea

- Outcomes of interest (for the review):
  - Overall survival: reported
  - Progression-free survival: reported
  - Quality of life: reported
  - Complete response: reported
  - On-study mortality: reported
  - Serious adverse events: reported
  - Adverse events (CTCAE grade ≥ 3): reported
    - Neutropenia: reported
    - Thrombocytopenia: reported
    - Anaemia: reported
    - Leukopenia: reported
    - Lymphopenia: reported
    - Infections: reported
    - Diarrhoea: reported
    - Pneumonia: reported
    - Nausea: reported
  - Minimal residual disease negativity: reported
- Additional study outcomes
  - Very good partial response
  - Overall response rate
  - Time to disease progression
  - Time to response
  - Duration of response
  - Time to subsequent antimyeloma treatment

Notes	• Sponsor/Funding: Janssen Research & Development, LLC • Type of publication (full text or abstract only): full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "permuted block randomization by an interactive web based randomization system. Each subject was assigned a unique subject number"
Allocation concealment (selection bias)	Low risk	Quote: "interactive web based randomization system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of overall survival assessment (detection bias)	Low risk	Comment: not blinded, but awareness of intervention cannot bias detection of outcome; participants are dead or alive

MAIA *(Continued)*

Blinding of progression free survival assessment (detection bias)	High risk	Quote: "open-label" Comment: not blinded, awareness of intervention can bias detection of outcome
Blinding of safety assessment (detection bias)	High risk	Quote: "open-label" Comment: not blinded, awareness of intervention can bias detection of outcome
Blinding of quality of life assessment (detection bias)	High risk	Quote: "open label" Comment: not blinded, awareness of intervention can bias detection of outcome
Incomplete survival data (attrition bias)	High risk	Comment: trial is still going; missing participants in both arms are reasoned; but approximately 39% of participants in the intervention group and 64% of participants in the control group discontinued the study. The status of these participants is unclear
Incomplete safety data (attrition bias)	Low risk	Comment: all reported participants received at least one study drug
Selective reporting (reporting bias)	Low risk	Comment: protocol and results for all pre-specified primary and secondary outcomes available
Other bias	Low risk	Comment: no information to suggest other sources of bias

OCTANS

Study characteristics	
Methods	• Design: randomised (2:1), open-label, phase III multicentre trial • Sample size: n = 220 participants enrolled (actual); Arm A: daratumumab plus velcade (bortezomib) plus melphalan-prednisone n = 146, Arm B: velcade plus melphalan-prednisone n = 74 • Duration of treatment: 9 x 42-day cycles • Median follow-up: 12.3 months • Ongoing: yes • Estimated study completion date: 18 December 2023 • Trial registration numbers: NCT03217812; 54767414MMY3011; CR108340
Participants	• Asian participants (from the following countries/regions: China, Hong Kong SAR, Taiwan, Korea, and Malaysia) with newly diagnosed multiple myeloma and ineligible for autologous stem cell transplantation • Inclusion criteria: newly diagnosed multiple myeloma and not considered candidate for high-dose chemotherapy with autologous stem cell transplant due to age (≥ 65 years) or comorbidities; ECOG performance status ≤ 2 • Exclusion criteria: primary amyloidosis; monoclonal gammopathy of undetermined significance; smouldering multiple myeloma; Waldenström's disease or other conditions with presence of IgM M protein in the absence of a clonal plasma cell infiltration with lytic bone lesions; prior or current systemic therapy or stem cell transplantation, except an emergency use of a short course of corticosteroids; NCI criteria grade ≥ 2 for peripheral neuropathy or neuropathic pain; malignancy within 3 years before the date of randomisation (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix or breast, or malignancy with minimal risk of recurrence within 3 years); radiation therapy within 14 days before randomisation; plasmapheresis within 28 days before randomisation; clinical signs of meningeal involvement of multiple myeloma; known or suspected COPD must have an FEV1 test; moderate or severe persistent asthma within the last 2 years or

OCTANS *(Continued)*

	currently uncontrolled asthma; seropositive for HIV, hepatitis B or history of hepatitis C; concurrent medical or psychiatric condition or disease (hazard for participating in this study); clinically significant cardiac disease; known allergies, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins or to their excipients, or known sensitivity to mammalian-derived products; plasma cell leukaemia or polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome; inability to comply with the study protocol; major surgery within 2 weeks before randomisation, during study, or within 2 weeks after the last dose of study treatment; live vaccination within 4 weeks before treatment; gastrointestinal disease that affects drug absorption • Baseline characteristics: ◦ Mean age: 69 years ◦ Country: China, Hong Kong SAR, Taiwan, Korea, and Malaysia
Interventions	• Arm A: 9 x 42-day cycles of bortezomib 1.3 mg/m^2 as subcutaneous injection twice-weekly in cycle 1 at weeks 1, 2, 4, 5, then once weekly in cycles 2 to 9 at weeks 1, 2, 4, 5; melphalan 9 mg/m^2 orally and prednisone 60 mg/m^2 orally once daily on days 1 to 4 of each cycle. In addition, participants will also receive daratumumab 16 mg/kg as intravenous infusion once weekly in cycle 1, once every 3 weeks in cycles 2 to 9, and once every 4 weeks thereafter until disease progression or unacceptable toxicity. • Arm B: 9 x 42-day cycles of bortezomib 1.3 mg/m^2 as subcutaneous injection twice-weekly in cycle 1 at weeks 1, 2, 4, 5, then once weekly in cycles 2 to 9 at weeks 1, 2, 4, 5; melphalan 9 mg/m^2 orally and prednisone 60 mg/m^2 orally once daily on days 1 to 4 of each cycle
Outcomes	• Primary: ◦ Rate of very good partial response or better • Secondary: ◦ Progression-free survival ◦ Quality of life ◦ Time to next treatment ◦ Overall response rate ◦ Stringent complete response ◦ Complete response ◦ Time to response ◦ Duration of response ◦ Overall survival ◦ On-study mortality ◦ Patient-reported outcomes ◦ Immunogenicity ◦ Safety ■ Serious adverse events ■ Adverse events (CTCAE grade ≥ 3) ■ Neutropenia ■ Thrombocytopenia ■ Anaemia ■ Leukopenia ■ Lymphopenia ■ Infections ■ Diarrhoea ■ Pneumonia ◦ Minimal residual disease negativity ◦ Pharmacokinetics of daratumumab • Outcomes of interest (for the review): ◦ Overall survival: reported ◦ Progression-free survival: reported ◦ Quality of life: reported

OCTANS *(Continued)*

- Complete response: reported
- On-study mortality: reported
- Serious adverse events: reported
- Adverse events (CTCAE grade ≥ 3): reported
  - Neutropenia: reported
  - Thrombocytopenia: reported
  - Anaemia: reported
  - Leukopenia: reported
  - Lymphopenia: reported
  - Infections: reported
  - Diarrhoea: reported
  - Pneumonia: reported
  - Nausea: not reported
- Minimal residual disease negativity: reported

- Additional study outcomes:
  - Rate of very good partial response or better
  - Time to next treatment
  - Overall response rate
  - Stringent complete response
  - Time to response
  - Duration of response
  - Patient-reported outcomes
  - Immunogenicity
  - Pharmacokinetics of daratumumab

Notes	• Sponsor/Funding: Janssen Research & Development, LLC • Type of publication (full text or abstract only): full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized by means of a computer- generated randomization schedule in a 2:1 ratio to receive D-VMP or VMP to allow more patients to be exposed to D-VMP treatment"
Allocation concealment (selection bias)	Low risk	Quote: "randomized by means of a computer- generated randomization schedule in a 2:1 ratio to receive D-VMP or VMP to allow more patients to be exposed to D-VMP treatment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of overall survival assessment (detection bias)	Unclear risk	No information available
Blinding of progression free survival assessment (detection bias)	High risk	Quote: "open-label" Comment: not blinded, awareness of intervention can bias detection of outcome
Blinding of safety assessment (detection bias)	High risk	Quote: "open-label"

OCTANS *(Continued)*

		Comment: not blinded, awareness of intervention can bias detection of outcome
Blinding of quality of life assessment (detection bias)	High risk	Quote: "open label" Comment: not blinded, awareness of intervention can bias detection of outcome
Incomplete survival data (attrition bias)	High risk	Quote: "at the clinical cutoff (July 2, 2020), 31 (21,5%) patients in the D-VMP group and 26 (36,6%) patients in the VMP group discontinued treatment during cycles 1 through 9." The status of these participants is unclear.
Incomplete safety data (attrition bias)	Low risk	Comment: all reported participants received at least one study drug
Selective reporting (reporting bias)	Unclear risk	Comment: There are no information about the outcome overall survival. All other pre-specified primary and secondary outcomes are available
Other bias	Low risk	Comment: no information to suggest other sources of bias

ALT: alanine transaminase
AST: aspartate aminotransferase
COPD: chronic obstructive pulmonary disease
CRAB: Hypercalcaemia; Renal insufficiency; Anaemia; Bone lesions with 1 or more osteolytic lesions
CTCAE: Common Terminology Criteria for Adverse Events
ECOG: Eastern Cooperative Oncology Group
FEV1: forced expiratory volume in the first minute
IgM: immunoglobulin M
IMWG: International Myeloma Working Group
ISS: International Staging System
NCI: National Cancer Institute

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cavo 2018	Propensity score matching
Dimopoulos 2020	Matching-adjusted indirect treatment comparison
Facon 2019	Meta-analysis
Gil-Sierra 2020	Meta-analysis
Manier 2019	Meta-analysis and no daratumumab
San-Miguel 2018	Review
Sekine 2019	Review
Syed 2019	Review
Thein 2019	Not a randomised controlled trial
van Beekhuizen 2019	Meta-analysis

Characteristics of ongoing studies *[ordered by study ID]*

CEPHEUS

Study name	CEPHEUS
Methods	• Design: randomised, open-label, phase III multicentre trial • Sample size: n = 395 participants enrolled (actual); Arm A: daratumumab plus velcade (bortezomib) plus lenalidomide plus dexamethasone, Arm B: velcade (bortezomib) plus lenalidomide plus dexamethasone • Duration of treatment: 8 x 21-day cycles • Median follow-up: not reported • Ongoing: yes • Estimated study completion date: 30 April 2025 • Trial registration numbers: NCT03652064; EUCTR2018-001545-13-ES; 54767414MMY3019; CR108529; JPRN-JapicCTI-184162
Participants	Inclusion criteria: diagnosed multiple myeloma documented per IMWG criteria, bone marrow plasmacytosis with ≥ 10% plasma cells or biopsy-proven plasmacytoma, at least 1 of the CRAB criteria or biomarkers of malignancy criteria; measurable disease, as assessed by central laboratory; ECOG performance status 0 to 2; a woman of childbearing potential must have 2 negative pregnancy tests within 10 to 14 days prior to dosing and within 24 hours prior to dosing; a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 3 months after receiving the last dose of any component of the treatment regimen • Exclusion criteria: frailty index of ≥ 2 according to myeloma geriatric assessment score; prior therapy for multiple myeloma other than a short course of corticosteroids; prior or concurrent invasive malignancy within 5 years of date of randomisation (exceptions are basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years); peripheral neuropathy or neuropathic pain ≥ NCI criteria grade 2; focal radiation therapy within 14 days of randomisation except for palliative radiotherapy for symptomatic pain management; radiotherapy within 14 days prior to randomisation on measurable extramedullary plasmacytoma is not permitted even in the setting of palliation for symptomatic management
Interventions	• Arm A: bortezomib 1.3 mg/m^2 as subcutaneous injection, twice-weekly on days 1, 4, 8, and 11 of each 21-day cycle in cycle 1 to 8, lenalidomide 25 mg orally on days 1 to 14 in cycle 1 to 8 and on days 1 to 21 in cycle 9 (cycle of 28 days) and beyond until disease progression or unacceptable toxicity, whichever occurs first, dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle in cycle 1 to 8 and 40 mg orally on days 1, 8, 15, 22 in cycle 9 and beyond (each cycle of 28 days) followed by daratumumab-lenalidomide-dexamethasone until disease progression or unacceptable toxicity, daratumumab 1800 mg as subcutaneous injection once every week in cycle 1 to 2, then every 3 weeks in cycle 3 to 8. In cycle 9 and beyond, participants will receive daratumumab 1800 mg as subcutaneous injection once every 4 weeks until documented disease progression or unacceptable toxicity. • Arm B: bortezomib 1.3 mg/m^2 as subcutaneous injection, twice-weekly on days 1, 4, 8, and 11 of each 21-day cycle in cycle 1 to 8, lenalidomide 25 mg orally on days 1 to 14 in cycle 1 to 8 and on days 1 to 21 in cycle 9 (cycle of 28 days) and beyond until disease progression or unacceptable toxicity, whichever occurs first, dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle in cycle 1 to 8 and 40 mg orally on days 1, 8, 15, 22 in cycle 9 and beyond (each cycle of 28 days) followed by lenalidomide-dexamethasone until disease progression or unacceptable toxicity

Outcomes	• Primary:
	  ◦ Minimal residual disease negativity
	• Secondary:
	  ◦ Progression-free survival
	  ◦ Minimal residual disease negativity at 1 year

CEPHEUS *(Continued)*

- Durable minimal residual disease negativity
- Overall response rate
- Very good partial response
- Complete response
- Progression-free survival on next line of therapy
- Overall survival
- Time to response
- Duration of response
- Maximum observed serum concentration of daratumumab
- Minimum observed serum concentration of daratumumab
- Number of participants with antidaratumumab antibodies
- Number of participants with anti-rHuPH20 antibodies

- Outcomes of interest (for the review):
  - Overall survival: reported
  - Progression-free survival: reported
  - Quality of life: not reported
  - Complete response: reported
  - On-study mortality: not reported
  - Serious adverse events: not reported
  - Adverse events (CTCAE grade ≥3): not reported
    - Neutropenia: not reported
    - Thrombocytopenia: not reported
    - Anaemia: not reported
    - Leukopenia: not reported
    - Lymphopenia: not reported
    - Infections: not reported
    - Diarrhoea: not reported
    - Pneumonia: not reported
    - Nausea: not reported
  - Minimal residual disease negativity: reported
- Additional study outcomes:
  - Durable minimal residual disease negativity
  - Overall response rate
  - Very good partial response
  - Progression-free survival on next line of therapy
  - Time to response
  - Duration of response
  - Maximum observed serum concentration of daratumumab
  - Minimum observed serum concentration of daratumumab
  - Number of participants with antidaratumumab antibodies
  - Number of participants with anti-rHuPH20 antibodies

Starting date	• 6 November 2018
Contact information	• Not reported
Notes	• Sponsor/Funding: Janssen Research & Development, LLC • Type of publication (full text or abstract only): conference abstract

NCT03217812

Study name	A phase 3, multicenter, randomized, controlled, open-label study of velcade (bortezomib) melphalan-prednisone (vmp) compared to daratumumab in combination with vmp (d-vmp), in subjects with previously untreated multiple myeloma who are ineligible for high-dose therapy (Asia Pacific region)
Methods	• Design: randomised, open-label, phase III multicentre trial • Sample size: n = 220 participants enrolled (actual); Arm A: velcade (bortezomib) plus melphalan plus prednisone plus daratumumab, Arm B: velcade (bortezomib) plus melphalan plus prednisone • Duration of treatment: 9 cycles • Median follow-up: not reported • Ongoing: yes • Estimated study completion date: 18 December 2023 • Trial registration numbers: 54767414MMY3011; CR108340; NCT03217812
Participants	• Participants with newly diagnosed multiple myeloma who are ineligible for high-dose therapy plus stem cell transplantation • Inclusion criteria: newly diagnosed multiple myeloma and not considered candidate for high-dose chemotherapy with stem cell transplantation; presence of CRAB criteria and measurable secretory disease; must meet certain clinical laboratory criteria; women of childbearing potential must have negative pregnancy test within 14 days prior to randomisation • Exclusion criteria: primary amyloidosis, monoclonal gammopathy of undetermined significance, or smouldering multiple myeloma; Waldenström's disease, or IgM M-protein presence in absence of a clonal plasma cell infiltration with lytic bone lesions; prior or current systemic therapy or stem cell transplantation; peripheral neuropathy ≥ NCI criteria grade 2; prior (within 3 years before the date of randomisation) history of malignancies, other than multiple myeloma (except for basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or the breast), unless the participant has been cured with minimal risk of recurrence within 3 years; radiation therapy within 14 days of randomisation; known seropositivity for hepatitis B
Interventions	• Arm A: bortezomib 1.3 mg/m^2 as subcutaneous injection, twice-weekly on days 1, 2, 4, and 5 in cycle 1 followed by once weekly at weeks 1, 2, 4, and 5 in cycle 2 to 9, melphalan 9 mg/m^2 (if serum creatine is > 2 mg/dL at baseline, participants must be administrated 4.5 mg/m^2 of melphalan, instead of 9 mg/m^2) orally, once daily on days 1 to 4, prednisone 60 mg/m^2 orally, once daily on days 1 to 4 of each cycle up to cycle 9, daratumumab 16 mg/kg as intravenous infusion or subcutaneously once weekly for 6 weeks in cycle 1 and then every 3 weeks in cycles 2 to 9 and thereafter once every 4 weeks until documented disease progression or unacceptable toxicity or end of study • Arm B: bortezomib 1.3 mg/m^2 as subcutaneous injection, twice-weekly on days 1, 2, 4, and 5 in cycle 1 followed by once weekly at weeks 1, 2, 4, and 5 in cycle 2 to 9, melphalan 9 mg/m^2 (if serum creatine is > 2 mg/dL at baseline, participants must be administrated 4.5 mg/m^2 of melphalan, instead of 9 mg/m^2) orally, once daily on days 1 to 4, prednisone 60 mg/m^2 orally, once daily on days 1 to 4 of each cycle up to cycle 9

Outcomes	• Primary:
	  ◦ Very good partial response or better rate at 6 months after last participant first dose
	  ◦ Very good partial response or better rate at 3 years after last participant first dose
	• Secondary:
	  ◦ Progression-free survival
	  ◦ Time to next treatment
	  ◦ Overall response rate
	  ◦ Complete response
	  ◦ Stringent complete response rate
	  ◦ Time to response
	  ◦ Overall survival
	  ◦ Duration of response

NCT03217812 *(Continued)*

- Time to very good partial response or better
- Duration of very good partial response or better
- Quality of life based on EQ-5D questionnaires
- Quality of life based on EORTC QLQ-C30 questionnaires
- Number of participants with antidaratumumab antibodies
- Adverse events
- Clinical efficacy of D-VMP in high-risk molecular subgroups

- Outcomes of interest (for the review):
  - Overall survival: reported
  - Progression-free survival: reported
  - Quality of life: reported
  - Complete response: reported
  - On-study mortality: not reported
  - Serious adverse events: not reported
  - Adverse events (CTCAE grade ≥ 3): reported
    - Neutropenia: not reported
    - Thrombocytopenia: not reported
    - Anaemia: not reported
    - Leukopenia: not reported
    - Lymphopenia: not reported
    - Infections: not reported
    - Diarrhoea: not reported
    - Pneumonia: not reported
    - Nausea: not reported
  - Minimal residual disease negativity: not reported
- Additional study outcomes:
  - Very good partial response or better rate at 6 months after last participant first dose
  - Very good partial response or better rate at 3 years after last participant first dose
  - Time to next treatment
  - Overall response rate
  - Stringent complete response
  - Time to response
  - Duration of response
  - Time to very good partial response or better
  - Duration of very good partial response or better
  - Number of participants with antidaratumumab antibodies
  - Clinical efficacy of D-VMP in high-risk molecular subgroups

Starting date	• 23 November 2017
Contact information	• Not reported
Notes	• Sponsor/Funding: Janssen Research & Development, LLC

NCT03710603

Study name	A phase 3 study comparing daratumumab, velcade (bortezomib), lenalidomide, and dexamethasone (d-vrd) vs velcade, lenalidomide, and dexamethasone (vrd) in subjects with previously untreated multiple myeloma who are eligible for high-dose therapy
Methods	• Design: randomised, open-label, phase III multicentre trial

NCT03710603 *(Continued)*

- Sample size: n = 690 participants enrolled (actual); Arm A: velcade (bortezomib) plus lenalidomide plus dexamethasone plus daratumumab, Arm B: velcade (bortezomib) plus lenalidomide plus dexamethasone
- Duration of treatment: 6 cycles
- Median follow-up: not reported
- Ongoing: yes
- Estimated study completion date: November 2029
- Trial registration numbers: 54767414MMY3014; EUCTR2018-002992-16-GR; NCT03710603

Participants	• Participants with newly diagnosed multiple myeloma who are eligible for high-dose therapy plus stem cell transplantation • Inclusion criteria: age ≥ 18 years or ≤ 70 years; bone marrow plasmacytosis with ≥ 10% plasma cells or biopsy-proven plasmacytoma, at least 1 of the CRAB criteria or biomarkers of malignancy criteria; measurable disease according to certain definitions; adequate bone marrow, liver, and kidney function; women of childbearing potential must either abstain continuously from heterosexual intercourse or must use 2 methods of reliable birth control simultaneously during the treatment period, during any dose interruptions, and for 3 months after the last dose of any component of the treatment regimen; women of childbearing potential must have negative pregnancy tests at screening; a woman must agree not to donate eggs (ova, oocytes); male subjects of reproductive potential must always use a latex or synthetic condom and must not donate sperm; signed informed consent • Exclusion criteria: prior or current systemic therapy or stem cell transplant except a short course of corticosteroids; peripheral neuropathy or neuropathic pain grade 2 or higher; prior or concurrent invasive malignancy within 5 years of date of randomisation (exceptions are basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years); radiation therapy within 14 days of randomisation; plasmapheresis within 28 days of randomisation; clinical signs of meningeal involvement of multiple myeloma; COPD; moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification; seropositive for HIV, hepatitis B or active hepatitis C infection; concurrent medical or psychiatric illness; cardial diseases/conditions according to certain definitions; strong CYP3A4 inducer within 5 half-lives prior to randomisation; allergy, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients or sensitivity to mammalian-derived products or lenalidomide; not able to comply with the study protocol; pregnant or breastfeeding, or planning to become pregnant, or a man who plans to father a child; major surgery within 2 weeks before randomisation or planned during the study; received an investigational drug or used an invasive investigational medical device; contraindications to the use of any components of the backbone treatment regimens; gastrointestinal disease that may significantly alter the absorption of oral drugs; vaccination within 4 weeks of first study agent administration; unable or unwilling to undergo antithrombotic prophylactic treatment
Interventions	• Arm A: bortezomib 1.3 mg/m^2 as subcutaneous injection, twice-weekly on days 1, 4, 8, and 11 in cycle 1 to 6, lenalidomide 25 mg orally on days 1 to 21 in cycle 1 to 6, dexamethasone 40 mg orally on days 1 to 4 and on days 9 to 12 of each 28-day cycle in cycle 1 to 6, daratumumab 1800 mg as subcutaneous injection once every week in cycle 1 to 2, then every 2 weeks in cycle 3 to 6. Participants receive bortezomib, lenalidomide, and dexamethasone for induction and consolidation, followed by lenalidomide maintenance until disease progression or unacceptable toxicity. • Arm B: bortezomib 1.3 mg/m^2 as subcutaneous injection, twice-weekly on days 1, 4, 8, and 11 in cycle 1 to 6, lenalidomide 25 mg orally on days 1 to 21 in cycle 1 to 6, dexamethasone 40 mg orally on days 1 to 4 and on days 9 to 12 of each 28-day cycle in cycle 1 to 6. Participants receive bortezomib, lenalidomide, and dexamethasone plus daratumumab for induction and consolidation followed by daratumumab and lenalidomide maintenance until disease progression or unacceptable toxicity.
Outcomes	• Primary: ◦ Progression-free survival • Secondary:

NCT03710603 *(Continued)*

- Postconsolidation minimal residual disease negativity
- Overall response rate
- Progression-free survival on next line of therapy
- Overall survival
- Time to response
- Duration of response
- Pharmacokinetic concentrations of daratumumab
- Number of participants with antidaratumumab antibodies and number of participants with anti-rHuPH20 antibodies
- Quality of life based on EORTC QLQ-C30
- ORTC QLQ- 20-item multiple myeloma module (MY-20) score
- EQ-5D-5L health utility values
- Stem cell yield after mobilisation
- Time to engraftment post-ASCT

- Outcomes of interest (for the review):
  - Overall survival: reported
  - Progression-free survival: reported
  - Quality of life: reported
  - Complete response: not reported
  - On-study mortality: not reported
  - Serious adverse events: not reported
  - Adverse events (CTCAE grade ≥ 3): not reported
    - Neutropenia: not reported
    - Thrombocytopenia: not reported
    - Anaemia: not reported
    - Leukopenia: not reported
    - Lymphopenia: not reported
    - Infections: not reported
    - Diarrhoea: not reported
    - Pneumonia: not reported
    - Nausea: not reported
  - Minimal residual disease negativity: not reported
- Additional study outcomes:
  - Postconsolidation minimal residual disease negativity
  - Overall response rate
  - Progression-free survival on next line of therapy
  - Time to response
  - Duration of response
  - Pharmacokinetic concentrations of daratumumab
  - Number of participants with antidaratumumab antibodies and number of participants with anti-rHuPH20 antibodies
  - Stem cell yield after mobilisation
  - Time to engraftment post-ASCT

Starting date	• 14 December 2018
Contact information	• Not reported
Notes	• Sponsor/Funding: European Myeloma Network; Janssen Research & Development, LLC

NCT03742297

Study name	Induction therapy with bortezomib-melphalan and prednisone (vmp) followed by lenalidomide and dexamethasone (rd) versus carfilzomib, lenalidomide and dexamethasone (krd) plus/minus daratumumab, 18 cycles, followed by consolidation and maintenance therapy with lenalidomide and daratumumab: phase iii, multicenter, randomized trial for elderly fit newly diagnosed multiple myeloma patients aged between 65 and 80 years
Methods	• Design: randomised, open-label, phase III multicentre trial • Sample size: n = 462 participants enrolled (actual); Arm A: carfilzomib plus lenalidomide plus dexamethasone plus daratumumab, Arm B: carfilzomib plus lenalidomide plus dexamethasone, Arm C: bortezomib plus melphalan plus prednisone plus lenalidomide plus dexamethasone • Duration of treatment: 18 cycles • Median follow-up: not reported • Ongoing: yes • Estimated study completion date: January 2031 • Trial registration numbers: NCT03742297; GEM2017FIT; RV-CL-MM-PETHEMA-008223
Participants	• Participants with newly diagnosed multiple myeloma who require start active treatment according to the IMWG published in 2014 • Inclusion criteria: age ≥ 65 years or ≤ 80 years; geriatric assessment in haematology scale: ≤ 42; signed informed consent; measurable disease defined in secretory, poor secretory, and non-secretory multiple myeloma; ECOG performance status 0 to 2; life expectancy more than 3 months; adequate organ functions; must be able to adhere to all study requirements; must agree to use a condom while taking lenalidomide even if they had a successful vasectomy or practise complete abstinence, including during periods of dose interruptions and for at least 30 days after treatment completion; should commit to not donate semen or sperm during treatment, including during periods of dose interruptions, and for at least 90 days after treatment completion • Exclusion criteria: age ≥ 81 years or ≤ 64 years; geriatric assessment in haematology scale: ≥ 43; participants who have previously received treatment for multiple myeloma, except for steroid pulses in case of emergency, bisphosphonates or antialgesic radiotherapy or due to the presence of plasmacytomas requiring some emergency; does not agree to use a condom or to practice complete abstinence; left ventricular ejection fraction < 40%; prior history of malignancies, other than multiple myeloma (except for basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or the breast), unless the participant has been free of the disease for ≥ 5 years; other relevant diseases or adverse clinical conditions; known seropositivity for HIV, hepatitis B or active hepatitis C infection; do not comply with the treatment or follow-up protocol; uncontrolled endocrine diseases; peripheral neuropathy ≥ grade 2 within 14 days prior to inclusion; hypersensibility to any of the study drugs or their excipients; treated with any investigational drug during the previous 30 days; acute diffuse infiltrative pulmonary disease and/or pericardial disease; unable or unwilling to undergo antithrombotic therapy; severe chronic obstructive pulmonary disease or asthma with FEV1 less than 50% • Baseline characteristics: ◦ ECOG performance status: 0 to 2
Interventions	• Arm A: carfilzomib 20 mg/m^2 on day 1 and 36 mg/m^2 on days 2, 8, 9, and 15 in cycle 1, 36 mg/m^2 on days 1, 2, 8, 9, and 15 in cycle 2 and 56 mg/m^2 on days 1, 8, and 15 in cycles 3 to 18, lenalidomide 25 mg on days 1 to 21, dexamethasone 40 mg on days 1, 8, 15, and 22, daratumumab 16 mg/kg as intravenous infusion on days 1, 8, 15, and 22 in cycles 1 and 2, on days 1 and 15 in cycles 3 and 4, and on day 1 in cycles 5 to 18 • Arm B: carfilzomib 20 mg/m^2 on day 1 and 36 mg/m^2 on days 2, 8, 9, and 15 in cycle 1, 36 mg/m^2 on days 1, 2, 8, 9, and 15 in cycle 2 and 56 mg/m^2 on days 1, 8, and 15 in cycles 3 to 18, lenalidomide 25 mg on days 1 to 21, dexamethasone 40 mg on days 1, 8, 15, and 22 • Arm C: bortezomib-melphalan-prednisone x 9 + lenalidomide-dexamethasone x 9: bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32 in 1 x 6-week cycle, melphalan 9 mg/m^2 on days 1 to 4, prednisone 60 mg/m^2 on days 1 to 4, followed by lenalidomide and dexamethasone at low dose on days 1, 8, 15, and 22 in 8 x 4-week cycles
Outcomes	• Primary:

NCT03742297 *(Continued)*

- Efficacy in terms of numbers of complete responses (time frame: 18 months)
- Secondary:
  - Not reported
- Outcomes of interest (for the review):
  - Overall survival: not reported
  - Progression-free survival: not reported
  - Quality of life: not reported
  - Complete response: not reported
  - On-study mortality: not reported
  - Serious adverse events: not reported
  - Adverse events (CTCAE grade ≥ 3): not reported
    - Neutropenia: not reported
    - Thrombocytopenia: not reported
    - Anaemia: not reported
    - Leukopenia: not reported
    - Lymphopenia: not reported
    - Infections: not reported
    - Diarrhoea: not reported
    - Pneumonia: not reported
    - Nausea: not reported
  - Minimal residual disease negativity: not reported
- Additional study outcomes:
  - Efficacy in terms of numbers of complete responses (time frame: 18 months)

Starting date	• 22 October 2018
Contact information	• Not reported
Notes	• Sponsor/Funding: Pethema Foundation

NCT03993912

Study name	A phase iii study comparing lenalidomide and subcutaneous daratumumab (r-dara sc) vs lenalidomide and dexamethasone (rd) in frail subjects with previously untreated multiple myeloma who are ineligible for high dose therapy
Methods	• Design: randomised, open-label, phase III multicentre trial • Sample size: n = 294 participants enrolled (actual); Arm A: daratumumab plus lenalidomide plus dexamethasone, Arm B: lenalidomide plus dexamethasone • Duration of treatment: 28-day cycles until progression • Median follow-up: not reported • Ongoing: yes • Estimated study completion date: October 2027 • Trial registration numbers: NCT03993912; EUCTR2018-003535-30-FR
Participants	• Participants with newly diagnosed multiple myeloma who are ineligible for high-dose therapy plus stem cell transplantation • Inclusion criteria: newly diagnosed multiple myeloma and not considered candidate for high-dose chemotherapy with stem cell transplantation; age must be ≥ 65 years; presence of CRAB criteria and measurable secretory disease; frailty score ≥ 2; within 5 days prior to first drug intake participants must fulfil certain laboratory values; measurable international scoring system with β2-microglobulin and albumin values for randomisation; a man who is sexually active with a woman of childbearing potential must agree to use a latex or synthetic condom, even if they

NCT03993912 *(Continued)*

	had a successful vasectomy; must not donate sperm during the study, for 4 weeks after the last dose of lenalidomide, and for 4 months after the last dose of daratumumab; women must be post-menopausal; must sign an informed consent form; must be affiliated with an appropriate social security system • Exclusion criteria: primary amyloidosis, monoclonal gammopathy of undetermined significance, or smouldering multiple myeloma; Waldenström's disease, or IgM M-protein presence in absence of a clonal plasma cell infiltration with lytic bone lesions; prior or current systemic therapy or stem cell transplantation; malignancy within 5 years before the date of randomisation; radiation therapy within 14 days of randomisation; plasmapheresis within 28 days of randomisation; meningeal involvement; COPD; seropositive for HIV, hepatitis B or history of hepatitis C; concurrent medical or psychiatric condition or disease (hazard for participating in this study); significant cardiac disease; allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients; plasma cell leukaemia or POEMS syndrome; not able to comply with the study protocol; major surgery; received an investigational drug or used an invasive investigational medical device within 4 weeks before randomisation; refusal to consent or protected by legal regime; contraindications to required prophylaxis for deep vein thrombosis and pulmonary embolism; gastrointestinal disease that may significantly alter the absorption of oral drugs • Baseline characteristics: not reported
Interventions	• Arm A: daratumumab 1800 mg as subcutaneous injection once weekly for 8 weeks, then once every other week for 16 weeks, thereafter once every 4 weeks, until progression. Lenalidomide 25 mg orally on days 1 to 21 of each 28-day cycle, until progression. Dexamethasone 20 mg orally on days 1, 8, 15, 22 of each 28-day cycle for the first 2 cycles, then discontinued • Arm B: lenalidomide 25 mg orally on days 1 to 21 of each 28-day cycle, until progression. Dexamethasone 20 mg orally on days 1, 8, 15, 22 of each 28-day cycle, until progression

Outcomes	• Primary:
	  ○ Progression-free survival
	• Secondary:
	  ○ Time to treatment failure
	  ○ Time to next treatment
	  ○ Progression-free survival on next line of therapy
	  ○ Overall survival
	  ○ Complete response
	  ○ Very good partial response or better
	  ○ Overall response rate
	  ○ Occurrence of grade 3 or more side effects
	  ○ Safety and tolerability of daratumumab SC when administered in combination with lenalidomide (Revlimid): NCI-CTCAE V5.0
	  ○ Quality of life based on MY20 questionnaires
	  ○ Quality of life based on EORTC QLQ-C30 questionnaires
	  ○ Quality of life based on EQ-5D questionnaires
	  ○ Minimal residual disease negativity at 12 months
	  ○ Event-free survival
	• Outcomes of interest (for the review):
	  ○ Overall survival: reported
	  ○ Progression-free survival: reported
	  ○ Quality of life: reported
	  ○ Complete response: reported
	  ○ On-study mortality: not reported
	  ○ Serious adverse events: not reported
	  ○ Adverse events (CTCAE grade ≥ 3): reported
	  ■ Neutropenia: not reported
	  ■ Thrombocytopenia: not reported
	  ■ Anaemia: not reported

NCT03993912 *(Continued)*

- Leukopenia: not reported
- Lymphopenia: not reported
- Infections: not reported
- Diarrhoea: not reported
- Pneumonia: not reported
- Nausea: not reported

- Minimal residual disease negativity: reported

- Additional study outcomes:
  - Time to treatment failure
  - Time to next treatment
  - Progression-free survival on next line of therapy
  - Very good partial response or better
  - Overall response rate

Starting date	• 17 October 2019
Contact information	• Not reported
Notes	• Sponsor/Funding: CHRU de Lille

NCT04268498

Study name	Phase 2, open-label randomized study of daratumumab, carfilzomib, lenalidomide, and dexamethasone vs carfilzomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma
Methods	• Design: randomised, open-label, phase II clinical trial • Sample size: n = 306 participants enrolled (estimated); Arm A: daratumumab plus carfilzomib plus lenalidomide plus dexamethasone, Arm B: bortezomib plus lenalidomide plus dexamethasone, Arm C: carfilzomib plus lenalidomide plus dexamethasone • Duration of treatment: not reported • Median follow-up: not reported • Ongoing: yes • Estimated study completion date: February 2027 • Trial registration numbers: EUCTR2019-001645-41-SE; ORG 19-339; NCT04268498
Participants	• Participants with newly diagnosed multiple myeloma • Inclusion criteria: newly diagnosed multiple myeloma based on: bone marrow plasmacytosis, measurable secretory disease within the past 4 weeks in serum or urine; presence of SLiM-CRAB criteria; creatinine clearance ≥ 60 mL/min; age limit of ≤ 75 years; ECOG performance status 0 to 2; absolute neutrophil count ≥ 1.0 K/uL, haemoglobin ≥ 8 g/dL, and platelet count ≥ 75 K/uL; adequate hepatic function; must be able to tolerate 1 of the following thromboprophylactic strategies: aspirin, low-molecular-weight heparin or warfarin (Coumadin) or alternative anticoagulant; must be registered into the mandatory risk evaluation and mitigation strategy program; women of childbearing potential must have negative pregnancy test 10 to 14 days and again within 24 hours prior to prescribing lenalidomide for cycle 1 plus ongoing pregnancy testing abstinence from heterosexual intercourse or begin 2 acceptable methods of birth control simultaneously, agreed ongoing pregnancy testing; men must agree to use a latex condom during sexual contact • Exclusion criteria: > 1 cycle of prior treatment or concurrent systemic treatment for multiple myeloma; plasma cell leukaemia; POEMS syndrome; amyloidosis; known COPD with FEV1 < 50%; pregnant or lactating females; uncontrolled hypertension or diabetes; seropositive for HIV, hepatitis B or hepatitis C; significant cardiovascular disease; pulmonary hypertension; refractory gastrointestinal disease; uncontrolled intercurrent illness including but not limited to active in-

NCT04268498 *(Continued)*

	fection or psychiatric illness/social situations; significant neuropathy ≥ grade 3 or grade 2; contraindication to any concomitant medication; major surgery within 3 weeks prior to first dose
Interventions	• Arm A: carfilzomib 20 mg/m^2 per dose on day 2 and 56 mg/m^2 per dose on days 8 and 15 in cycle 1 followed by 56 mg/m^2 per dose on days 1, 8, and 15 in cycle 2 to 8; lenalidomide 25 mg/day on day 2 to 21 every 28 days in cycle 1 followed by 25 mg/day on day 1 to 21 every 28 days in cycle 2 to 8; dexamethasone 20 mg/dose on days 1, 2, and 22 and 40 mg/dose on days 8 and 15 in cycle 1 followed by 40 mg/dose on days 1, 8, and 15 and 20 mg/dose on day 22 in cycle 2 followed by 40 mg/dose on days 1, 8, and 15 in cycle 3 to 4 followed by 20 mg/dose on days 1, 8, and 15 in cycle 5 to 8; daratumumab 16 mg/kg on days 1, 8, 15, and 22 in cycle 1 to 2 followed by 16 mg/kg on days 1 and 15 in cycle 3 to 6 followed by 16 mg/kg on day 1 in cycle 7 to 8 • Arm B: bortezomib 1.3 mg/m^2 subcutaneous or intravenous on days 1, 4, 8, 11 of 21-day treatment cycles in cycle 1 to 8; lenalidomide 25 mg/day on days 1 to 14 of 21-day treatment cycles in cycle 1 to 8; dexamethasone 20 mg/dose orally or intravenous on days of bortezomib infusion • Arm C: carfilzomib 20 mg/m^2 per dose on day 1 and 56 mg/m^2 per dose on days 8 and 15 in cycle 1 followed by 56 mg/m^2 per dose on days 1, 8, and 15 in cycle 2 to 8; lenalidomide 25 mg/day on days 2 to 21 every 28 days in cycle 1; lenalidomide 25 mg/day on days 1 to 21 every 28 days in cycle 2 to 8; dexamethasone 20 mg/dose on days 1, 2, and 22 and 40 mg/dose on days 8 and 15 in cycle 1 followed by 40 mg/dose on days 1, 8, and 15 and 20 mg/dose on day 22 in cycle 2 followed by 40 mg/dose on days 1, 8, and 15 in cycle 3 to 4 followed by 20 mg/dose on days 1, 8, and 15 in cycle 5 to 8

Outcomes	• Primary:
	  ○ Minimal residual disease negativity (time frame: up to 32 weeks)
	• Secondary:
	  ○ Overall survival
	  ○ Progression-free survival
	  ○ Event-free survival
	  ○ Rate of response
	  ○ Incidence of treatment-related toxicity
	  ○ Minimal residual disease negativity (time frame: up to 3 years)
	• Outcomes of interest (for the review):
	  ○ Overall survival: reported
	  ○ Progression-free survival: reported
	  ○ Quality of life: not reported
	  ○ Complete response: not reported
	  ○ On-study mortality: not reported
	  ○ Serious adverse events: not reported
	  ○ Adverse events (CTCAE grade ≥ 3): reported
	  ■ Neutropenia: not reported
	  ■ Thrombocytopenia: not reported
	  ■ Anaemia: not reported
	  ■ Leukopenia: not reported
	  ■ Lymphopenia: not reported
	  ■ Infections: not reported
	  ■ Diarrhoea: not reported
	  ■ Pneumonia: not reported
	  ■ Nausea: not reported
	  ○ Minimal residual disease negativity: reported
	• Additional study outcomes:
	  ○ Rate of response

Starting date	• 11 February 2020
Contact information	• Philip Arlen, MD; Tel: 305-243-5247, Email: paa107@miami.edu

NCT04268498 *(Continued)*

Notes	• Sponsor/Funding: University of Miami; Amgen

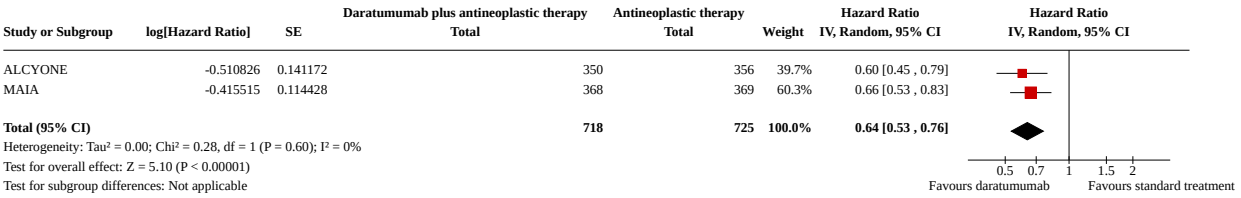
ASCT: autologous stem cell transplant
COPD: chronic obstructive pulmonary disease
CRAB: Hypercalcaemia; Renal insufficiency; Anaemia; Bone lesions with 1 or more osteolytic lesions
CTCAE: Common Terminology Criteria for Adverse Events
ECOG: Eastern Cooperative Oncology Group
FEV1: forced expiratory volume in the first minute
IMWG: International Myeloma Working Group
NCI: National Cancer Institute
POEMS: Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin changes
SC: subcutaneous
SLiM: S stands for at least 60% of bone marrow plasma cells are clonal; Li stands for involved:uninvolved serum free light chain ratio ≥ 100; M stands for > 1 focal lesions on magnetic resonance imaging (MRI) studies

DATA AND ANALYSES

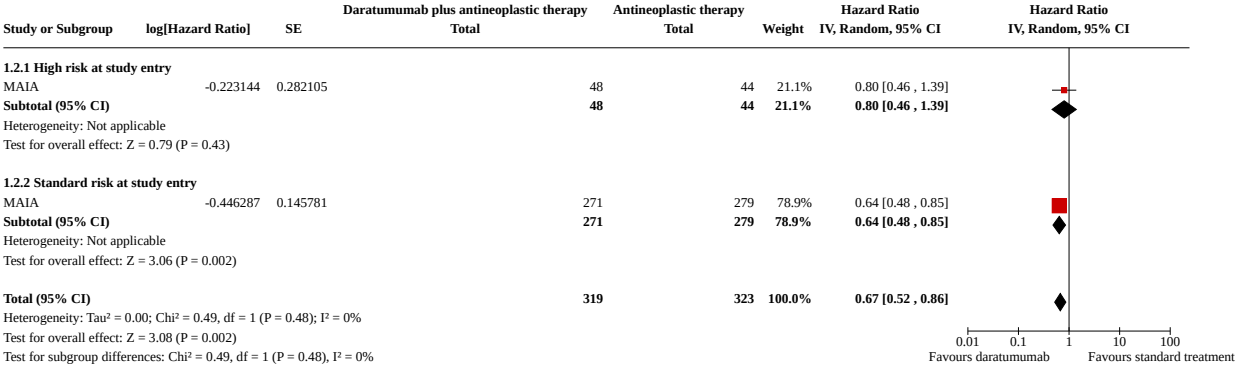
Comparison 1. Overall survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	2	1443	Hazard Ratio (IV, Random, 95% CI)	0.64 [0.53, 0.76]
1.2 Overall survival - cytogenetic profile at study entry	1	642	Hazard Ratio (IV, Random, 95% CI)	0.67 [0.52, 0.86]
1.2.1 High risk at study entry	1	92	Hazard Ratio (IV, Random, 95% CI)	0.80 [0.46, 1.39]
1.2.2 Standard risk at study entry	1	550	Hazard Ratio (IV, Random, 95% CI)	0.64 [0.48, 0.85]
1.3 Overall survival - International Staging System disease stage	1	737	Hazard Ratio (IV, Random, 95% CI)	0.68 [0.53, 0.87]
1.3.1 International Staging System disease stage I	1	201	Hazard Ratio (IV, Random, 95% CI)	0.79 [0.43, 1.45]
1.3.2 International Staging System disease stage II	1	319	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.42, 0.88]
1.3.3 International Staging System disease stage III	1	217	Hazard Ratio (IV, Random, 95% CI)	0.72 [0.49, 1.05]

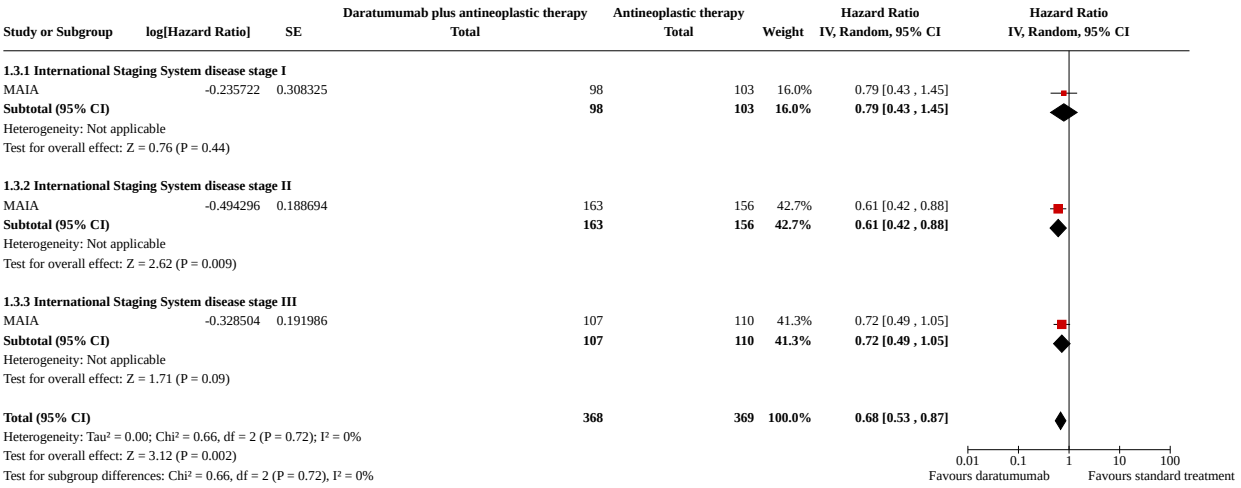
Analysis 1.1. Comparison 1: Overall survival, Outcome 1: Overall survival



Analysis 1.2. Comparison 1: Overall survival, Outcome 2: Overall survival - cytogenetic profile at study entry



Analysis 1.3. Comparison 1: Overall survival, Outcome 3: Overall survival - International Staging System disease stage



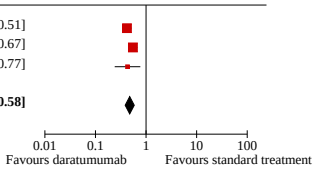
Comparison 2. Progression-free survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Progression-free survival	3	1663	Hazard Ratio (IV, Random, 95% CI)	0.48 [0.39, 0.58]

Analysis 2.1. Comparison 2: Progression-free survival, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Daratumumab plus antineoplastic therapy Total	Antineoplastic therapy Total	Weight	Hazard Ratio IV, Random, 95% CI
ALCYONE	-0.867501	0.103437	350	356	44.3%	0.42 [0.34 , 0.51]
MAIA	-0.597837	0.10154	368	369	45.0%	0.55 [0.45 , 0.67]
OCTANS	-0.84397	0.297391	146	74	10.8%	0.43 [0.24 , 0.77]
Total (95% CI)			**864**	**799**	**100.0%**	**0.48 [0.39 , 0.58]**

Heterogeneity: Tau² = 0.01; Chi² = 3.60, df = 2 (P = 0.17); I² = 44%
Test for overall effect: Z = 7.06 (P < 0.00001)
Test for subgroup differences: Not applicable



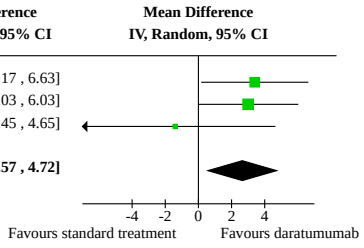
Comparison 3. Quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 EORTC 3 month	3	1302	Mean Difference (IV, Random, 95% CI)	2.65 [0.57, 4.72]
3.2 EORTC 9 month	3	1119	Mean Difference (IV, Random, 95% CI)	1.79 [-1.21, 4.78]
3.3 EORTC 12 month	3	1096	Mean Difference (IV, Random, 95% CI)	2.19 [-0.13, 4.51]
3.4 EQ-5D 3 month	2	1051	Mean Difference (IV, Random, 95% CI)	3.51 [0.92, 6.10]
3.5 EQ-5D 9 month	2	874	Mean Difference (IV, Random, 95% CI)	2.54 [0.26, 4.82]
3.6 EQ-5D 12 month	2	848	Mean Difference (IV, Random, 95% CI)	2.77 [-2.32, 7.87]

Analysis 3.1. Comparison 3: Quality of life, Outcome 1: EORTC 3 month

Study or Subgroup	Daratumumab plus antineoplastic therapy Mean	SD	Total	Antineoplastic therapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ALCYONE	7.3	18.0496	262	3.9	19.0322	245	41.2%	3.40 [0.17 , 6.63]
MAIA	4.5	18.5758	303	1.5	18.4296	272	47.0%	3.00 [-0.03 , 6.03]
OCTANS	7.4	22.253067	146	8.8	21.300821	74	11.8%	-1.40 [-7.45 , 4.65]
Total (95% CI)			**711**			**591**	**100.0%**	**2.65 [0.57 , 4.72]**

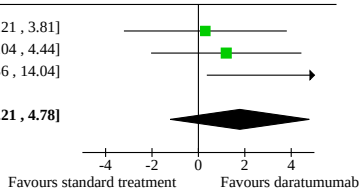
Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Quality of life, Outcome 2: EORTC 9 month

Study or Subgroup	Daratumumab plus antineoplastic therapy Mean	SD	Total	Antineoplastic therapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ALCYONE	10.4	18.3094	228	10.1	18.1197	189	40.3%	0.30 [-3.21 , 3.81]
MAIA	8.2	18.2923	268	7	17.8113	214	43.9%	1.20 [-2.04 , 4.44]
OCTANS	12.8	25.065268	146	5.6	24.127982	74	15.8%	7.20 [0.36 , 14.04]
Total (95% CI)			**642**			**477**	**100.0%**	**1.79 [-1.21 , 4.78]**

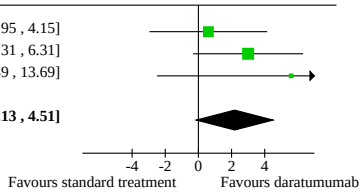
Heterogeneity: Tau² = 2.58; Chi² = 3.15, df = 2 (P = 0.21); I² = 37%
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Quality of life, Outcome 3: EORTC 12 month

Study or Subgroup	Daratumumab plus antineoplastic therapy Mean	SD	Total	Antineoplastic therapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ALCYONE	11.1	18.0621	222	10.5	18.3054	185	42.7%	0.60 [-2.95 , 4.15]
MAIA	8.4	18.0147	260	5.4	18.3329	209	49.1%	3.00 [-0.31 , 6.31]
OCTANS	13.6	27.694064	146	8	29.544908	74	8.2%	5.60 [-2.49 , 13.69]
Total (95% CI)			**628**			**468**	**100.0%**	**2.19 [-0.13 , 4.51]**

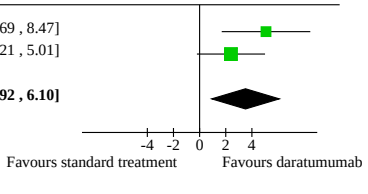
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Quality of life, Outcome 4: EQ-5D 3 month

Study or Subgroup	Daratumumab plus antineoplastic therapy Mean	SD	Total	Antineoplastic therapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ALCYONE	9.28	20.195	258	4.2	18.417	241	41.5%	5.08 [1.69 , 8.47]
MAIA	4.9	15.574	290	2.5	15.6184	262	58.5%	2.40 [-0.21 , 5.01]
Total (95% CI)			**548**			**503**	**100.0%**	**3.51 [0.92 , 6.10]**

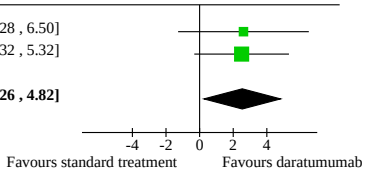
Heterogeneity: Tau² = 1.21; Chi² = 1.51, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 2.66 (P = 0.008)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Quality of life, Outcome 5: EQ-5D 9 month

Study or Subgroup	Daratumumab plus antineoplastic therapy Mean	SD	Total	Antineoplastic therapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ALCYONE	12.5	20.616	225	9.89	19.516	186	34.4%	2.61 [-1.28 , 6.50]
MAIA	10.2	15.4369	256	7.7	15.3249	207	65.6%	2.50 [-0.32 , 5.32]
Total (95% CI)			**481**			**393**	**100.0%**	**2.54 [0.26 , 4.82]**

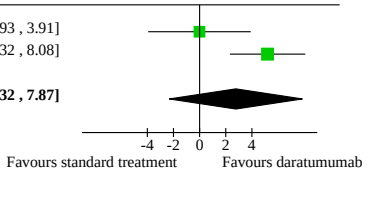
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.18 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Quality of life, Outcome 6: EQ-5D 12 month

Study or Subgroup	Daratumumab plus antineoplastic therapy Mean	SD	Total	Antineoplastic therapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ALCYONE	10.79	20.271	216	10.8	19.386	179	46.6%	-0.01 [-3.93 , 3.91]
MAIA	10.1	15.9584	247	4.9	15.2874	206	53.4%	5.20 [2.32 , 8.08]
Total (95% CI)			**463**			**385**	**100.0%**	**2.77 [-2.32 , 7.87]**

Heterogeneity: Tau² = 10.49; Chi² = 4.40, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Not applicable



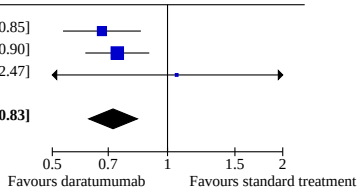
Comparison 4. On-study mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 On-study mortality	3	1644	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.62, 0.83]

Analysis 4.1. Comparison 4: On-study mortality, Outcome 1: On-study mortality

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	83	346	126	354	39.1%	0.67 [0.53 , 0.85]
MAIA	115	364	156	365	58.0%	0.74 [0.61 , 0.90]
OCTANS	15	144	7	71	3.0%	1.06 [0.45 , 2.47]
Total (95% CI)		**854**		**790**	**100.0%**	**0.72 [0.62 , 0.83]**
Total events:	213		289			

Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 4.39 (P < 0.0001)
Test for subgroup differences: Not applicable



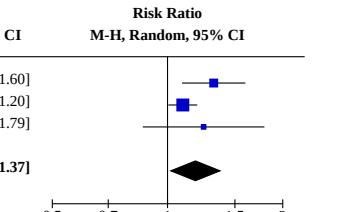
Comparison 5. Serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Serious adverse events	3	1644	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.02, 1.37]

Analysis 5.1. Comparison 5: Serious adverse events, Outcome 1: Serious adverse events

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	151	346	117	354	31.9%	1.32 [1.09 , 1.60]
MAIA	281	364	257	365	54.9%	1.10 [1.01 , 1.20]
OCTANS	63	144	25	71	13.2%	1.24 [0.86 , 1.79]
Total (95% CI)		**854**		**790**	**100.0%**	**1.18 [1.02 , 1.37]**
Total events:	495		399			

Heterogeneity: Tau² = 0.01; Chi² = 3.88, df = 2 (P = 0.14); I² = 48%
Test for overall effect: Z = 2.22 (P = 0.03)
Test for subgroup differences: Not applicable



Comparison 6. Adverse events (CTCAE grade ≥3)

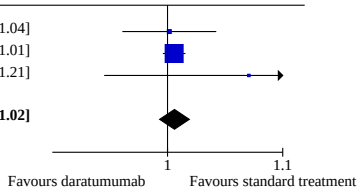
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Adverse events (CTCAE grade ≥ 3)	3	1644	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.99, 1.02]
6.2 Infections	3	1644	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.30, 1.78]
6.3 Neutropenia	3	1644	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.75, 1.39]
6.4 Thrombocytopenia	3	1644	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.07]
6.5 Anaemia	3	1644	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.14]
6.6 Leukopenia	3	1644	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.69, 1.80]
6.7 Lymphopenia	3	1644	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.05, 1.67]
6.8 Diarrhoea	3	1644	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.88, 1.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.9 Pneumonia	3	1644	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.41, 2.94]
6.10 Nausea	2	1429	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.79, 1.87]

Analysis 6.1. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 1: Adverse events (CTCAE grade ≥ 3)

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	324	346	331	354	9.5%	1.00 [0.96 , 1.04]
MAIA	364	364	363	365	89.5%	1.01 [1.00 , 1.01]
OCTANS	128	144	59	71	1.0%	1.07 [0.95 , 1.21]
Total (95% CI)		**854**		**790**	**100.0%**	**1.01 [0.99 , 1.02]**
Total events:	816		753			

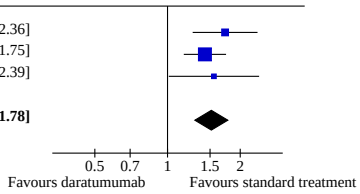
Heterogeneity: Tau² = 0.00; Chi² = 2.11, df = 2 (P = 0.35); I² = 5%
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 2: Infections

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	88	346	52	354	25.8%	1.73 [1.27 , 2.36]
MAIA	151	364	106	365	60.8%	1.43 [1.17 , 1.75]
OCTANS	60	144	19	71	13.3%	1.56 [1.01 , 2.39]
Total (95% CI)		**854**		**790**	**100.0%**	**1.52 [1.30 , 1.78]**
Total events:	299		177			

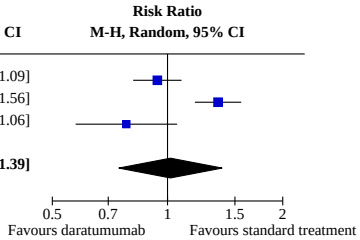
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 5.21 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 3: Neutropenia

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	171	346	186	354	35.8%	0.94 [0.81 , 1.09]
MAIA	223	364	165	365	36.0%	1.36 [1.18 , 1.56]
OCTANS	57	144	36	71	28.2%	0.78 [0.58 , 1.06]
Total (95% CI)		**854**		**790**	**100.0%**	**1.02 [0.75 , 1.39]**
Total events:	451		387			

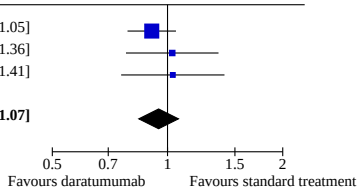
Heterogeneity: Tau² = 0.06; Chi² = 17.90, df = 2 (P = 0.0001); I² = 89%
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 4: Thrombocytopenia

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	168	346	189	354	66.9%	0.91 [0.79 , 1.05]
MAIA	79	364	77	365	18.4%	1.03 [0.78 , 1.36]
OCTANS	67	144	32	71	14.7%	1.03 [0.76 , 1.41]
Total (95% CI)		**854**		**790**	**100.0%**	**0.95 [0.84 , 1.07]**
Total events:	314		298			

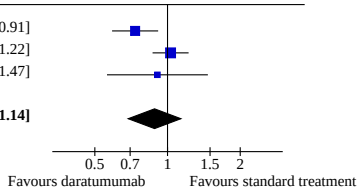
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 5: Anaemia

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	94	346	131	354	38.4%	0.73 [0.59 , 0.91]
MAIA	154	364	150	365	43.4%	1.03 [0.87 , 1.22]
OCTANS	35	144	19	71	18.2%	0.91 [0.56 , 1.47]
Total (95% CI)		**854**		**790**	**100.0%**	**0.88 [0.69 , 1.14]**
Total events:	283		300			

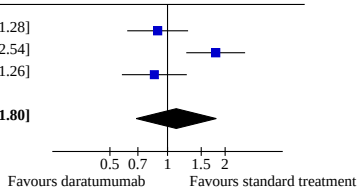
Heterogeneity: Tau² = 0.03; Chi² = 5.69, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 6.6. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 6: Leukopenia

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	46	346	53	354	33.5%	0.89 [0.62 , 1.28]
MAIA	73	364	41	365	33.9%	1.79 [1.25 , 2.54]
OCTANS	45	144	26	71	32.6%	0.85 [0.58 , 1.26]
Total (95% CI)		**854**		**790**	**100.0%**	**1.11 [0.69 , 1.80]**
Total events:	164		120			

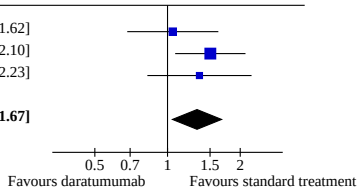
Heterogeneity: Tau² = 0.15; Chi² = 10.15, df = 2 (P = 0.006); I² = 80%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 6.7. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 7: Lymphopenia

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	37	346	36	354	29.0%	1.05 [0.68 , 1.62]
MAIA	72	364	48	365	48.8%	1.50 [1.08 , 2.10]
OCTANS	44	144	16	71	22.2%	1.36 [0.83 , 2.23]
Total (95% CI)		**854**		**790**	**100.0%**	**1.32 [1.05 , 1.67]**
Total events:	153		100			

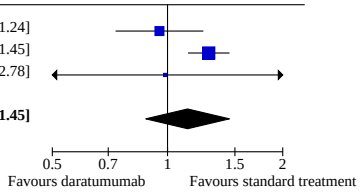
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 6.8. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 8: Diarrhoea

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	81	346	87	354	38.1%	0.95 [0.73 , 1.24]
MAIA	239	364	187	365	56.4%	1.28 [1.13 , 1.45]
OCTANS	10	144	5	71	5.4%	0.99 [0.35 , 2.78]
Total (95% CI)		**854**		**790**	**100.0%**	**1.13 [0.88 , 1.45]**
Total events:	330		279			

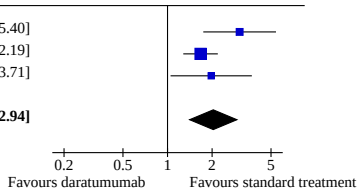
Heterogeneity: Tau² = 0.03; Chi² = 4.43, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 6.9. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 9: Pneumonia

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	45	346	15	354	26.3%	3.07 [1.74 , 5.40]
MAIA	110	364	66	365	50.9%	1.67 [1.28 , 2.19]
OCTANS	40	144	10	71	22.8%	1.97 [1.05 , 3.71]
Total (95% CI)		**854**		**790**	**100.0%**	**2.04 [1.41 , 2.94]**
Total events:	195		91			

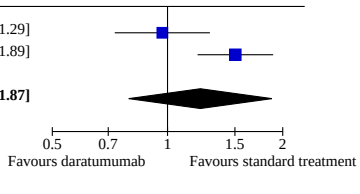
Heterogeneity: Tau² = 0.05; Chi² = 3.71, df = 2 (P = 0.16); I² = 46%
Test for overall effect: Z = 3.79 (P = 0.0001)
Test for subgroup differences: Not applicable



Analysis 6.10. Comparison 6: Adverse events (CTCAE grade ≥3), Outcome 10: Nausea

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	72	346	76	354	48.0%	0.97 [0.73 , 1.29]
MAIA	132	364	88	365	52.0%	1.50 [1.20 , 1.89]
Total (95% CI)		**710**		**719**	**100.0%**	**1.22 [0.79 , 1.87]**
Total events:	204		164			

Heterogeneity: Tau² = 0.08; Chi² = 5.56, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable



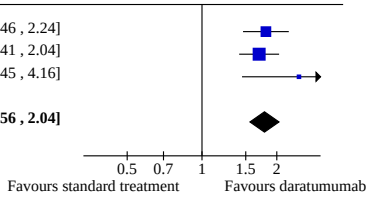
Comparison 7. Complete response

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Complete response	3	1663	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.56, 2.04]

Analysis 7.1. Comparison 7: Complete response, Outcome 1: Complete response

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	160	350	90	356	40.4%	1.81 [1.46 , 2.24]
MAIA	188	368	111	369	53.1%	1.70 [1.41 , 2.04]
OCTANS	63	146	13	74	6.5%	2.46 [1.45 , 4.16]
Total (95% CI)		**864**		**799**	**100.0%**	**1.78 [1.56 , 2.04]**
Total events:	411		214			

Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 8.42 (P < 0.00001)
Test for subgroup differences: Not applicable



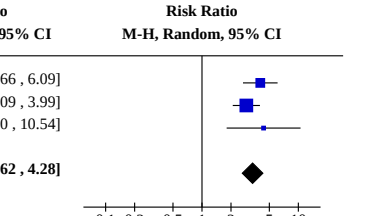
Comparison 8. Minimal residual disease negativity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Minimal residual disease negativity	3	1663	Risk Ratio (M-H, Random, 95% CI)	3.35 [2.62, 4.28]

Analysis 8.1. Comparison 8: Minimal residual disease negativity, Outcome 1: Minimal residual disease negativity

Study or Subgroup	Daratumumab plus antineoplastic therapy Events	Total	Antineoplastic therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALCYONE	99	350	25	356	35.2%	4.03 [2.66 , 6.09]
MAIA	118	368	41	369	57.1%	2.89 [2.09 , 3.99]
OCTANS	43	146	5	74	7.7%	4.36 [1.80 , 10.54]
Total (95% CI)		**864**		**799**	**100.0%**	**3.35 [2.62 , 4.28]**
Total events:	260		71			

Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 9.66 (P < 0.00001)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Trial outcomes

Outcomes	Name of trial			
	ALCYONE	AMaRC 03-16	MAIA	OCTANS
Progression-free survival	X	X	X	X
Overall response rate	X	X	X	X
Percentage of participants with very good partial response or better	X		X	X
Complete response	X		X	X
Percentage of participants with negative minimal residual disease	X	X	X	X

Table 1. Trial outcomes *(Continued)*

Overall survival	X	X	X	X
Progression-free survival on next line of therapy	X		X	
Stringent complete response	X			X
Time to disease progression	X		X	
Time to response	X		X	X
Duration of response	X		X	X
Time to next treatment	X		(X)	X
Percentage of participants with best M-protein response	X			
Change from baseline in EORTC QLQ-C30 emotional functioning score	X			
Change from baseline in EQ-5D-5L visual analogue scale	X		X	
Change from baseline in EQ-5D-5L utility score	X		X	
Change from baseline in EORTC QLQ-C30 Global Health Status	X	X	X	X
On-study mortality	X		X	X
Adverse events	X	X	X	X

APPENDICES

Appendix 1. International Staging System (ISS)

Stage	Criteria
I	Serum beta-2 microglobulin < 3.5 mg/L plus serum albumin ≥ 3.5 g/dL
II	Not stage I or III[a]
III	Serum beta-2 microglobulin ≥ 5.5 mg/L

[a]There are two possibilities for stage II: serum beta-2 microglobulin < 3.5 mg/L and serum albumin < 3.5 g/dL; or serum beta-2 microglobulin 3.5 mg/L to < 5.5 mg/L irrespective of the serum albumin level (Greipp 2005).

Appendix 2. CENTRAL search strategy (new)

ID	Search
#1	MeSH descriptor: [Multiple Myeloma] explode all trees
#2	myelom*:ti,ab,kw
#3	MeSH descriptor: [Plasmacytoma] explode all trees
#4	(plasm*cytom* or plasm*zytom* or plasma cytoma*):ti,ab,kw
#5	(plasma* NEAR/3 neoplas*):ti,ab,kw
#6	(plasma cell NEAR/1 (leukaem* or leukem* or tumor* or tumour*)):ti,ab,kw
#7	((plasmacytic* or plasmocytic* or plasmocyte*) NEAR/1 (leukem* or leukaem*)):ti,ab,kw
#8	kahler*:ti,ab,kw
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	(daratumumab* or dara-tumumab*):ti,ab,kw
#11	darzalex*:ti,ab,kw
#12	(human CD38 or human CD 38):ti,ab,kw
#13	(anti-CD38 monoclonal antibod* or antiCD38 monoclonal antibod* or anti-CD 38 monoclonal antibod* or antiCD 38 monoclonal antibod*):ti,ab,kw
#14	#10 or #11 or #12 or #13
#15	#9 and #14 in Trials

Appendix 3. MEDLINE search strategy (new)

#	Search
1	exp MULTIPLE MYELOMA/
2	myelom*.tw,kf.
3	exp Plasmacytoma/
4	(plasm?cytom* or plasm?zytom* or plasma cytoma*).tw,kf.
5	(plasma* adj3 neoplas*).tw,kf.
6	(plasma cell adj1 (leukaem* or leukem* or tumor* or tumour*)).tw,kf.
7	((plasmacytic* or plasmocytic* or plasmocyte*) adj1 (leukem* or leukaem*)).tw,kw.
8	kahler*.tw,kf.

(Continued)

9	or/1-8
10	(daratumumab* or dara-tumumab*).tw,kw,nm.
11	darzalex*.tw,kf,nm.
12	(human CD38 or human CD 38).tw,kf,nm.
13	(anti-CD38 monoclonal antibod* or antiCD38 monoclonal antibod*).tw,kf,nm.
14	(HuMax-CD38 or UNII-4Z63YK6E0E or 4Z63YK6E0E or JNJ 54767414 or JNJ54767414 or 945721-28-8).tw,kf,nm.
15	or/10-14
16	9 and 15
17	randomized controlled trial.pt.
18	controlled clinical trial.pt.
19	randomi?ed.ab.
20	placebo.ab.
21	drug therapy.fs.
22	randomly.ab.
23	trial.ab.
24	groups.ab.
25	or/17-24
26	exp animals/ not humans/
27	25 not 26
28	clinical trial, phase iii/
29	("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.
30	(28 or 29) not 26
31	27 or 30
32	16 and 31

Appendix 4. Embase search strategy

#	Search

(Continued)

1	multiple myeloma/
2	myelom*.tw,kw.
3	plasmacytoma/
4	plasma cell leukemia/
5	(plasma* adj3 neoplas*).tw,kw.
6	(plasma cell adj1 (leukaem* or leukem* or tumor* or tumour* or neoplasm*)).tw,kw.
7	(plasm?cytom* or plasm?zytom* or plasma cytoma*).tw,kw.
8	((plasmacytic* or plasmocytic* or plasmocyte*) adj1 (leukem* or leukaem*)).tw,kw.
9	kahler*.tw,kw.
10	or/1-9
11	daratumumab/
12	(daratumumab* or dara-tumumab*).tw,kw.
13	darzalex*.tw,kw.
14	(human CD38 or human CD 38).tw,kw.
15	(anti-CD38 monoclonal antibod* or antiCD38 monoclonal antibod* or anti-CD 38 monoclonal antibod* or antiCD 38 monoclonal antibod*).tw,kw.
16	(HuMax-CD38 or UNII-4Z63YK6E0E or 4Z63YK6E0E or JNJ 54767414 or JNJ54767414 or 945721-28-8).tw,kw.
17	or/11-16
18	10 and 17
19	Randomized controlled trial/
20	Controlled clinical study/
21	random*.ti,ab.
22	randomization/
23	intermethod comparison/
24	placebo.ti,ab.
25	(compare or compared or comparison).ti.
26	(open adj label).ti,ab.
27	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

(Continued)

28	double blind procedure/
29	parallel group$1.ti,ab.
30	(crossover or cross over).ti,ab.
31	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
32	(controlled adj7 (study or design or trial)).ti,ab.
33	(volunteer or volunteers).ti,ab.
34	trial.ti.
35	or/19-34
36	(animal experiment/ or Animal experiment/) not (human experiment/ or human/)
37	35 not 36
38	phase 3 clinical trial/
39	("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.
40	(38 or 39) not 36
41	37 or 40
42	10 and 17 and 41
43	limit 42 to medline
44	42 not 43
45	remove duplicates from 44

Appendix 5. EU Clinical Trials Register search strategy

We searched the following keywords:

- myeloma and daratumumab
- myeloma and darzalex
- myeloma and anti-CD38

Appendix 6. WHO ICTRP search strategy

We searched the following keywords:

- daratumumab
- darzalex
- anti-CD 38

Appendix 7. ClinicalTrials.gov search strategy

We searched the following keywords:

- myeloma or plasmacytoma
- plasma cell leukemia or plasma cell leukaemia
- plasma cell tumor or plasma cell tumour or plasma cell neuplasm or plasmacytoma or plasmocytoma
- plasmacytic leukaemia or plasmacytic leukemia
- daratumumab or dara-tumumab or darzalex
- human CD38 or human CD 38 or anti-CD38 or antiCD38 or anti-CD 38 or antiCD 38

Appendix 8. ISRCTN search strategy

We search the following keywords:

- daratumumab
- darzalex
- anti-CD38

HISTORY

Protocol first published: Issue 4, 2020

CONTRIBUTIONS OF AUTHORS

Peter Langer (PL): database search, data extraction, risk of bias assessment, analysis, interpretation, draft of the review

Dr Lukas John (LS): clinical expertise and advice, proofreading

Ina Monsef (IM): search strategy development

Prof Dr Dr h.c. Christof Scheid (CS): clinical expertise and advice, proofreading

Dr Vanessa Piechotta (VP): data extraction and risk of bias assessment, proofreading

Prof Dr Nicole Skoetz (NS): database search, data extraction, analysis, interpretation, methodological and clinical expertise and advice, proofreading

All review authors have read and accepted the final version of this review.

DECLARATIONS OF INTEREST

Peter Langer (PL): none known. He is a staff member of Cochrane Haematology, but was not involved in the editorial process for this review.

Dr Lukas John (LJ): declares support from Janssen Biotech for serving on an advisory board on how to improve participation in clinical studies.

Ina Monsef (IM): none known. She is an Information Specialist of Cochrane Haematology, but was not involved in the editorial process for this review.

Prof Dr Dr h.c. Christof Scheid (CS): declares support from Janssen Biotech in the form of honoraria for presentations and symposia and support for clinical study on daratumumab by University of Cologne, as well as a consultancy for Janssen Global Services.

Dr Vanessa Piechotta (VP): none known. She was Managing Editor of Cochrane Haematology, but was not involved in the editorial process for this review.

Prof Dr Nicole Skoetz (NS): none known. She is Co-ordinating Editor of Cochrane Haematology, but was not involved in the editorial process for this review.

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Internal sources

- University Hospital of Cologne, Department I of Internal Medicine, Germany

  Evidence-based Medicine

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Outcomes

After consultation with our clinical colleagues, we decided to report for quality of life the commonly used EORTC QLG Core Questionnaire (EORTC QLQ-C30) and a specific time frame for this continuous treatment (at least 12 months).

We added Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 as a criterion for adverse events, as well as serious adverse events as an outcome.

We changed the rate of complete remission (after treatment) to complete response to reflect standard International Myeloma Working Group (IMWG) reporting.

Data synthesis

Due to heterogeneous studies with different backbone chemotherapies, we changed the methods to use the random-effects model as the standard model and the fixed-effect model as a sensitivity analysis.

NOTES

Part of this review (methods) is from the standard Cochrane Haematology review template.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibodies, Monoclonal [therapeutic use]; Antineoplastic Agents [therapeutic use]; *Antineoplastic Combined Chemotherapy Protocols [therapeutic use]; *Bias; Bortezomib [therapeutic use]; *Multiple Myeloma [drug therapy]; Progression-Free Survival; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Aged; Female; Humans; Middle Aged

5. Ergebnisse

5.1. Zusammenfassung der Ergebnisse

Die Ergebnisse dieser Übersichtsarbeit belegten die Vorteile einer Daratumumab-basierten Therapie bei Personen mit einem neu diagnostizierten Multiplen Myelom, die nicht für eine Hochdosistherapie mit Stammzelltransplantation geeignet waren. Die Ergänzung von Daratumumab führte zu einer wahrscheinlich verlängerten Lebenserwartung, geht jedoch mit einem erhöhten Risiko für schwerwiegende unerwünschte Ereignisse einher. Das Risiko für allgemeine unerwünschte Ereignisse, die gemäß den Common Terminology Criteria for Adverse Events (CTCAE) als Grad ≥ 3 eingestuft wurden, zeigte kaum einen Unterschied zur herkömmlichen Therapie des Multiplen Myeloms. Allerdings wurde in der Daratumumab-basierten Therapie ein erhöhtes Risiko für Infektionen beobachtet.[3]

5.2. Suchergebnisse

Bei der Durchsuchung von online Datenbanken von 2010 bis September 2023 wurden 3486 potenziell relevante Datensätze für diese Übersichtsarbeit gefunden. Davon entsprachen vier Studien (ALCYONE; AMaRC 03-16; MAIA; OCTANS) mit insgesamt 1783 Teilnehmern den Auswahlkriterien. Sechs weitere, die den Kriterien entsprachen, wurden als noch laufende Studien eingestuft und sollen in Kürze veröffentlicht werden.[3]

5.3. Eingeschlossene Studien

Alle vier einbezogenen Studien waren offene zweiarmige, randomisierte und kontrollierte Studien und wurden in Ländern mit hohem und mittlerem Einkommen erstellt. Drei multizentrische Studien wurden in mehreren Ländern durchgeführt (ALCYONE; MAIA; OCTANS). Eine Studie (AMaRC 03-16) wurde in einem Land durchgeführt. In allen Studien wurden antineoplastische Therapien sowohl mit als auch ohne Daratumumab untersucht. In der ALCYONE-Studie wurde Daratumumab mit Bortezomib und Melphalan-Prednison kombiniert, in der AMaRC 03-16-Studie mit Bortezomib, Cyclophosphamid und Dexamethason, in der MAIA-Studie mit Lenalidomid und Dexamethason und in der OCTANS-Studie mit Bortezomib und Melphalan-Prednison.[3]

5.3.1. Endpunkte der eingeschlossenen Studien

Zwei Studien (ALCYONE; MAIA) beinhalteten alle Endpunkte, die für diese Übersichtsarbeit ausgewählt wurden. Aufgrund fehlender Informationen konnten in zwei Studien (AMaRC 03-16; OCTANS) nicht alle Endpunkte analysiert werden. Es wurden zwei Subgruppenanalysen für den primären Endpunkt Gesamtüberleben ausgewertet. Allerdings berichtete nur die MAIA-Studie über Subgruppenergebnisse.[3]

5.3.2. Verzerrungsrisiko der eingeschlossenen Studien

Die AMaRC 03-16-Studie wurde als Kurzfassung veröffentlicht, daher bleibt die Verzerrung hinsichtlich der meisten Bereiche unklar. Für keine der vier Studien wurde eine Verblindung durchgeführt, daraus folgt ein hohes Risiko für die Verzerrung der Performance und der Detection. Die beiden größeren Studien, ALCYONE und MAIA, sowie die OCTANS-Studie wurden als Volltexte veröffentlicht. Abgesehen von der Verblindung war das Risiko einer Verzerrung bei diesen Studien gering.[3]

5.3.3. Therapieeffekte der eingeschlossenen Studien

Die Ergebnisse der Analysen zeigten insgesamt Vorteile der Daratumumab-basierten Therapie. Es konnte in moderater Evidenz eine wahrscheinliche Verbesserung im Gesamtüberleben nachgewiesen werden, wobei das mediane Gesamtüberleben in den beiden größeren Studien noch nicht erreicht wurde. In den beiden kleineren Studien waren für diesen Endpunkt noch keine Informationen verfügbar. Es wurden zwei Subgruppenanalysen für den primären Endpunkt erstellt. Allerdings berichtete nur eine Studie über Subgruppenergebnisse (MAIA). Hier wurden keine Subgruppenunterschiede für das zytogenetische Risiko (hohe Risiko versus Standardrisiko) oder für das Internationale Staging-System (I versus II versus III) festgestellt. Im progressionsfreien Überleben kam es in moderater Evidenz zu einer wahrscheinlichen Verbesserung in der Daratumumab-basierten Therapie. Auf der Basis des EORTC QLQ-C30 Fragebogens konnte in niedriger Evidenz, 12 Monate nach Therapiebeginn, für die Lebensqualität ein sehr leichter Vorteil in der Daratumumab-basierten Therapiegruppe berichtet werden. Eine wahrscheinliche Abnahme der studienbegleitenden Mortalität zeigte sich in moderater Evidenz bei der Behandlung mit Daratumumab. Zudem konnte in moderater Evidenz ein wahrscheinlich erhöhtes Risiko für schwerwiegende unerwünschte Ereignisse in der Daratumumab-basierten Therapie verzeichnet werden. Unter den unerwünschten Ereignissen (CTCAE Grad ≥ 3) zeigten sich in moderater Evidenz im Vergleich kaum Unterschiede. Allerdings ist während der Behandlung mit Daratumumab in moderater Evidenz ein wahrscheinlich erhöhtes Risiko für Infektionen (CTCAE Grad ≥ 3) zu berücksichtigen.[3]

6. Diskussion

6.1. Ergebnisse der Übersichtsarbeit

Da die mediane Gesamtüberlebenszeit noch nicht erreicht war, konnte die Wirkung von Daratumumab in diesem Fall nicht vorhergesagt werden. Zum Zeitpunkt der Datenerhebung zeichnete sich jedoch ein klarer Trend zugunsten der Daratumumab-Gruppe ab. Hervorzuheben war, dass die Kontrollgruppen aller Studien unterschiedliche Therapiekombinationen aufwiesen. Im Hinblick auf das progressionsfreie Überleben deuteten die Ergebnisse auf einen Vorteil der Therapie mit Lenalidomid und Dexamethason (MAIA) im Vergleich zu Bortezomib plus Melphalan-Prednison hin (ALCYONE; OCTANS). In der Heterogenität über alle 4 Studienarme hinweg zeigten die Interventionsarme mit Daratumumab als kontinuierliche Therapie ein längeres progressionsfreies Überleben. Ergänzt werden sollte, dass eine Langzeittherapie, wie im Kontrollarm in MAIA, eine deutlich bessere Therapie ergab als eine begrenzte Therapie, wie in den Kontrollarmen in ALCYONE und OCTANS. Angesichts des großen Konfidenzintervalls in der Lebensqualität bestand auch für die Daratumumab-basierte Therapie eine mögliche Abnahme der Lebensqualität. Interessant wäre außerdem gewesen, welche Todesursachen in die studienbegleitende Mortalität integriert und wie diese von der Gesamtmortalität unterschieden wurden. Zudem variierte die studienbegleitende Mortalität in Abhängigkeit der Beobachtungszeiträume in den einzelnen Studienarmen, hier zum Nachteil der kontinuierlichen Therapie. Auch unerwünschte Ereignisse wurden ausschließlich in dem Zeitraum erfasst, in dem der Teilnehmer behandelt wurde. Hier ist ein relativer Vergleich aller Studienarme nicht möglich, da so ein behandelter Teilnehmer mit einem unbehandelten Teilnehmer verglichen wurde. Die Beobachtungszeiträume hätten für alle Studienarme gleich sein müssen, um das gleiche Risiko für das Auftreten eines Ereignisses zu haben. Wie die Ergebnisse dieser Übersichtsarbeit zeigten, gab es auch klinisch eine Tendenz zu einem häufigeren Auftreten von Infektionen (CTCAE-Grad ≥ 3) unter Daratumumab. Mit dem Ziel einer Verlängerung des Gesamtüberlebens sollte das Risiko von Infektionen vom Kliniker gemeinsam mit den Patienten individuell abgewogen werden.[3]

6.2. Stärken und Schwächen

Diese Cochrane Übersichtsarbeit stellte eine unabhängige Bewertung der Evidenz dar. Es wurde geprüft, ob es relevante Interessen gab, die einen Interessenkonflikt darstellen könnten. Die Methodik dieser systematischen Übersichtsarbeit, die von Cochrane entwickelt wurde, legt eine äußerst strukturierte, transparente und reproduzierbare Methodik fest.[20]

Indem die Ergebnisse aller randomisierten kontrollierten Studien zusammengefasst wurden, konnten die Einschränkungen einzelner Studien, wie etwa die kleinen Stichprobengrößen und mangelnde statistische Aussagekraft, überwunden werden.

Zusammenfassend berichteten zwei Studien (ALCYONE; MAIA) von allen Endpunkten, die für diese Übersichtsarbeit interessant waren, während zwei Studien (AMaRC 03-16; OCTANS) aufgrund fehlender Informationen nicht alle Endpunkte berichteten. Es wurden zwei Subgruppenanalysen für den primären Endpunkt Gesamtüberleben ausgewertet. Allerdings berichtete nur eine Studie über Subgruppen Ergebnisse (MAIA).[3]

Außerdem war zu beachten, dass Daratumumab als humaner monoklonaler IgG1κ-Antikörper in seinem Molekulargewicht dem des M-Proteins ähnelte und nicht vom IgGκ-M-Protein unterschieden werden konnte. Die fehlende Unterscheidung zwischen körpereigenem M-Protein und therapeutischen Antikörpern könnte zu falsch-positiven Interferenzen, Ungenauigkeiten und insbesondere zu einer Herabstufung des Therapieerfolgs der Studienteilnehmer führen.[21,22]

6.3. Zukünftige Forschung

Eine weitere etablierte Erstlinientherapie besteht aus Bortezomib, Lenalidomid und Daratumumab. Interessant wäre, ob diese Kombination im Vergleich zur gleichen Kombination ohne Daratumumab zu vorteilhaften Ergebnissen führt. Es stellt sich zudem die Frage, ob Daratumumab auch Vorteile in der Therapie von Menschen zeigt, die für eine Hochdosistherapie mit autologer Stammzelltransplantation geeignet sind. Die Ergebnisse dieser Übersichtsarbeit dürften für die Behandlung weiterer hämatologischer Malignome, in denen das Zelloberflächenantigen CD38 exprimiert wird, interessant sein. Hierzu zählt zum Beispiel die Chronische Lymphatische Leukämie.[4] Sobald die mediane Gesamtüberlebenszeit erreicht ist, wird ein Antrag für die Aufnahme von Daratumumab in die WHO-Musterliste der unentbehrlichen Arzneimittel gestellt.[3]

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8. Vorabveröffentlichungen von Ergebnissen

Langer P, John L, Monsef I, Scheid C, Piechotta V, Skoetz N. Daratumumab and antineoplastic therapy versus antineoplastic therapy only for adults with newly diagnosed multiple myeloma ineligible for transplant. *Cochrane Database Syst Rev* 2024; (5). https://doi.org//10.1002/14651858.CD013595.pub2.