Evidence report

Multiple myeloma
(newly diagnosed, stem cell transplantation suitable)

Quadruplet followed by stem cell transplantation or quadruplet therapy only?

Version 1

SHARE TO CARE
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LIST OF ABBREVIATIONS

AMNOG: Pharmaceuticals Market Reorganisation Act
ASCT: Autologous stem cell transplantation
d: Dexamethasone
DA: Decision aid
Dara: Daratumumab
EORTC: European Organisation for Research and Treatment of Cancer
EQ-5D-5L: EuroQol Five Dimension Five Level Questionnaire
FAQs: Frequently asked questions
FDA: Food and Drug Administration
FSP: Full study population
G-CSF: Granulocyte Colony-Stimulating Factor
HDT: High-dose chemotherapy
HrQoL: Health-related quality of life
IMWG: International Myeloma Working Group
IQWiG: Institute for Quality and Efficiency in Health Care
Isa: Isatuximab
MM: Multiple myeloma
MRD: Minimal residual disease
OS: Overall survival
PFS: Progression-free survival
PICOS: Participants, intervention, comparators, outcomes, and study design
QLQ: Quality of Life Questionnaire
R: Lenalidomide
SDM: Shared decision making
T: Thalidomide
TD: Transplant-deferred
TIE: Transplant-ineligible
V: Bortezomib
VAS: Visual Analogue Scale

PROJECT OBJECTIVES

A key aim of the project is to inform patients on different therapy options as part of shared decision making (SDM). This evidence report is prepared to inform an evidence-based online decision aid (DA) which addresses patients with newly diagnosed multiple myeloma (MM) for whom a stem cell transplantation is considered suitable. The report relies on teamwork with clinical experts from two German university medical centres and patients from patient organisations.

INTRODUCTION TO THE DISEASE

Multiple myeloma is a type of blood cancer. It affects the plasma cells in the bone marrow which proliferate in an uncontrolled manner. Other than healthy plasma cells, the cancer cells produce unfunctional antibodies, called M-proteins or paraproteins.

Due to the proliferation of the cancer cells, the bone marrow contains decreasingly healthy cells. Therefore, the function of the haematopoietic system and the immune system is compromised. The M-protein is also responsible for organ damage, especially in the kidneys. As the cancer cells interfere with bone metabolism, bone stability decreases. Patients typically experience fatigue, bone pain, sometimes with complications like fractures and nerve compression, frequent infections, anaemia and decrease of renal function.

So far, it is usually not possible to heal multiple myeloma completely. But the treatments may suppress the course of the disease so that symptoms regress mostly or completely for a certain time and patients have a good quality of life and live longer. However, multiple myeloma may relapse, also several times, and become non-responsive (refractory) to certain treatments [1,2].

THE DECISION PROBLEM

Current guidelines recommend autologous stem cell transplantation (ASCT) as first-line treatment for multiple myeloma if this option is suitable for the patient [1,2]. This recommendation relies mostly on data comparing triplet therapy with ASCT to triplet therapy alone [3,4]. In these trials, progression-free survival (PFS) was significantly longer with ASCT although there was no difference in overall survival (OS).

Recent guidelines, however, recommend a quadruplet for induction therapy before ASCT [1]. For these drug combinations, recent trials showed a much longer progression-free survival and a much better response to therapy than with the triplets [5–7]. This is also reflected in the results for minimal residual disease (MRD) negativity (Table 1). At the same time, ASCT is a burdensome treatment for patients with considerable short-term and long-term toxicity.

This raises the question if upfront ASCT (rather than ASCT in a later line of therapy or no ASCT at all) has still added benefit if patients respond well to quadruplet induction therapy and if there are any subgroups for whom ASCT may still be beneficial [8].

Table 1: MRD negativity

MRD negativity means that no myeloma cells can be detected in the bone marrow with highly sensitive diagnostic methods. Depending on the method, this corresponds to a sensitivity to detect 1 myeloma cell in 10^5 to 10^6 bone marrow cells. MRD negativity is considered to be an excellent response to therapy [9]. However, MRD negativity status can be transient.

In January 2026, the US Food and Drug Administration (FDA) issued a draft guidance for industry which accepts MRD negativity (at a sensitivity of 10^{-5} in the bone marrow, not image-based) as an (intermediate) surrogate endpoint acceptable for accelerated approval of multiple myeloma drugs. This approach allows to provide early access to effective medicines for myeloma patients although the correlation of MRD with patient-relevant outcomes is not unequivocal. Waiting for robust PFS and OS data, on the other hand, would take a long time because the newer medicines prolong the time to progression and death considerably. Nevertheless, applicants should submit long-term data on PFS and OS subsequently to corroborate the effectiveness [10]. However, there is no binding guidance on the timing of MRD measurement or the duration of MRD negativity.

The most recent guidance of the European Medicines Agency, being reluctant to accept MRD negativity as surrogate outcome, is from 2022 and considered older evidence than the FDA report [11]. However, also a more recent scientific advice points out several weaknesses of the evidence base of MRD negativity as endpoint in clinical trials [12].

Despite the scientific controversies, MRD negativity is also discussed as decision criterion whether to treat patients with ASCT. This approach is tested in the MIDAS trial. This trial randomized patients reaching MRD negativity after induction therapy with IsaKRd to ASCT or further cycles of IsaKRd. MRD negativity (with a 10^{-6} sensitivity) after treatment completion (except maintenance therapy) was not statistically significantly different between the treatment groups (86 % with ASCT, 84 % with quadruplet therapy only) with a median follow-up of 17 months. This implies that at least in the short term and for this surrogate endpoint, ASCT has no benefit for these selected patients who responded well to induction therapy [13].

However, the data from the MIDAS trial are not suitable to answer the decision problem for this evidence report: The trial is ongoing and data on PFS and OS are yet to be reported. There are no data available on sustained MRD negativity (e.g. over 1 year), either. Additionally, the quadruplet used in the trial (IsaKRd) has no marketing authorization in the EU for first-line therapy and it is unknown if the results apply also to

the quadruplets which are authorized and recommended in guidelines, DaraVRd and IsaVRd.

METHODS

Before preparing the evidence report, we conducted a scoping process with the clinical experts. Together we defined the characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), used as inclusion criteria for the evidence report, as well as the frequently asked questions (FAQs) which the DA should answer. The FAQs were checked against the needs assessment conducted with patients and adapted where necessary.

INCLUSION CRITERIA

This decision aid only applies to patients who are newly diagnosed and have not previously received therapy for myeloma. Additionally, ASCT is considered a suitable treatment option for them. This is mainly the case if patients are below a certain age and comorbidities are not present. The exact age cut-off, however, is a matter of clinical debate. Many trials only include patients who are 65 years or younger. In clinical practice and in some trials, ASCT is considered suitable up to 70 years in the absence of limiting comorbidities. According to current guideline recommendations, biological and not only calendarial age should be considered when deciding about suitability of ASCT [3,4].

Patients, for whom a stem cell transplantation is not considered medically suitable, are not the target group of this DA. There is a separate DA for these patients.

The inclusion and exclusion criteria are described in Table 2, following the PICOS scheme of population, intervention, comparator, outcomes and study design.

Table 2: Inclusion criteria

	Included	**Excluded**
Population	Patients with newly diagnosed multiple myeloma for whom stem cell transplantation (ASCT) is suitable	Relapsed/refractory multiple myeloma; patients for whom stem cell transplantation is not suitable; patients with monoclonal gammopathies; diseases with monoclonal immunoglobulin disposition (e.g. AL amyloidosis); solitary plasmacytoma; plasma cell neoplasms with associated paraneoplastic syndrome
Intervention	Quadruplet therapy with daratumumab or isatuximab (DaraVRd, DaraVTd or IsaVRd for induction/consolidation) **plus** ASCT, followed by continuous therapy	n.a.
Comparator	Quadruplet therapy with daratumumab or isatuximab (DaraVRd, DaraVTd or IsaVRd for induction therapy) with **deferred** ASCT or **without** ASCT at all; followed by continuous therapy	n.a.
Outcomes	All-cause mortality, survival time, symptoms, health status, progression, quality of life, adverse events	n.a.
Study design	Stepwise approach: Guidelines, systematic reviews, RCTs	Other study designs

n.a.= not applicable; Dara: daratumumab; Isa: isatuximab; V: bortezomib; T: thalidomide; R: lenalidomide; d: dexamethasone; ASCT: autologous stem cell transplantation; RCT: randomised controlled trials

Frequently asked questions

The FAQs underpinning the literature searches were developed in collaboration with the patients and clinical experts during the scoping-process. The following FAQs were identified:

- FAQ 1: What does the treatment involve?
- FAQ 2: Will I live longer?
- FAQ 3: Will the treatment help my symptoms and how fast?
- FAQ 4: Will the treatment help that my disease does not progress?
- FAQ 5: How will the treatment impact my quality of life?
- FAQ 6: What are the short- or long-term risks or side effects?
- FAQ 7: How do I know that the treatment works?
- FAQ 8: How does the treatment impact my daily life?

Literature searches

Our literature search followed a pragmatic stepwise approach. As the treatment of multiple myeloma is a rapidly evolving field, we restricted the search for evidence syntheses to years 2020 to 2025. The choice of this period was guided by the dates of marketing authorization and publication of relevant trials.

- First, we searched for evidence-based guidelines which are suitable for data extraction.
- If we did not find any suitable references, we proceeded to HTA reports and the corresponding dossiers according to the Pharmaceuticals Market Reorganisation Act (AMNOG when these provided more detailed analyses.
- If these searches were futile or the retrieval insufficient to answer the FAQs, we proceeded to systematic reviews.
- To cover the latest evidence and supplement data from evidence syntheses, we additionally searched for publications of randomised controlled trials. When journal publications of a trial did not provide enough details, we additionally checked trial registry entries for results and/or publications not identified in the database searches.
- All searches were supplemented by handsearching when necessary.

The search strategies are described in detail in Appendix 1.

For the description of the disease and the treatment options, we hand searched the websites of relevant and reliable medical professional and patient organisations in Germany and selected other countries.

Handling of citations

Identified references from the bibliographic database searches were downloaded as RIS files and transferred into Rayyan App for abstract screening. Excluded references were tagged with the reasons for exclusion. Results of the abstract screening were exported as RIS file. Results of the full-text screening were documented in Appendix 1.

Quality assurance within the search process

One reviewer (IH) developed the search strategy, a second reviewer (JP) checked the strategy according to the PRESS Peer Review of Electronic Search Strategies Checklist [5].

STUDY SELECTION

One reviewer (IH) inspected the title and abstract of each reference identified by the search and documented reasons for exclusion. For potentially relevant articles, the full article was obtained, inspected, and inclusion criteria applied. Reasons for exclusion were documented. All decisions were checked by a second reviewer (JP). Any disagreements were resolved through discussion.

DATA EXTRACTION

For the data extraction, we preferred evidence syntheses, followed by the source with the most recent data cut-off and/or most detailed and/or relevant data to answer the FAQ. For each study, data were extracted by one reviewer (IH) and checked by another (JP). Any disagreements were resolved through discussion.

APPRAISING RISK OF BIAS AND CERTAINTY OF THE EVIDENCE

For the risk of bias assessment, we used Risk Of Bias instrument for Use in SysTematic reviews-for Randomised Controlled Trials (ROBUST-RCT) for randomized controlled trials [6]. Due to the high-quality methods and quality assurance procedures, risk of bias was not formally assessed for the reports by the Institute for Quality and Efficiency in Health Care (IQWiG). We adopted the risk of bias assessment of these reports for the included trials.

The certainty of the identified evidence is presented using the GRADE approach which assesses risk of bias, publication bias, imprecision, inconsistency, and indirectness according to the assessment criteria published by the GRADE working group [7].

The certainty of the evidence is rated as follows:

- High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low certainty: We are very uncertain about the estimate.

Where systematic reviews or other evidence syntheses presented risk of bias and/or GRADE assessments, we adopted the ratings for the evidence report.

One reviewer (IH) checked the risk of bias and rated the certainty of the evidence. The results were checked by a second reviewer (JP). Any disagreements were resolved through discussion.

RESULTS

LITERATURE SEARCHES AND INCLUSION ASSESSMENT

As a preliminary search of the evidence and consultation with experts revealed that there is no direct evidence for the PICOS, we resorted to an indirect approach. Therefore, we searched for evidence comparing:

- Triplet therapy with or without ASCT
- Quadruplet or triplet therapy, both with ASCT

Additionally, we searched for trials in a transplant-eligible population (possibly subgroup analyses) where one trial arm was quadruplet therapy without ASCT.

The search for guidelines did not identify suitable guidelines to inform the FAQs. Therefore, we proceeded to HTA reports and AMNOG dossiers. Additionally, we also searched for the journal publications for trials in the IQWiG reports/AMNOG dossiers for further details and possibly newer data cut-offs.

As the identified HTA report and AMNOG dossiers each only reported results from one trial, we additionally searched for systematic reviews with meta-analyses synthesizing relevant trials, also for the comparison triplet with or without ASCT. As the relevant trials (according to the criteria defined above) were already known from a preliminary search and consultation of experts, only systematic reviews were considered in which the meta-analyses included all relevant and no irrelevant trial and reported the outcomes of interest. However, we did not find any systematic reviews which met the criteria.

We also searched for RCTs (without limitation in terms of publication date) to find trials comparing relevant triplet therapy with or without ASCT.

For study selection, we preferred sources with more comprehensive data and/or more recent data cut-offs.

Overall, we included 1 HTA report [14] and two AMNOG dossiers [15,16] as well as seven journal publications reporting on six trials [3–7,17,18]. As for the GMMG-HD7 trial only few details were available, we also included an EMA report to inform the risk of bias assessment [19]. For one trial, we also identified a conference abstract [20] with a longer follow-up than the respective journal publication [3]. As there is no detailed journal publication, we did not use the conference abstract for the general data extraction but included the reported results as further information.

Details of the search strategy and the retrieval are described in Appendix 1 and details of the decisions concerning data extraction are discussed in the section “Overview of the evidence”.

For the description of the treatments, we included information from Myeloma UK [21–28] and from the patient guideline of the German programme for oncological guidelines [29] identified by hand-searching.

Risk of bias assessment

Results of the risk of bias assessments are reported in Appendix 2. Overall, risk of bias was high for most outcomes and trials.

Overview of the evidence

This evidence report relies only on indirect evidence. The strategy for the evidence synthesis is illustrated in Figure 1.

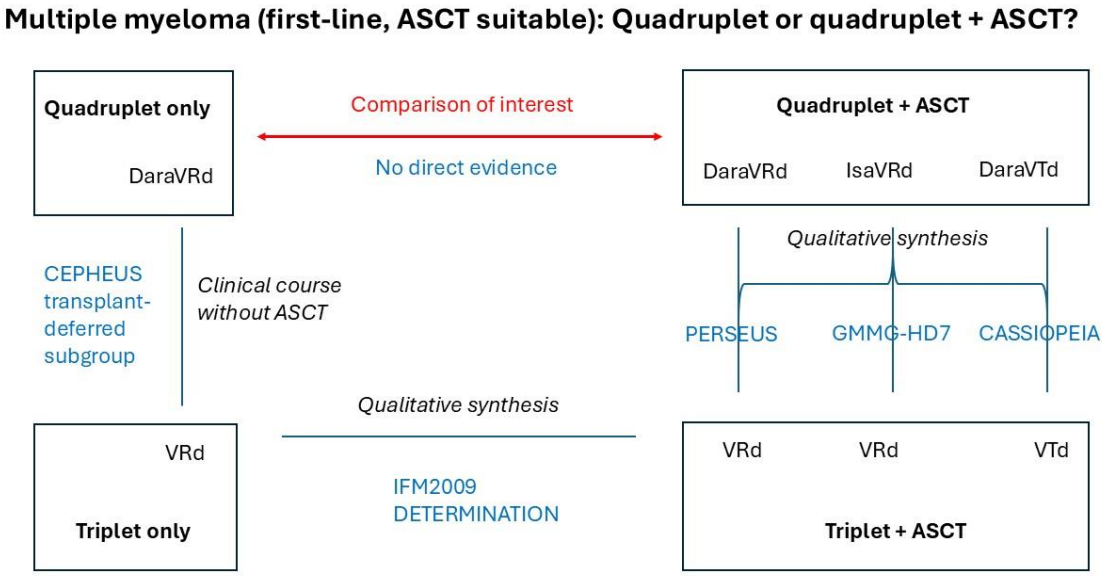


Figure 1: Strategy for evidence synthesis. Blue: Included trials. ASCT: Autologous stem cell transplantation, Dara: daratumumab, Isa: isatuximab, V: bortezomib, R: lenalidomide, T: thalidomide, d: dexamethasone.

For this evidence report, we included trials which compared triplet therapy + ASCT with triplet therapy alone (IFM-2009 and DETERMINATION, designed as corresponding trials) to describe the added benefit of ASCT in the context of the older therapies. To describe the added benefit of quadruplets in comparison to triplets in the context of ASCT, we included the trials CASSIOPEIA, PERSEUS and GMMG-HD7. As there is no direct evidence comparing quadruplet + ASCT to quadruplet alone, we included as a proxy the subgroup of transplant-deferred patients in the CEPHEUS trial. The data for this subgroup have been calculated from the data for the full study population in the journal publication and the transplant-

ineligible subgroup data in the IQWiG report and AMNOG dossier wherever possible (see Appendix 3). The results for the subgroup will be compared to the results of the quadruplet arm in PERSEUS as both trials use the same quadruplets.

Characteristics of the trials

The details of the trials are described in Table 3.

Populations: In five of the trials, the population was transplant-eligible and median age was 60 years or slightly younger. The CEPHEUS trial included two groups of patients: transplant-ineligible and transplant-eligible for whom ASCT was deferred. The latter comprised about 27 % of the full study population. The median age for the transplant-deferred subgroup is not available from the published data. An assessment report by the European Medicines agency, however, assumes that patients, who are eligible for treatment with ASCT but refuse that treatment option, are more fit and less comorbid than patients who are truly ineligible [30].

Induction therapy: Two of the trials (IFM 2009, DETERMINATION) compared triplet therapy with or without ASCT. Three trials (CASSIOPEIA, PERSEUS, GMMG-HD7) used ASCT in both arms and compared quadruplet with triplet therapy for induction. However, they tested different quadruplet and triplet combinations, respectively. In the CEPHEUS trials, the intervention was quadruplet or triplet therapy, without ASCT.

Most of the trials or trial arms with ASCT had an induction phase, followed by ASCT and consolidation. In the GMMG-HD7 trial, testing a quadruplet with isatuximab, however, the induction phase was slightly longer than in the daratumumab trials and no consolidation was used.

Both IFM 2009 and DETERMINATION included a run-in phase (one cycle of induction therapy) after recruiting and before randomisation. However, no additional inclusion or exclusion criteria were applied after the run-in phase.

Maintenance therapy: Two of the trials (CASSIOPEIA and GMMG-HD7) re-randomized patients before entering the maintenance phase. In CASSIOPEIA, however, the options for maintenance were the CD38 antibody alone or observation only. Only lenalidomide and the combination of daratumumab and lenalidomide currently have a marketing authorization for maintenance therapy and are recommended in the EHA-EMN guidelines. Therefore, also one of the maintenance options (IsaR) in GMMG-HD7 is currently not authorized.

Lenalidomide was part of the maintenance therapy in most trials, in CEPHEUS supplemented by dexamethasone for the patients who received a triplet. Trials testing the quadruplets usually used the respective CD38 antibody plus lenalidomide or lenalidomide alone as maintenance therapy in the respective treatment arms. In GMMG-HD7, the first cycle of maintenance therapy was supplemented by dexamethasone.

In all trials, the duration of maintenance therapy was mainly limited by disease progression or unacceptable toxicity. However, the details were different in the trials: DETERMINATION

had no time limit for maintenance therapy, whereas in IFM 2009, maintenance therapy was stopped after 1 year in both arms. Maintenance therapy containing a CD38 antibody was limited to 2 years in CASSIOPEIA and PERSEUS (for patients with complete response or better and sustained MRD for 1 year) and to 3 years in GMMG-HD7. In PERSEUS and GMMG-HD7, continuation with lenalidomide only was not limited in either trial arm except by disease progression or unacceptable toxicity.

Table 3: Characteristics of the included trials

Trial Identifier Status Recruiting period	Population	Interventions				
		Induction therapy	ASCT	Consolidation	Continuous therapy	Median treatment duration
IFM2009 NCT01191060 completed 2010–2012	TE n = 700 Median age: 59–60 years	3 cycles VRd (both arms) 3 weeks per cycle 9 weeks total	ASCT vs no ASCT	VRD (both arms) 2 cycles-vs. 5 cycles 3 weeks per cycle	R (both arms) [a], maximum 1 year	Not reported
DETERMINATION NCT01208662 ongoing 2010–2018	TE n = 722 Median age: 55–57 years	3 cycles VRd (both arms) 3 weeks per cycle 9 weeks total	ASCT vs no ASCT	VRD (both arms) 2 cycles-vs 5 cycles 3 weeks per cycle	R (both arms) [a], no maximum	36 vs 28 months
CASSIOPEIA NCT02541383 completed 2015–2017	TE n = 1085 Median age: 58–59 years	4 cycles DaraVTd or VTd 4 weeks per cycle 16 weeks total	ASCT (both arms)	2 cycles DaraVTd or VTd 4 weeks per cycle	Re-randomization: Daratumumab monotherapy or observation only, [a] maximum 2 years	First sequence: 9 months in both arms Full sequence:

PERSEUS NCT03710603 ongoing 2019–2020	TE n = 709 Median age: 60 years	4 cycles DaraVRd or VRd 4 weeks per cycle 16 weeks total	ASCT (both arms)	2 cycles DaraVRd or VRd 4 weeks per cycle	DaraR or R [a] Dara discontinued after at least 2 years therapy in patients with sustained MRD	46 vs 42 months
GMMG-HD7 NCT03617731 ongoing 2018–2020	TE n = 662 Median age: 59–60 years	3 cycles IsaVRd or VRd 6 weeks per cycle 18 weeks total	ASCT (both arms)	--	Re-randomization: IsaR or R [a] maximum 3 years	Not reported
CEPHEUS [12,17] NCT03652064 ongoing 2018–2019	TD subgroup only: n = 103 Median age not known	8 cycles DaraVRd or VRd 3 weeks per cycle 24 weeks total	No ASCT (both arms)	--	DaraRd or Rd [a]	56 vs. 34 months
[a] until progression or unacceptable toxicity TE: transplant-eligible; TD: transplant-deferred						

Description of the evidence sources

For most trials, we included several evidence sources (Table 4) as some provided additional results or other details.

- For IFM 2009, we included a journal publication reporting patient-reported outcomes [18] additionally to the main journal publication [3] reporting the other outcomes.
- For DETERMINATION, only one journal publication is available [4].
- For CASSIOPEIA, data were extracted from a journal publication [6] as it included the most recent data cut-off (01.09.2023) compared to the IQWiG report and the corresponding AMNOG dossier (first cut-off 19.06.2018, second cut-off 01.05.2019). The IQWIG report [31], however, was used for the risk of bias assessments and details on the trial.
- For PERSEUS, we both included the journal publication [7] and the AMNOG dossier [15], both with the same data cut-off (01.08.2023). The corresponding IQWiG report [32], however, did not contain any usable data as the reviewers concluded that the trial did not use adequate therapy as a comparator and did not discuss the trial data further.
- For CEPHEUS, we included both the journal publication [17] as well as the IQWiG report [14] and the corresponding AMNOG dossier [16], all with the data cut-off 07.05.2024. An EMA report contains additional analyses for safety outcomes for the transplant-deferred subgroup [30].
- For GMMG-HD7, only data for the first sequence are available in a journal publication [5]. As both the IQWiG report and the AMNOG dossier do not contain usable data, we included the EMA report on GMMG-HD7 [30] to supplement the journal publication for the risk of bias assessment.

Data on adverse events for CASSIOPEIA are only available separately for induction and maintenance therapy, and for GMMG-HD7, so far only for induction therapy. As patients would be interested in side effects of the full treatment sequence, data from these trials will not be included in the respective section of this evidence report (see FAQ 6).

Table 4: Evidence sources

Source	FAQ1: Treatment modalities	FAQ2: Survival	FAQ 3: Progression	FAQ4: Symptoms	FAQ5: Quality of life	FAQ6: Risks or side effects
Moreau 2024 (CASSIOPEIA) [6]		✓	✓			
AMNOG dossier DaraVRd (PERSEUS) [15]		✓	✓	✓	✓	✓
Sonneveld 2024 (PERSEUS) [7]		✓	✓			
Mai 2025 (GMMG-HD7) [5]		✓	✓			
Attal 2017 (IFM 2009)[3]		✓	✓			✓
Roussel 2020 (IFM 2009) [18]				✓	✓	✓
Richardson 2022 (DETERMINATION) [4]		✓	✓	✓	✓	✓
Usmani 2025 (CEPHEUS) [17]		✓	✓			✓
IQWiG report DaraVRd (CEPHEUS) [14]		✓		✓	✓	✓
AMNOG dossier DaraVRd (CEPHEUS) [16]			✓	✓	✓	✓
EMA report DaraVRd (CEPHEUS) [30]						✓
Myeloma UK Treatment Guides [21–23,25,26,33–35]	✓					✓
Patient guideline Multiple Myeloma [29]	✓					✓

FAQ 1: What does the treatment involve?

Supportive therapy

Independent of specific therapies for myeloma, doctors can offer options to treat symptoms of the disease or side effects of myeloma-specific therapy, i.e. (upfront) ASCT or quadruplet therapy alone (ASCT deferred) [29]. This supportive therapy includes (as needed) medicines and other treatments:

- To strengthen the bones and to prevent or treat fractures (e.g. bisphosphonates or in certain situations therapy)
- To treat pain (e.g. pain medication, in certain situations radiotherapy or surgery)
- To prevent or treat blood clots (e.g. anticoagulants)
- To prevent or treat infections (e.g. antibiotics, antivirals)
- To treat anaemia (e.g. erythropoietin, blood transfusions)

No upfront ASCT (quadruplet therapy only)

If patients choose not to undergo ASCT, they are usually offered quadruplet therapy, mostly DaraVRd or IsaVRd. Therapy is usually divided into induction therapy and maintenance/continuous therapy. Usually, therapy is given until the disease progresses or the toxicity becomes unacceptable.

All drug combinations are used within treatment cycles of several weeks, consisting of treatment days and days without treatment. The respective cycle lengths and treatment days depend on the drug combinations, the drug involved as well as the phase of the treatment (induction therapy or continuous therapy). Depending on the drug combination, continuous therapy usually includes the CD38 antibody, lenalidomide and dexamethasone according to the clinical trial protocols (see description of maintenance therapy above).

For daratumumab and isatuximab, additional medicines are required at every treatment to prevent infusion/injection reactions. On a case-by-case basis, further medicines might be necessary to prevent or treat infections (antibiotics, antivirals), to prevent or treat blood clots (anticoagulants) or to prevent or treat decreasing numbers of red blood cells (erythropoietin, blood transfusion) or white blood cells (G-CSF).

All treatments require regular blood checks before and during the treatment to assess treatment response and possible adverse effects.

Quadruplet plus ASCT

For the specific treatment of myeloma for the target group of this decision aid, current guidelines recommend ASCT if this treatment is suitable for the patient [1,2]. Standard of care is induction therapy over several cycles with a quadruplet, mainly DaraVRd or IsaVRd. Induction therapy is followed by high-dose chemotherapy (HDT) and ASCT and possibly consolidation therapy. After these treatment steps, maintenance therapy follows (Table 5).

Table 5: Course of treatment option ASCT [1,36]

Procedural step	Aim	Medicines involved	Notes
Induction therapy	To reduce myeloma cells in the bone marrow	First option: DaraVRd, IsaVRd If first option is not available: DaraVTd, VRd (no marketing authorization in the EU)	Daratumumab-based quadruplets: 4 to 6 cycles Isatuximab-based quadruplets: 3 cycles
Stem cell mobilisation and collection	To mobilise stem cells from the bone marrow to the blood where they can be collected	G-CSF, with or without one cycle of cyclophosphamide; additionally, plerixafor in patients with insufficient mobilisation	
High-dose chemotherapy (HDT)	To kill myeloma cells in the bone marrow and in the blood	High-dose melphalan	Also affects healthy cells
ASCT	To re-infuse healthy stem cells	Patient's own stem cells	Possibly two courses of ASCT (tandem ASCT) for high-risk disease or selected other patient groups
Consolidation therapy	To deepen and prolong response	Same as induction therapy	Daratumumab-based quadruplets: 2 cycles, if ≤ 4 induction cycles; otherwise, none Isatuximab-based quadruplets: none:
Maintenance therapy	To prolong remission	R or DaraR	Ongoing research on the optimal maintenance strategy (medicines used, duration, situations in which maintenance therapy is not warranted)

Dara: daratumumab; Isa: isatuximab; V: bortezomib; R: lenalidomide; d: dexamethasone; G-CSF: Granulocyte Colony-Stimulating Factor; ASCT: autologous stem cell transplantation

Depending on clinical practice in the respective myeloma centre, high-dose chemotherapy and ASCT are given either in an outpatient or an inpatient setting. In an inpatient setting, a hospital stay of two to three weeks may be required. During this time, patients will be in isolation for a better prevention of infection. Visitors, however, are allowed with special precautions.

Following ASCT, it may take some months before the immune system is fully restored and patients can return to their usual everyday life.

Change of treatment options

In case of unacceptable toxicity, doctors can reduce the dose, omit some medicines or change the treatment. A change of treatment is also possible if the disease does not respond to the treatment or progresses. Once HDT has been applied, it would be life-threatening to forego stem cell transfusion.

Instead of opting out of ASCT entirely, it might also be possible to defer ASCT . In this case, patients receive induction cycles and are offered stem cell mobilisation, collection and storage for an ASCT on further lines of therapy (salvage therapy after relapse). The availability of this option may vary according to clinical practice.

However, it might not be possible to choose ASCT at a later line of therapy if age and/or developing comorbidities lead to non-eligibility for ASCT. Especially patients with high-risk disease should discuss a possible decision to defer ASCT very carefully with their doctor [8].

Conclusion for the decision aid

- The decision aid should describe the treatment options as outlined above as well as the possible variations in clinical practice and the details when a change of treatment options is possible.

FAQ 2: WILL I LIVE LONGER?

Overall mortality has been reported in all trials (Table 6).

Table 6: Overall mortality

	Median follow-up	**More intensive therapy** Proportion with event Median time to event	**Less intensive therapy** Proportion with event Median time to event	**Effect**
Triplet + ASCT vs. triplet only				
IFM 2009 [3] [a]	43 – 44 months	19 per 100 n.r.	18 per 100 n.r.	n.s. [g]
DETERMINATION [4] [b]	76 months	24 per 100 n.r.	25 per 100 n.r.	n.s. [g]
Quadruplet + ASCT vs. triplet + ASCT				
PERSEUS [15] [c] full sequence	48 –47 months	10 per 100 n.r.	12 per 100 n.r.	HR 0.73 (0.47; 1.14)
CASSIOPEIA [6] [d] Full sequence	80 months	15 per 100 n.r.	26 per 100 n.r.	HR 0.55 (0.42; 0·73)
GMMG-HD7 [5] [e] first sequence	48 months	15 per 100 n.r.	13 per 100 n.r.	HR 1.13 (0.75; 1.71)
Quadruplet vs. triplet, both without ASCT				
CEPHEUS [14,17] [f]	59 months	34 per 100 n.r.	26 per 100 n.r.	n.c.
without COVID deaths		19 per 100 n.c.	14 per 100 n.c.	n.c.

Effect sizes are reported as point estimate and 95% confidence interval. ASCT: autologous stem cell transplantation; HR: hazard ratio; n.a.: not applicable, n.c.: not calculable, n.s.: not significant, n.r.: not reached.

[a] Overall survival at 4 years: 81% with upfront ASCT, 82% with deferred ASCT. HR only available for overall survival HR 1.16 (0.80; 1.68), not for overall mortality. Salvage transplantation: n = 136 (79% of patients with subsequent therapy) in triplet group, n = 21 (17% of patients with subsequent therapy) second transplantation in triplet + ASCT group

[b] Deaths: 88/365 for triplet + ASCT, 90/357 with triplet only. HR only available for overall survival HR 1.10 (0.73; 1.65), not for overall mortality. Salvage transplantation: 28 % of patients with less intensive therapy received ASCT in further lines of therapy (Table S7).

[c] Table 4-24, until the end of maintenance therapy, data cut-off 01.08.2023

[d] Data cut-off 01.09.2023. Events: DaraVTd 83/543, VTd 139/542

[e] Data Supplement, p. 18: Events Overall Survival 49/331 IsaVRd, 42/329 VRd; Data Supplement, Fig A5

[f] Own calculations for transplant-deferred subgroup (see Appendix 3), therefore no information about HR and CI available

[g] No information about HR and CI in journal publication

Direct evidence

Upfront vs. no or delayed ASCT with triplet induction

In trials comparing upfront ASCT vs. delayed or no ASCT on the backbone of triplet induction (IFM 2009 and DETERMINATION), there was no statistically significant difference between the groups with a follow-up of approximately 4 to 6 years. Long-term results from the IFM 2009 trial, reported in a conference abstract, indicate that after a follow-up of 93 months (nearly 8 years) there is still no difference in overall survival [20].

It should be noted that in the IFM 2009 trial, about 80 % of patients with progression and subsequent therapy in the triplet only arm received salvage ASCT as second-line therapy. Therefore, this trial delivers evidence for the deferral of ASCT rather than foregoing of ASCT. In the DETERMINATION trial, however, only 28 % of patients in the triplet only arm received ASCT in further lines of therapy.

In DETERMINATION, there are also a subgroup analysis according to genetic high-risk. Although the point estimate indicates a higher benefit for ASCT than in the full study population (Figure S8), the confidence intervals overlap considerably with the estimates for the full study population. It should be also noted that the analyses are exploratory and there is no information about the statistical interaction [4].

Quadruplet or triplet for induction therapy before ASCT

A benefit in overall survival for quadruplet vs. triplet therapy as induction before ASCT has been shown only for the CASSIOPEIA trial (DaraVTd vs. VTd) so far. Overall survival data for PERSEUS and GMMG-HD7 are still immature.

Indirect evidence

In the transplant-deferred subgroup of the CEPHEUS trial, overall mortality with triplet therapy was similar as in the No-ASCT-arm of the DETERMINATION trial (although DETERMINATION had a slightly longer follow-up).

Results from trial arms with triplet therapy and ASCT were also similar across trials with comparable follow-up (IFM 2009 and PERSEUS full sequence; and DETERMINATION and CASSIOPEIA full sequence, respectively).

In IFM 2009 and DETERMINATION, recruiting started nearly ten years before the recruiting in the other trials. Therefore, the results have to be interpreted in the context of possibly other available options for subsequent therapies in the earlier and the later trials.

Overall mortality, however, was higher in the CEPHEUS transplant-deferred subgroup than in the CASSIOPEIA trial although the follow-up for the latter was about 20 months longer and included a possibly substandard maintenance therapy (Dara only instead of DaraRd). It should be noted, however, that there is no information about the median age of the transplant-deferred subgroup of the CEPHEUS trial. If these patients were older than

patients in CASSIOPEIA, results would be biased towards higher mortality. The overall mortality in CEPHEUS is immature, and estimates might change when results with longer follow-up become available.

Overall, it is difficult to ascertain if the apparently higher mortality in CEPHEUS is due to the deferral of ASCT or due to other factors.

Influence of COVID deaths

As the CEPHEUS trial was conducted during the COVID pandemic, there were several COVID deaths in both groups. In the discussion with the clinical experts, they pointed out that these deaths would not occur today with the available COVID immunisations and immunity due to previous infections. Therefore, it might be more appropriate to communicate the numbers without the COVID deaths.

However, it should be also considered that a major adverse effect of the CD38 antibodies is increased risk of infection, also severe infections. If there was a future pandemic or a severe influenza season with a vaccine mismatch, it might be possible that the number of deaths would be closer to the mortality figures in CEPHEUS including COVID deaths.

Table 7: GRADE rating for outcome overall mortality

Domain	**Downgrading**	**Certainty**	**Notes**
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	n.a.		No effect estimate available
Indirectness	↓↓		Comparison relies on indirect evidence. It is unclear, if populations are comparable.
Inconsistency	n.a.		Not enough data to assess inconsistency
Publication bias	n.a.		No concern
Overall	↓↓↓	**very low**	

Conclusion for the decision aid

- About 34 per 100 patients who choose to forego ASCT as first-line therapy and choose quadruplet therapy only, have died after about five years and 66 per 100 are still alive. If COVID deaths are not accounted for, the corresponding numbers are 19 deaths per 100 after about five years and 81 per 100 still alive. This should be reported as “about 80 per 100” in the decision aid.
- The decision aid should explain in a box with additional information that the numbers do not account for COVID deaths and that they could be higher in circumstances with a high risk of infection. The numbers from the trial should be given as reference.

- It is unclear if the proportion would be lower with quadruplet + ASCT. The evidence is very uncertain and the possible difference, if any, cannot reliably quantified.

FAQ 3: Will the treatment help that my disease does not progress?

All trials assessed progression according to the criteria of the International Myeloma Working Group (IMWG) based on biochemical and/or radiological markers [37]. It should be noted that this definition of progression is not necessarily directly linked to patient experience (e.g. worsening of symptoms).

In the trials, progression is operationalised in different ways. All trials report on PFS. However, as PFS is a composite outcome, it is not easy to interpret. Some trials also report "time to progression". As this operationalisation, however, has not been assessed in the CEPHEUS trial, it is not useful for cross-trial comparisons and is therefore not included in this evidence report.

PFS has been defined as time to progression or death, whatever comes first in all trials (Table 8).

Table 8: Progression-free survival

	Median follow-up	More intensive therapy Proportion with event Median time to event	Less intensive therapy Proportion with event Median time to event	Effect
Triplet + ASCT vs Triplet				
IFM 2009 [3] [a]	43–44 months	45 per 100 50 months	60 per 100 36 months	HR 0.65 (0.53; 0.80)
DETERMINATION [4] [b]	76 months	38 per 100 68 months	53 per 100 46 months	HR 1.53 (1.23; 1.91) [h]
Quadruplet + ASCT vs Triplet + ASCT				
PERSEUS [15] [c] full sequence	48 –47 months	14 per 100 n.r.	29 per 100 n.r.	HR 0.42 (0.30; 0,59)
CASSIOPEIA [6] [d] full sequence	80 months	47 per 100 84 months	62 per 100 53 months	HR 0.61 (0·52; 0·72)
GMMG-HD7 [5] [e] first sequence	48 months	24 per 100 n.r.	31 per 100 n.r.	HR 0.70 (0.52; 0.95)
Quadruplet vs. triplet, both without ASCT				
CEPHEUS [16,17] [f]	59 months	36 per 100 n.r.	44 per 100 n.r.	n.c.

Effect sizes are reported as point estimate and 95% confidence interval.
ASCT: autologous stem cell transplantation; HR: hazard ratio; n.a.: not applicable, n.c.: not calculable, n.r.: not reached.

[a] 157/350 triplet + ASCT; 211/350 triplet only
[b] 139/365 triplet + ASCT; 189/357 triplet only
[c] Module B, Table 4-28
[d] PFS from first randomisation: 255/543 events with quadruplet, 335/542 events with triplet
[e] PFS from first randomisation. Data supplement, p. 18: For PFS 78/331 events with IsaVRd, 101/329 events with VRd
[f] Own calculations (see Appendix 3), therefore no information about HR and CI available
[h] HR calculated for less intensive therapy vs. more intensive therapy, therefore HR > 1

Direct evidence

Upfront vs. no or delayed ASCT with triplet induction

In trials comparing upfront ASCT vs. delayed or no ASCT on the backbone of triplet induction (IFM 2009 and DETERMINATION), there was a statistically significant difference between the groups for PFS [3,4]. Long-term results from the IFM 2009 trial with a follow-up of 93 months, i.e. nearly 8 years, reported in a conference abstract, confirm the benefit for PFS for the more intensive therapy [20].

In both trials, there are subgroup analyses for PFS according to genetic high-risk. The results are, however, contradictory: Whereas the point estimate in DETERMINATION [4] indicates a higher benefit of ASCT in high-risk patients than in standard risk patients (Figure S3), the direction of the effect is the opposite in IFM 2009 [3] (Figure 2). It should be noted that only a small group of patients were genetically high-risk and the confidence intervals overlap considerably with the estimates for the full study population. There are also no results from a statistical interaction test, and all subgroup analyses are exploratory.

Quadruplet or triplet for induction therapy before ASCT

For all trials reporting data, PFS is significantly shorter with quadruplet vs. triplet therapy as induction before ASCT. Median PFS, however, has only been reached in the CASSIOPEIA trial so far.

Indirect evidence

In the transplant-deferred subgroup of the CEPHEUS trial, PFS with triplet therapy was lower than in the No-ASCT-arm of both the DETERMINATION and the IFM 2009 trial. It should be noted, however, that the follow-up of IFM 2009 was shorter than in CEPHEUS and still there were more events. Results from trial arms with triplet therapy and ASCT were also not similar across trials with comparable follow-up (IFM 2009 and PERSEUS full sequence; and DETERMINATION and CASSIOPEIA full sequence, respectively).

For all these comparisons with the exception of CASSIOPEIA, the trial intervention for less intensive therapy (VRd) was identical. It seems rather unlikely that concomitant interventions or changes in care account for this difference in progression risk. This might indicate that there is a systematic difference in the trial populations which makes cross-trial comparisons difficult.

In the trials with a quadruplet arm, proportions for PFS events were 14 and 24 per 100, respectively, in PERSEUS and GMMG-HD7 with a follow-up of about 4 years and 47 per 100 in CASSIOPEIA with a follow-up of about 6.5 years. In CEPHEUS, the proportion was 36 per 100 with a follow-up of about 5 years (corresponding to 64 per 100 being alive without progression). Based on these data, it might be possible that there is only a small difference (if any) between quadruplet + ASCT and quadruplet only.

Unfortunately, there are no details available which allow further analysis. Median PFS has not been reached except for CASSIOPEIA. As there is no Kaplan-Meier curve available for the transplant-deferred subgroup in the CEPHEUS trial, the survival curves cannot be compared beyond the data reported in the trial publications.

Table 9: Results for MRD negativity

Despite the scientific controversies (see Table 1), results on MRD negativity might provide some additional insight on the value of ASCT. It should be noted, however, that cross-trial comparisons are complicated by different levels of MRD negativity, time frames and lengths of follow-up. In the IFM 2009 trial comparing triplet + ASCT vs. triplet, MRD negativity at a level of 10^{-4} was found for 79 % of patients with ASCT and 65 % without ASCT (MRD not detected during the study with a follow-up of 44 and 43 months, respectively). The difference was statistically significant [3]. Data from the DETERMINATION trial cannot be directly compared to IFM 2009 data as MRD was only assessed in about a third of the participants, only from start of maintenance therapy and at a different sensitivity level (10^{-5}). Although the proportion of participants with MRD negativity is higher with ASCT (54 %) than without ASCT (40 %), the difference is not statistically different [4]. This should be interpreted in the context of the low numbers analysed. In the PERSEUS trial and in the CEPHEUS trial, MRD negativity was assessed at the 10^{-5} sensitivity level in regular intervals during the trials. Comparing quadruplet arms across trials, MRD negativity at any time during the trial was 75 % with ASCT in PERSEUS [7] and 62 % without ASCT in CEPHEUS (transplant-deferred population, own calculations) [16,17]. It should be noted, however, that follow-up time was shorter in PERSEUS (48 months) than in CEPHEUS (59 months). It might be possible that MRD negativity in the PERSEUS trial might decline with longer follow-up. Comparison of sustained MRD negativity (for at least 12 months), however, is not complicated by lengths of follow-up. It was 65 % with ASCT in PERSEUS [7] and 55 % without ASCT in CEPHEUS (transplant-deferred population, own calculations, see Appendix 3) [16,17]. For the GMMG-HD7 trial, MRD negativity is only available after transplant so far [5], but not for the full treatment sequence and therefore not reported here. Overall, MRD negativity is numerically higher in all trial arms with ASCT than without ASCT. However, statistical significance is only established for the IFM 2009 trial on a triplet backbone. Therefore, it is difficult to ascertain the magnitude of the difference, if any.

Summary

Overall, considering proportions according to follow-up time, it is not clear whether there is a difference in PFS with or without ASCT and if yes, what is the possible magnitude of the

difference. However, there are some indications that MRD negativity might be higher with ASCT. But it is not clear either whether this translates to a higher benefit for patients in the long term. The certainty of the evidence is very low (Table 10).

Table 10: GRADE rating for outcome progression-free survival

Domain	Downgrading	Certainty	Notes
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	↓		No precise comparison possible due to lack of comparable data
Indirectness	↓		Comparison relies on indirect evidence. It is unclear, if populations are comparable.
Inconsistency	n.a.		Not enough data to assess inconsistency
Publication bias	n.a.		No concern
Overall	↓↓↓	**very low**	

Conclusion for the decision aid

- About 64 per 100 patients who choose to forego ASCT as first-line therapy and choose quadruplet therapy only, are alive without progression after five years.
- It cannot be assessed if the proportion would be higher with quadruplet + ASCT. If there is any difference, it cannot be quantified reliably.
- There are some indications that quadruplet + ASCT might suppress the disease better than quadruplet therapy alone (as indicated by MRD negativity). It is, however, not clear, if and how this translates into a benefit in progression-free survival.
- The certainty of the evidence is very low.

FAQ 4: Will the treatment help my symptoms and how fast?

The symptoms of MM such as (bone) pain and fatigue can improve with response to myeloma-specific therapy. However, fatigue and other symptoms can also be a side effect of myeloma treatments. Supportive therapies can help to relieve the symptoms, either from the disease or the side effects. When the disease progresses, symptoms might increase. Therefore, it is also an aim of the treatment to delay worsening of symptoms.

Data availability and operationalisations

Effects of therapy (supportive and myeloma-specific treatments) on symptoms have been assessed in the trials IFM 2009, CASSIOPEIA, PERSEUS and CEPHEUS. According to the study protocol, symptoms have also been assessed in the DETERMINATION trial, but results are only partially reported [4].

All trials used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) symptom scales for the assessment of symptoms as pain and fatigue. The trials PERSEUS, IFM 2009 and CEPHEUS additionally used the myeloma-specific questionnaire EORTC QLQ-MY20 for the assessment of disease symptoms and side effects and PERSEUS also the EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L) Visual Analogue Scale (VAS) for the assessment of health status. In DETERMINATION, also the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT-NTX) side-effects questionnaire was used.

For IFM 2009 and DETERMINATION, information is only available for the course of the symptoms. In the journal publication of the CEPHEUS trial (full study population), there are no data on the course of the symptoms. Also, data the transplant-deferred subgroup are not available separately.

Data on the course of symptoms as well as responder analysis for first relevant worsening of symptoms can be found in the AMNOG dossiers for PERSEUS, CASSIOPEIA and CEPHEUS. However, for the CEPHEUS trial, only data from the transplant-ineligible subgroup are available which is different from the target group of the DA this evidence report is prepared for. In fact, the transplant-deferred subgroup is presumably younger and fitter than the transplant-ineligible subgroup. Results have been included in this evidence report nevertheless as a benchmark for the transplant-deferred subgroup (at least as favourable outcomes as the transplant-ineligible subgroup). It should be noted, however, that the transplant-ineligible subgroup is supposedly more vulnerable to adverse effects of the treatment which might also influence the measured symptoms.

In the AMNOG process for CASSIOPEIA, a relevant change has been defined as ≥ 10 points for all instruments. For CEPHEUS and PERSEUS, which were assessed some years after the assessment of the CASSIOPEIA trial, relevant changes have been defined as ≥ 15 points for EQ-5D-5L and ≥ 10 points for EORTC QLQ-C30 and EORTC QLQ-MY20. These thresholds are adopted in this evidence report.

It should be noted that the follow-up time for morbidity endpoints had been defined differently in the trials:

- In IFM 2009, follow-up extended beyond the end of treatment (after maintenance), but symptoms were only assessed once in year 2 and once in year 3. The follow-up time for symptoms is not reported separately.
- In DETERMINATION, HrQoL questionnaires were administered on 9 occasions: baseline and time of randomization, prior to HDT and 60 and 120 days after, as well as at 1 year, 2 years and 3 years from baseline and at the end of study.
- In CASSIOPEIA, patients were only followed for 100 days after ASCT or until the second randomisation. Median follow-up for symptoms was 9 months in both groups.

- In PERSEUS and CEPHEUS, follow-up was restricted to 30 days after the last treatment for symptoms measured by EORTC QLQ-C30 and EORTC QLQ-MM20, but not for health status measured by EQ-5D VAS (until death or study end). Median follow-up for symptoms was 45 months (DaraVRd) and 44 months (VRd) in PERSEUS and 53 to 54 months (DaraVRd, depending on the instrument) in CEPHEUS.

As the follow-up for CASSIOPEIA is much shorter than in the other quadruplet trials, only the data from PERSEUS and CEPHEUS will be discussed in the sections below.

Direct evidence

Upfront vs. no or delayed ASCT with triplet induction

For IFM 2009 [18], the course of the symptoms is described by graphs with mean scores. Data including follow-up are only available for the symptoms pain and fatigue (Figure 2).

The course of the symptoms is similar with and without ASCT during induction. Generally, symptoms decrease in a clinically meaningful way over the course of the treatment in both groups. However, at the time of ASCT, patients experience more fatigue and pain (clinically relevant difference, ≥ 10 points), but both curves converge quickly afterwards and are again similar during maintenance. However, the available data only capture a follow-up of about 3 years and does not allow to extrapolate beyond.

For DETERMINATION, results for symptoms are only available for the side effects domain of EORTC QLQ-MM20 (Figure S11, E) for which the course is very similar to those reported in IFM 2009 for pain and fatigue. No relevant differences between both groups were visible in the domain disease symptoms of EORTC QLQ-MM20 and FACT-NTX (Figure S11, D, F) [4].

Quadruplet or triplet for induction therapy before ASCT

In the responder analysis for PERSEUS (full sequence) [15], no statistically significant differences were found for health status/EQ-5D VAS (Table 4-62) and most domains of EORTC QLQ-C30 (Table 4-75). However, proportions were statistically significantly higher with the quadruplet (DaraVRd) for fatigue and dyspnoea. Only for dyspnoea, also the time to event was statistically significantly shorter with the quadruplet.

Indirect evidence

As in IFM 2009 and DETERMINATION no responder analyses are available, indirect comparisons can only rely on comparison of the respective arms in PERSEUS and CEPHEUS. It should be noted, however, that this indirect comparison is probably highly biased, additionally to all aspects discussed in the subsection “Data availability and operationalisations”.

In PERSEUS, relevant change of symptoms over the course of the treatment with the quadruplet (+ ASCT) is only reported [15] for the domains pain (decrease, Table 4-69), insomnia (decrease, Table 4-71), diarrhoea (increase, Table 4-74) and disease symptoms (decrease, Table 4-80).

In CEPHEUS, relevant change of symptoms over the course of the treatment with the quadruplet alone is only reported [16] for the domains pain (decrease, Table 4-56) and diarrhoea (increase, Table 4-61).

Data for time to first relevant worsening are available is available for several symptoms (Table 11). In the PERSEUS trial (quadruplet with ASCT) with a median follow-up of 45 months, 40 to 70 % of patients experienced relevant worsening, depending on the symptom. In the CEPHEUS trial (quadruplet without ASCT), proportions were higher with about 60 to 80 % with a follow-up of 53/54 months. Time to event is considerably lower in CEPHEUS for some domains whereas there are only slight differences in proportions for most domains.

The higher proportions in CEPHEUS might be at least partially attributable to the longer follow-up. On the other hand, also median time to worsening was considerably shorter in this trial indicating a real difference. It should be noted, as only the data for the more vulnerable transplant-ineligible subgroup are available, it cannot be precluded that the transplant-deferred subgroup would fare much better. Whether the difference in fitness would fully account for the apparent magnitude of difference in effect sizes, cannot be reliably estimated.

Table 11: First relevant worsening of symptoms

	PERSEUS [15] [a] **Quadruplet + ASCT** **Proportion** **Median time to event**	**CEPHEUS** [14] [b] **Quadruplet only** **Proportion** **Median time to event**
Median follow-up	45 months	53–54 months
Fatigue	69 per 100 4 months	73 per 100 2 months
Nausea/ vomiting	44 per 100 47 months	60 per 100 6 months
Pain	53 per 100 17 months	57 per 100 4 months
Dyspnoea	57 per 100 21 months	73 per 100 3 months
Insomnia	60 per 100 9 months	73 per 100 3 months
Loss of appetite	51 per 100 24 months	73 per 100 4 months
Obstipation	57 per 100 13 months	67 per 100 3 per 100

Diarrhoea	70 per 100 17 months	82 per 100 5 months
Health status	40 per 100 n.r.	59 per 100 4 months

n.r.: not reached

[a] full sequence, data cut-off 01.08.2023. Health status: Table 4-62, symptoms Table 4-75

[b] transplant-ineligible subgroup, data cut-off 07.05.2024, Table 15

Summary

Due to the limited data and the differences in operationalisation, it is not possible to reliably estimate the impact of upfront ASCT or no or deferred ASCT additionally to quadruplet therapy on the course of the symptoms.

Other than for progression, induction before ASCT with a quadruplet seems to have no clear benefit for delaying worsening of symptoms in comparison to a triplet induction. Rather, there might be even disadvantages, presumably due to additional side effects of the quadruplet.

For the comparison of upfront and deferred ASCT (both with a quadruplet), it might be therefore reasonable to assume that the short-term course of the symptoms might be similar as in the comparison of triplet + ASCT and triplet in IFM 2009: Over the course of the treatment, symptoms (only reported for pain and fatigue) decrease in general. However, they might increase during ASCT but recover quickly afterwards to the level without ASCT.

If a quadruplet with ASCT was more effective in delaying progression in the long-term than a quadruplet without ASCT (see FAQ3), it would be expected to also delay worsening of symptoms as indicated by the indirect comparison of PERSEUS and CEPHEUS (full study population, see FAQ 2). However, there is relevant uncertainty as no data are available on symptoms for the transplant-deferred subgroup in CEPHEUS.

Overall, adding ASCT to a quadruplet might increase short-term symptoms. In the long term, it is unclear if the more intensive therapy delays worsening of some symptoms better than a quadruplet without ASCT. The certainty of the evidence is very low (Table 12).

Table 12: GRADE rating for outcome symptoms

Domain	Downgrading	Certainty	Notes
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	↓		No precise comparison possible due to lack of comparable data
Indirectness	↓		Comparison relies on indirect evidence. It is unclear, if populations are comparable.
Inconsistency	n.a.		Not enough data to assess inconsistency
Publication bias	n.a.		No concern
Overall	↓↓↓	**very low**	

Conclusion for the decision aid

- Both quadruplet + ASCT and quadruplet alone might decrease some disease symptoms over the course of the treatment. There are, however, also symptoms which might increase (e.g. due to adverse effects of the treatment).
- During ASCT, some symptoms might increase in the short-term but decrease to the previous level quickly afterwards.
- In the long term, it is unclear if the more intensive therapy (quadruplet + ASCT) delays worsening of symptoms better.
- The certainty of the evidence is very low.

FAQ 5: How will the treatment impact my quality of life?

In patients with MM, health-related quality of life (HrQoL) might be reduced by the psychological burden of the disease, but also when symptoms of the disease or side effects of the treatment interfere with everyday life. Psychological support can help to mitigate some aspects of HrQoL. When supportive therapy and myeloma-specific therapy improve symptoms, HrQoL might also increase. However, HrQoL might decline when the disease progresses and symptoms increase. The aim of the treatment is to improve HrQoL and to delay worsening HrQoL in the course of the disease.

Data availability and operationalisations

Effects of therapy (supportive and myeloma-specific treatments) on HrQoL have been assessed in the trials IFM 2009, DETERMINATION, CASSIOPEIA, PERSEUS and CEPHEUS.

All trials used the EORTC QLQ-C30 scales for the assessment of HrQoL (domains: global health status, physical function, role functioning, emotional functioning, cognitive functioning, social functioning). The trials PERSEUS, IFM 2009, DETERMINATION and CEPHEUS additionally used the myeloma-specific questionnaire EORTC QLQ-MY20 for the assessment of future perspective and body image. However, the journal publication for DETERMINATION only reports results for the HrQoL domains Global Health Score, physical function and role functioning [4].

The different domains of HrQoL can be described as follows:

- Global health status refers to a general self-assessment of health status and quality of life.
- Physical function refers e.g. to the ability to carry a heavy shopping bag, taking a longer or shorter walk, need for rest during the day or need for help with eating, getting dressed or taking a shower.
- Role functioning refers to the ability to work, any limitations in everyday life, hobbies or leisure time activities.
- Emotional functioning refers to feeling stressed, depressed, worried, or irritable.
- Cognitive functioning refers to the ability to concentrate, e.g. reading the papers or watching television, or to remember certain things.
- Social functioning refers to any limitations in being together with other people, as family or friends.
- Future perspective refers to thinking about the illness and worrying about health in the future and dying.
- Body image refers to feeling physically less attractive because of the disease or treatment.

For IFM 2009 and DETERMINATION, information is only available for the course of the symptoms. In the journal publication of the CEPHEUS trial (full study population), there are no detailed data on the course of all HrQoL domains, only for the domain Global health status. Also, data the transplant-deferred subgroup are not available separately.

Data for all domains on the course of HrQoL as well as responder analysis for first relevant worsening of symptoms can be found in the AMNOG dossiers for PERSEUS, CASSIOPEIA and CEPHEUS. However, for the CEPHEUS trial, only data for the transplant-ineligible subgroup are available, which is different from the target group for the DA this evidence report is prepared for. In fact, the transplant-deferred subgroup is presumably younger and fitter than the transplant-ineligible subgroup. Results have been included in this evidence report nevertheless as a benchmark for the transplant-deferred subgroup (at least as favourable outcomes as the transplant-ineligible subgroup). It should be noted, however, that the

transplant-ineligible subgroup is supposedly more vulnerable to adverse effects of the treatment which might also influence the measured symptoms.

In the AMNOG process, a relevant change has been defined as ≥ 10 points for all instruments. It should be noted that the follow-up time for HrQoL endpoints had been defined differently in the trials:

- In IFM 2009, follow-up extended beyond the end of treatment (after maintenance), but symptoms were only assessed once in year 2 and once in year 3. The follow-up time for symptoms is not reported separately.
- In DETERMINATION, HrQoL questionnaires were administered on 9 occasions: baseline and time of randomization, prior to HDT and 60 and 120 days after, as well as at 1 year, 2 years and 3 years from baseline and at the end of study.
- In CASSIOPEIA, patients were only followed for 100 days after ASCT or until the second randomisation. Median follow-up for symptoms was 9 months in both groups.
- In PERSEUS and CEPHEUS, follow-up was restricted to 30 days after the last treatment for symptoms measured by EORTC QLQ-C30 and EORTC QLQ-MM20, but not for health status measured by EQ-5D VAS (until death or study end). Median follow-up for HrQoL was 45 months (DaraVRd) and 44 months (VRd) in PERSEUS and 53 to 54 months (DaraVRd, depending on the instrument) in CEPHEUS.

As the follow-up for CASSIOPEIA is much shorter than in the other quadruplet trials, only the data from PERSEUS and CEPHEUS will be discussed in the sections below.

Direct evidence

Upfront vs. no or delayed ASCT with triplet induction

For IFM 2009 [18], the course of HrQoL is described by graphs with mean scores. Data including follow-up are only available for the domains global health status, physical function and role functioning (Figure 1). The same applies to DETERMINATION [4] (Fig S11).

In IFM 2009, the course of QoL is similar for all domains: Mean scores are similar with and without ASCT during induction. Generally, HrQoL increases in a clinically meaningful way (≥ 10 points) over the course of the treatment in both groups. However, at the time of ASCT, patients experience a drop in HrQoL (clinically relevant difference, ≥ 10 points), but both curves converge quickly afterwards and are again similar during maintenance. However, the available data only capture a follow-up of about 3 years and do not allow to extrapolate beyond. The results for DETERMINATION are very similar to those reported in IFM 2009.

Quadruplet or triplet for induction therapy before ASCT

In the responder analysis for PERSEUS (full sequence) [15], no statistically significant differences were found for time to event for any domain of EORTC QLQ-C30. However, the proportion for emotional functioning was lower with DaraVRd vs VRd (Table 4-93). For

EORTC QLQ-MY20, there was no statistically significant differences between quadruplet and triplet therapy in any domain, neither for time to event nor for the proportions (Table 4-100).

Indirect evidence

As in IFM 2009 and DETERMINATION no responder analyses are available, indirect comparisons can only rely on comparison of the respective arms in PERSEUS and CEPHEUS. It should be noted, however, that this indirect comparison is probably highly biased, additionally to all aspects discussed in the subsection “Data availability and operationalisations”.

In PERSEUS, relevant improvement of HrQoL over the course of the treatment with the quadruplet (+ ASCT) is only reported [15] for the domains role functioning (Table 4-88), physical function (Table 4-90), social function (Table 4-92) and future perspectives (Table 4-98). In CEPHEUS, relevant improvement of HrQoL over the course of the treatment with the quadruplet only is only reported [16] for the domains role functioning (Table 4-72) and future perspectives (Table 4-80).

Data for time to first relevant worsening are available for several domains of HrQoL (Table 13). In the PERSEUS trial (quadruplet with ASCT) with a median follow-up of about 4 years, 45 to 65 % of patients experienced relevant worsening, depending on the HrQoL domain. In the CEPHEUS trial (quadruplet without ASCT), proportions were higher with about 50 to 75 %. Time to event is shorter in CEPHEUS in all domains. However, the differences for HrQoL are not as pronounced as for symptoms (see FAQ 4).

The higher proportions in CEPHEUS might be at least partially attributable to the longer follow-up. On the other hand, also median time to worsening was considerably shorter for some domains in this trial indicating a real difference. It should be noted, as only the data for the more vulnerable transplant-ineligible subgroup are available, it cannot be precluded that the transplant-deferred subgroup would fare much better. Whether the difference in fitness would fully account for the apparent magnitude of difference in effect sizes, cannot be reliably estimated.

Table 13: First relevant worsening of HrQoL

	PERSEUS [15] [a] **Quadruplet + ASCT** **Proportion** **Median time to event**	**CEPHEUS** [14] [b] **Quadruplet only** **Proportion** **Median time to event**
Median follow-up	45 months	53–54 months
Global health status	53 per 100 21 months	62 per 100 2 months
Role functioning	54 per 100 10 months	65 per 100 2 months
Emotional functioning	51 per 100 24 months	54 per 100 9 months
Physical functioning	48 per 100 35 months	65 per 100 3 months
Cognitive functioning	64 per 100 11 months	75 per 100 3 months
Social functioning	65 per 100 5 months	67 per 100 3 months
Future perspective	45 per 100 n.r.	50 per 100 8 months
Body image	54 per 100 14 months	57 per 100 9 months

n.r.: not reached

[a] full sequence, data cut-off 01.08.2023. Global health status and EORTC-QOL-C30 domains: Table 4-93, EORTC-QOL-MY20 domains (future perspective, body image) Table 4-100

[b] transplant-ineligible subgroup, data cut-off 07.05.2024, Table 15

Summary

Due to the limited data and the differences in operationalisation, it is not possible to reliably estimate the impact of upfront or deferred ASCT additionally to quadruplet therapy on the course of HrQoL.

Other than for progression, induction before ASCT with a quadruplet seems to have no clear benefit for delaying worsening of HrQoL in comparison to a triplet induction.

For the comparison of upfront and deferred ASCT (both with a quadruplet), it might be reasonable to assume that the short-term course of the symptoms might be similar as in the comparison of triplet + ASCT and triplet in IFM 2009: Overall, HrQoL increases in a

meaningful way over the course of the treatment. HrQoL might decrease during ASCT but increases quickly afterwards to the level without ASCT.

If a quadruplet with ASCT was more effective in delaying progression in the long-term than a quadruplet without ASCT (see FAQ 3), it would be expected to also delay worsening of HrQoL as indicated by the indirect comparison of PERSEUS and CEPHEUS (full study population). However, there is relevant uncertainty as no data are available on HrQoL for the transplant-deferred subgroup in CEPHEUS.

Overall, adding ASCT to a quadruplet might decrease short-term HrQoL. In the long term, it is unclear if the more intensive therapy delays worsening of HrQoL better than a quadruplet without ASCT. The certainty of the evidence is very low (Table 14).

Table 14: GRADE rating for outcome health-related quality of life

Domain	**Downgrading**	**Certainty**	**Notes**
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	↓		No precise comparison possible due to lack of comparable data
Indirectness	↓		Comparison relies on indirect evidence. It is unclear, if populations are comparable.
Inconsistency	n.a.		Not enough data to assess inconsistency
Publication bias	n.a.		No concern
Overall	↓↓↓	**very low**	

Conclusion for the decision aid

- Both quadruplet + ASCT and quadruplet alone might increase HrQoL in some domains over the course of the treatment. There are, however, also domains for which no relevant change is noted.
- During ASCT, HrQoL might decrease in the short-term, but increase to the previous level quickly afterwards.
- In the long term, it is unclear if the more intensive therapy (quadruplet + ASCT) might delay worsening of HrQoL better.
- The certainty of the evidence is very low.

FAQ 6: What are the short- or long-term risks or side effects?

Due to differences in reporting (see section "Description of the evidence sources"), data on adverse events from CASSIOPEIA and GMMG-HD7 are not discussed in this section.

Data from the other trials are included in this FAQ. However, it should be noted that follow-up for adverse events was restricted in all trials to 30 days after the last dose of study medication.

Data on discontinuation due to adverse events are not reported, as definitions are either not clear or discrepant across trials. Therefore, only common adverse events, serious and severe adverse events as well as severe infections as AE of special interest are detailed in this evidence report.

Most common adverse events

Information on the most common AE (Table 15) has been extracted from the Treatment Guides for the individual medicines by Myeloma UK [21–26] and the patient guideline of the German guideline programme oncology [29]. It should be noted that the information is not exhaustive and is no substitute for the package leaflet.

Infusion reaction (also known as cytokine release syndrome) may happen during or after the infusion and is more likely at the start of the treatment. Symptoms can include feeling short of breath, cough, chills, nausea and (in severe cases) increased blood pressure. As this reaction is related to the mode of action of the medicines, it can also happen when daratumumab is given as an injection, although at a lower frequency.

Low blood counts means that the medicines decrease the number of red blood cells, white blood cells and platelets in the blood. This can cause anaemia (which can cause shortness of breath, tiredness and weakness) and fatigue, as well as increase the risk of infection and the risk of bleeding.

Symptoms of peripheral neuropathy are numbness, tingling and pain often in the hands or feet.

Table 15: Most common side effects [21–26,29]

Medicine	**Most important side effects**
Quadruplet therapy	
Daratumumab	Infusion reaction, peripheral neuropathy, low blood counts, risk of infection, anaemia and bleeding, muscle spasms, diarrhoea, constipation, fatigue, headaches, fluid retention (e.g. peripheral oedema)
Isatuximab	Infusion reaction, low blood counts, increased risk of infection, fever, diarrhoea, nausea, vomiting, reduced appetite or weight loss, dyspnoea, fatigue
Bortezomib	Peripheral neuropathy, blood pressure changes, low blood count, anaemia and bleeding, risk of infection, fatigue, muscle spasms, diarrhoea, constipation, nausea, vomiting, skin rash

Lenalidomide	Peripheral neuropathy, eye problems (blurred vision, cataract, swelling, infections), risk of infection, blood clots, skin rash, diarrhoea, constipation, fatigue, low blood counts, anaemia, bleeding
Dexamethasone	Mood changes, skin changes (stretch marks, thinning), insomnia, muscle weakness, fluid retention (e.g. peripheral oedema), gastric irritation or ulcers, increased appetite, increased blood sugar, risk of infection
Additional ASCT	
Stem cell mobilisation with G-CSF	Pain in the joints or bones, redness of the skin around the injection site, headache, fever, gastrointestinal complaints as feeling sick, loss of appetite or diarrhoea, bruising or bleeding gums, fatigue. If other medicines are used as well (e.g. plerixafor or chemotherapy), additional side effects are possible.
High-dose treatment with melphalan	Nausea, vomiting, appetite loss, altered sense of taste, diarrhoea, low blood counts, anaemia, bleeding, risk of infection, sore mouth and throat, hair thinning or loss

Serious adverse events

Data on serious adverse events are not reported for IFM 2009.

In the other trials, there were consistently higher proportions of serious adverse events with more intensive therapy (Table 16) although it is only known for the PERSEUS trial that differences of proportions are statistically significant. Also, median time to event (although only available for the PERSEUS trial) is numerically shorter with more intensive therapy although not in a statistically significant way.

Cross-trial comparisons of proportions are difficult as median follow-up is either not known or different between trials. It is, however, reasonable to assume that there might be more serious adverse events with quadruplet + ASCT than with quadruplet only. A quantification of the additional toxicity is not possible with the available data.

Table 16: Serious adverse events

	Median follow-up	More intensive therapy Proportion with event Median time to event	Less intensive therapy Proportion with event Median time to event	Effect
Triplet + ASCT vs. triplet only				
DETERMINATION [4] [a]	Not reported	64 per 100 Not reported	49 per 100 Not reported	Not reported
Quadruplet + ASCT vs. triplet + ASCT				
PERSEUS [15] [b] full sequence	47 months (quadruplet + ASCT) and 43 months (triplet + ASCT)	57 per 100 27 months	49 per 100 41 months	HR 1.14 (0.93; 1.40) RR 1.16 (1.00; 1.33)
Quadruplet vs. triplet, both without ASCT				
CEPHEUS [14,17] [c] transplant-deferred subgroup	56 months (quadruplet) and 35 months (triplet)	72 per 100 n.c.	60 per 100 n.c.	n.c.

Effect sizes are reported as point estimate and 95% confidence interval.
ASCT: autologous stem cell transplantation; HR: hazard ratio; n.c.: not calculable, n.r.: not reached
[a] Table S4. Median treatment duration is 36 vs. 28 months in the treatment groups.
[b] Table 4-105, data cut-off 01.08.2023
[c] Own calculations (see Appendix 3), therefore no information about HR and CI available

Severe adverse events

Information on severe adverse events (CTCAE ≥ 3) is available from all trials (Table 17). However, it is not clear for all trials if only Grade 3 and 4 events are included in this operationalisation or also Grade 5 events.

In all trials, there were consistently higher proportions of severe adverse events with more intensive therapy although it is only known for the PERSEUS trial that differences of proportions are statistically significant. Also, median time to event (only available for the PERSEUS trial) is statistically significant shorter with more intensive therapy.

Cross-trial comparisons of proportions are difficult as median follow-up is either not known or different between trials. It is, however, reasonable to assume that there might be more serious adverse events with quadruplet + ASCT than with quadruplet only. A quantification of the additional toxicity is not possible with the available data.

Table 17: Severe adverse events (CTCAE ≥ 3)

	Median follow-up	More intensive therapy Proportion with event Median time to event	Less intensive therapy Proportion with event Median time to event	Effect
Triplet + ASCT vs. triplet only				
IFM 2009 [3] [a]	Not reported	97 per 100 Not reported	83 per 100 Not reported	Not reported
DETERMINATION [4] [b]	Not reported	94 per 100 Not reported	78 per 100 Not reported	Not reported
Quadruplet + ASCT vs. triplet + ASCT				
PERSEUS [15] [c] full sequence	47 months (quadruplet + ASCT) and 43 months (triplet + ASCT)	92 per 100 1 month	86 per 100 5 months	HR 1.36 (1.16; 1.59) RR 1.07 (1.02; 1.13)
Quadruplet vs. triplet, both without ASCT				
CEPHEUS [14,17] [d] transplant-deferred subgroup	56 months (quadruplet) and 35 months (triplet)	91 per 100 n.c.	77 per 100 n.c.	n.c.

Effect sizes are reported as point estimate and 95% confidence interval.
ASCT: autologous stem cell transplantation; HR: hazard ratio; n.a.: not applicable, n.c.: not calculable, n.s.: not significant
[a] Table 3; Grade 3 or 4. Median follow-up for efficacy endpoints is 43 vs. 44 months for the treatment groups. Median treatment duration not reported.
[b] Table 3; Grade 3 or higher. Median treatment duration is 36 vs. 28 months for the treatment groups.
[c] Module 4, Table 4-105
[d] Own calculations (see Appendix 3), therefore no information about median time to event, HR and CI available

Severe infections

Information on severe infections (CTCAE ≥ 3) is available from all trials (Table 18). However, it is not clear for all trials if only Grade 3 and 4 events are included in this operationalisation or also Grade 5 events.

In all trials, there were consistently higher proportions of severe infections with more intensive therapy although it is only known for the PERSEUS trial that differences of

proportions are statistically significant. Median time to event (only available for the PERSEUS trial) is not reached, the corresponding hazard ratio is not statistically significant higher with more intensive therapy.

Cross-trial comparisons of proportions are difficult as median follow-up is either not known or different between trials. It is, however, reasonable to assume that there might be more serious adverse events with quadruplet + ASCT than with quadruplet only. A quantification of the additional toxicity is not possible with the available data.

Table 18: Severe infections (CTCAE ≥ 3)

	Median follow-up	**More intensive therapy** **Proportion with event**	**Less intensive therapy** **Proportion with event**	**Effect**
Triplet + ASCT vs. triplet only				
IFM 2009 [3] [a]	Not reported	20 per 100 Not reported	9 per 100 Not reported	Not reported
DETERMINATION [4] [b]	Not reported	18 per 100 Not reported	10 per 100 Not reported	Not reported
Quadruplet + ASCT vs. triplet + ASCT				
PERSEUS [15] [c] full sequence	47 months (quadruplet + ASCT) and 43 months (triplet + ASCT)	35 per 100 n.r.	28 per 100 n.r.	HR 1.19 (0.91; 1.55) RR 1.26 (1.01; 1.58)
Quadruplet vs. triplet, both without ASCT				
CEPHEUS [14,17] [d] transplant-deferred subgroup	56 months (quadruplet) vs. 35 months (triplet)	42 per 100 n.c.	32 per 100 n.c.	n.c.

Effect sizes are reported as point estimate and 95% confidence interval. Median time to event is either not reported or not reached in all trials.
ASCT: autologous stem cell transplantation; HR: hazard ratio; n.a.: not applicable; n.c.: not calculable; n.s.: not significant; n.r.: not reached
[a] Table 3; Grade 3 or 4
[b] Table 3; Grade 3 or higher
[c] Tab 4-109
[d] Own calculations (see Appendix 3), therefore no information about median time to event, HR and CI available

Severe gastrointestinal disorders

In both the IFM 2009 and the DETERMINATION trial, severe gastrointestinal disorders were more common in the triplet + ASCT group than in the triplet only group: 28 % vs. 7 % in IFM 2009 [3] (Table 3) and 19% vs. 8 % in DETERMINATION [4] (Table 3). Both differences were statistically significant. Differences were especially pronounced for nausea/vomiting and stomatitis as known side effects of high-dose chemotherapy.

Cross-trial comparisons of proportions are difficult as median follow-up is either not known or different between trials. It is, however, reasonable to assume that there might be more serious adverse events with quadruplet + ASCT than with quadruplet only. A quantification of the additional toxicity is not possible with the available data.

Second primary malignancies

It is known that melphalan is genotoxic. Therefore, the risk of second primary malignancies (SPM) might be increased with ASCT [8].

In the IFM 2009 trial with a median follow-up of about 4 years, 8.9 % of patients with ASCT and 7.4 % of patients with triplet therapy only experienced at least one SPM. The frequency of invasive SPM was 6.6 % and 4.9 %, respectively. Second primary haematologic cancers occurred in 1.4 % (ASCT) and 0.3 % (triplet only) (Table S4). The differences were not statistically significant [3].

In the DETERMINATION trial with a follow-up of 76 months, 10.7% of patients with ASCT and 10.4% of patients with triplet therapy only experienced at least one SPM. The frequency of invasive SPM was 6.8 % and 5.3 %, respectively. Second primary haematologic cancers occurred in 3.6 % (ASCT) and 2.5 % of patients (triplet only) (Table S5). The difference, however, was only statistically significant for acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) [4].

In PERSEUS (treatment arm quadruplet + ASCT) with a follow-up of 48 months, any SPM was observed in 10.5 %, haematological SPM in 2.8 % of patients (Table S5). Data on invasive SPM are not reported separately [7].

In CEPHEUS (quadruplet without ASCT, full study population) with a follow-up of 59 months, any SPM occurred in 7.6 % of patients, haematological SPM in 0.5 % of patients (Supplementary Table 5). Data on invasive SPM are not reported separately [17].

Summary

Although cross-trial comparisons are difficult due to differences in reporting and follow-up, it might be reasonable to assume that with quadruplet therapy + ASCT, serious and severe adverse effects, especially severe infections and severe gastrointestinal disorders, as well as secondary leukaemia might be more common than with quadruplet only. The certainty of the evidence, however, is very low (Table 19) and it is not possible to reliably quantify any treatment effects.

Table 19: GRADE rating for outcome adverse events

Domain	Downgrading	Certainty	Notes
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	↓		No precise comparison possible due to lack of comparable data
Indirectness	↓		Comparison relies on indirect evidence. It is unclear, if populations are comparable.
Inconsistency	n.a.		Not enough data to assess inconsistency
Publication bias	n.a.		No concern
Overall	↓↓↓	**very low**	

Conclusion for the decision aid

- Most common adverse events can be described according to Table 15.
- There might be more serious AE, severe AE, severe infections and severe gastrointestinal disorders (especially nausea/vomiting, stomatitis) as well as a higher risk for second primary malignancies with quadruplet + ASCT than with quadruplet only.
- Over 4 to 5 years, about 11 per 100 patients with ASCT experience a second primary malignancy, with quadruplet only about 8 per 100 patients. Second haematological cancers occur in 3 per 100 patients with ASCT and in less than 1 per 100 patients with quadruplet only.
- However, the certainty of the evidence is very low. Differences between more and less intensive therapy cannot be reliably quantified.

FAQ 7: How do I know that the treatment works?

Treatment (supportive therapy and/or myeloma-specific medicines) can improve at least some symptoms. However, side effects can also add to the symptom burden. Therefore, a positive effect of the treatment may not be perceptible for patients or at least not in the short term. This might be especially true for ASCT which is burdensome for patients.

Independent from symptoms, response to treatment is regularly checked by blood and urine tests [2].

FAQ 8: How does the treatment impact my daily life?

During induction, treatment requires visits at the doctor's office once or twice a week. Infusions (required for isatuximab and a certain form of daratumumab) can take up to some

hours in the first cycles, whereas injections (also available for daratumumab) are quicker. Taking medication at home is required on most other days with some breaks within a treatment cycle. During the treatments, there will be regular blood checks. This applies to both treatment options.

ASCT will be even more disruptive to everyday life. For most patients, a hospital stay for several weeks will be required for treatment. Recovery afterwards will take several months up to half a year. If there are severe infections while recovering from ASCT, additional hospital stays may be necessary. Many patients will experience fatigue during recovery. This will most probably interfere with family and professional life.

For both treatments, the risk of infection is increased, but at a higher level with ASCT (during treatment and recovery). Patients should discuss with their doctor vaccinations, if prophylactic medication is required and which other measures they should take to prevent infections. After ASCT, it will be necessary to renew all vaccinations.

HDT/ASCT may affect fertility. Patients should discuss this issue with their doctor if it is relevant for them.

With both treatment options, patients should discuss with their doctor any supplements they wish to take. Especially for bortezomib, there are known interactions with high doses of vitamin C and green tea. Patients should avoid both. They should also discuss with their doctor if drinking alcohol is allowed. There are known interactions with alcohol and bortezomib which might increase adverse effects as dizziness and fatigue [21].

DISCUSSION

SUMMARY OF MAIN FINDINGS

This evidence report aimed to synthesise the evidence for the decision “Quadruplet therapy + ASCT or quadruplet therapy only for newly diagnosed multiple myeloma in transplant-eligible patients?” As there is no direct evidence to answer this question, we resorted to an indirect strategy. As a result, the certainty of the evidence was assessed as very low for all outcomes, and it is not possible to reliably quantify the effects.

- Overall survival: About 34 per 100 patients who choose to forego ASCT as first-line therapy and choose quadruplet therapy only, have died after about five years and 66 per 100 are still alive. It is unclear if the proportion would be lower with quadruplet + ASCT.
- Progression: About 64 per 100 patients who choose to forego ASCT as first-line therapy and choose quadruplet therapy only, are alive without progression after five years. It is not clear whether there is a difference in PFS with or without ASCT. If there would be a difference, there is uncertainty about the magnitude. However, there are some indications that MRD negativity might be higher with ASCT. Whether

this translates to a higher benefit for patients in the long term, cannot be reliably estimated.

- Symptoms: Adding ASCT to a quadruplet might increase short-term symptoms. In the long term, it is unclear if the more intensive therapy delays worsening of some symptoms better than a quadruplet without ASCT.
- HrQoL: Adding ASCT to a quadruplet might decrease short-term HrQoL. In the long term, it is unclear if the more intensive therapy delays worsening of HrQoL better than a quadruplet without ASCT.
- Adverse events: It might be reasonable to assume that with quadruplet therapy + ASCT, serious and severe adverse effects, especially severe infections and severe gastrointestinal disorders, as well as second primary malignancies might be more common than with quadruplet only.

Overall, the main trade-offs for the decision are:

- Indications for better MRD negativity with ASCT, although it is not clear whether this translates to better overall survival or progression-free survival in the long-term.
- Probably more serious and severe adverse events with ASCT and in the short-term a temporary drop in HrQoL and increase of symptoms.

STRENGTH, LIMITATIONS AND UNCERTAINTIES

The strengths of this evidence report are the systematic research for evidence, the thorough discussion of the results and the use of several data sources for the trials, where available. We also included risk of bias assessments from IQWiG reports, wherever possible.

Nevertheless, there are also limitations and uncertainties for the answers to the decision question:

- The main limitation is the lack of direct evidence. Therefore, we resorted to triangulation of the available evidence on quadruplets with or without ASCT, mainly informed by the direct comparisons available for triplet with or without ASCT. We acknowledge, however, that there is not enough information on the comparability of populations across trials. There is additional uncertainty as the trials comparing ASCT/no ASCT on a triplet backbone recruited patients years before the modern trials with quadruplet backbone and the availability of more advanced subsequent therapy might influence overall survival.
- To approximate the target group of this decision aid, we calculated results for the transplant-deferred subgroup of the CEPHEUS trial based on the available data in the journal publication (full study population) and the IQWiG report and AMNOG dossier (transplant-ineligible subgroup). However, this was not possible for the outcomes symptoms and HrQoL due to a lack of data. We therefore included data on the transplant-ineligible subgroup as a surrogate for both of these outcomes. It should

be noted that this is rather a worse-case scenario for which the applicability to the target group of the DA is limited. Besides, the transplant-deferred subgroup comprises only about a quarter of the full study population which might limit the precision of the estimates.

- Although we tried to integrate evidence for different quadruplet options whenever possible, triangulation mostly relied on comparison of the respective treatment arms of the PERSEUS and CEPHEUS trials, both using DaraVRd (with ASCT in PERSEUS, without ASCT in CEPHEUS). As only point estimates and not confidence intervals are available for the comparison of PERSEUS and CEPHEUS results, it is difficult to estimate if the apparent differences are real. As follow-up times differed, the comparison of proportions is difficult. Median time to event, which is less susceptible to different lengths of follow-up, however, was not available for many outcomes (especially overall survival and PFS).
- To overcome this limitation, we included details on MRD negativity as an intermediate surrogate outcome. However, the outcome MRD negativity at any time during the trial suffered from the limitation of different follow-up times in PERSEUS and CEPHEUS. Comparable data were only available for the outcome sustained MRD negativity over 12 months, but not for longer follow-up. Overall, it is not clear how the apparent better sustained MRD negativity translates into patient-relevant outcomes.
- The risk of bias for most trials and outcomes was high.

It should be noted that currently, several other treatment strategies for newly diagnosed multiple myeloma are evaluated. One strategy is MRD-guided therapy (as in the MIDAS trial, see Table 1), i.e. to assess MRD negativity after induction therapy and, depending on the result, proceed to ASCT or not. However, this is not standard of care for the time being.

It is to be expected that the availability of further therapeutic options in the next years will require a re-assessment of the value of ASCT as first-line therapy in multiple myeloma. Current trials are evaluating e.g. CAR-T cell therapy or bispecific antibodies as an alternative to ASCT [8].

REFERENCES

1. Dimopoulos MA, Terpos E, Boccadoro M, et al. EHA–EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma. *Nat Rev Clin Oncol*. 2025;22(9):680-700. doi:10.1038/s41571-025-01041-x

2. Leitlinienprogramm Onkologie: Multiples Myelom. February 2022. Accessed 6. October 2025. https://www.leitlinienprogramm-onkologie.de/leitlinien/multiples-myelom

3. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *New England Journal of Medicine*. 2017;376(14):1311-1320. doi:10.1056/NEJMoa1611750

4. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. *New England Journal of Medicine*. 2022;387(2):132-147. doi:10.1056/NEJMoa2204925

5. Mai EK, Bertsch U, Pozek E, et al. Isatuximab, Lenalidomide, Bortezomib, and Dexamethasone Induction Therapy for Transplant-Eligible Newly Diagnosed Multiple Myeloma: Final Part 1 Analysis of the GMMG-HD7 Trial. *J Clin Oncol*. 2025;43(11):1279-1288. doi:10.1200/JCO-24-02266

6. Moreau P, Hulin C, Perrot A, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab and followed by daratumumab maintenance or observation in transplant-eligible newly diagnosed multiple myeloma: long-term follow-up of the CASSIOPEIA randomised controlled phase 3 trial. *The Lancet Oncology*. 2024;25(8):1003-1014. doi:10.1016/S1470-2045(24)00282-1

7. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *New England Journal of Medicine*. 2024;390(4):301-313. doi:10.1056/NEJMoa2312054

8. Mo CC, Liu Y, Hartley-Brown MA, Nadeem O, Midha S, Richardson PG. SOHO State of the Art Updates and Next Questions | Late/Deferred ASCT in Myeloma. *Clinical Lymphoma, Myeloma and Leukemia*. 2025;25(11):775-787. doi:10.1016/j.clml.2025.06.003

9. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328-e346. doi:10.1016/S1470-2045(16)30206-6

10. Commissioner O of the. Minimal Residual Disease and Complete Response in Multiple Myeloma: Use as Endpoints to Support Accelerated Approval. 20 January 2026. Accessed 9. February 2026. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/minimal-residual-disease-and-complete-response-multiple-myeloma-use-endpoints-support-accelerated

11. Reflection paper on the use of measurable residual disease as a clinical endpoint in multiple myeloma studies - Scientific guideline | European Medicines Agency (EMA). 6 August 2018. Accessed 27. October 2025. https://www.ema.europa.eu/en/reflection-

paper-use-measurable-residual-disease-clinical-endpoint-multiple-myeloma-studies-scientific-guideline

12. The IMF Proudly Announces the Completion of EMA-CHMP"s Qualification Advice to i2TEAMM Novel Biomarker Procedure Application on the Use of MRDnegCR as an Intermediate Early Endpoint for Conditional Market Approval in Myeloma Clinical Trials. International Myeloma Foundation. Accessed 7. January 2026. https://www.myeloma.org/news-events/multiple-myeloma-news/imf-proudly-announces-ema-chmp-positive-qualification-advice-i2teamm-novel-biomarker-procedure

13. Perrot A, Lambert J, Hulin C, et al. Measurable Residual Disease–Guided Therapy in Newly Diagnosed Myeloma. *New England Journal of Medicine*. 2025;393(5):425-437. doi:10.1056/NEJMoa2505133

14. [A25-108] Daratumumab (neu diagnostiziertes multiples Myelom, Stammzelltransplantation nicht geeignet) – Nutzenbewertung gemäß § 35a SGB V. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). doi:10.60584/A25-108

15. AMNOG dossier DaraVRd (transplant-eligible). Accessed 8. January 2026. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1154/#dossier

16. AMNOG dossier DaraVRd (transplant-ineligible or transplant-deferred). Accessed 8. January 2026. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1222/#dossier

17. Usmani SZ, Facon T, Hungria V, et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. *Nat Med*. 2025;31(4):1195-1202. doi:10.1038/s41591-024-03485-7

18. Roussel M, Hebraud B, Hulin C, et al. Health-related quality of life results from the IFM 2009 trial: treatment with lenalidomide, bortezomib, and dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma. *Leukemia & Lymphoma*. 2020;61(6):1323-1333. doi:10.1080/10428194.2020.1719091

19. *Assessment Report Sarclisa, Procedure No. EMEA/H/C/004977/II/0035*. European Medicines Agency; 2025. https://www.ema.europa.eu/en/documents/variation-report/sarclisa-h-c-004977-ii-0035-epar-assessment-report-variation_en.pdf

20. Perrot A, Lauwers-Cances V, Cazaubiel T, et al. Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the IFM 2009 Trial. *Blood*. 2020;136:39. doi:10.1182/blood-2020-134538

21. Bortezomib (Velcade®) Treatment Guide. Myeloma UK. November 2024. Accessed 1. October 2025. https://www.myeloma.org.uk/library/bortezomib-velcade-treatment-guide/

22. Daratumumab (Darzalex®) Treatment Guide. Myeloma UK. November 2024. Accessed 1. October 2025. https://www.myeloma.org.uk/library/daratumumab-darzalex-treatment-guide/

23. Dexamethasone Treatment Guide. Myeloma UK. October 2024. Accessed 1. October 2025. https://www.myeloma.org.uk/library/dexamethasone-treatment-guide/

24. High-dose therapy and autologous stem cell transplant Infoguide. Myeloma UK. Accessed 12. November 2025. https://www.myeloma.org.uk/library/high-dose-therapy-and-autologous-stem-cell-transplant-infoguide/

25. Isatuximab (Sarclisa®) Treatment Guide. Myeloma UK. October 2022. Accessed 1. October 2025. https://www.myeloma.org.uk/library/isatuximab-treatment-guide/

26. Lenalidomide (Revlimid®) Treatment Guide. Myeloma UK. November 2024. Accessed 1. October 2025. https://www.myeloma.org.uk/library/lenalidomide-revlimid-treatment-guide/

27. Supportive care treatments. Myeloma UK. Accessed 1. October 2025. https://www.myeloma.org.uk/understanding-myeloma/treating-myeloma/supportive-care-treatments/

28. Treating myeloma. Myeloma UK. Accessed 1. October 2025. https://www.myeloma.org.uk/understanding-myeloma/treating-myeloma/

29. Patientenleitlinie Multiples Myelom. Leitlinien-Programm Onkologie. November 2022. Accessed 3. September 2025. https://www.leitlinienprogramm-onkologie.de/patientenleitlinien/multiples-myelom

30. *Assessment Report Darzalex, Procedure No. EMEA/H/C/004077/II/0076*. European Medicines Agency; 2025. https://www.ema.europa.eu/en/documents/variation-report/darzalex-h-c-004077-ii-0076-epar-assessment-report-variation_en.pdf

31. [A20-50] Daratumumab (neu diagnostiziertes multiples Myelom, Stammzelltransplantation geeignet) - Addendum zum Auftrag A20-15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Accessed 8. January 2026. https://www.iqwig.de/projekte/a20-50.html

32. [A24-114] Daratumumab (neu diagnostiziertes multiples Myelom, autologe Stammzelltransplantation geeignet) – Nutzenbewertung gemäß § 35a SGB V. Accessed 8. January 2026. https://www.iqwig.de/projekte/a24-114.html

33. Cyclophosphamide Treatment Guide. Myeloma UK. August 2022. Accessed 1. October 2025. https://www.myeloma.org.uk/library/cyclophosphamide-treatment-guide/

34. Prednisolone Treatment Guide. Myeloma UK. October 2024. Accessed 1. October 2025. https://www.myeloma.org.uk/library/prednisolone-treatment-guide/

35. Melphalan Treatment Guide. Myeloma UK. August 2024. Accessed 1. October 2025. https://www.myeloma.org.uk/library/melphalan-treatment-guide/

36. High-dose therapy and autologous stem cell transplant Infoguide. Myeloma UK. Accessed 24. October 2025. https://www.myeloma.org.uk/library/high-dose-therapy-and-autologous-stem-cell-transplant-infoguide/

37. International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. International Myeloma Foundation. Accessed 24. September 2025. https://www.myeloma.org/resource-library/international-myeloma-working-group-imwg-uniform-response-criteria-multiple

APPENDIX 1: SEARCH AND RETRIEVAL OF THE EVIDENCE

Guidelines

Search strategy

Source	Search date	Search term	Filters or exclusion criteria	Retrieval
GIN International Guidelines Library https://guidelines.ebmportal.com/	24.10.2025	myeloma	Filters: 2020-2025; status: published	3
Website International Myeloma Working Group (IMWG) https://www.myeloma.org/imwg-publications	24.10.2025	n.a. (hand-searching)	Excluded: Guidelines for relapsed/refractory multiple myeloma only	0
Website European Society For Medical Oncology (ESMO) https://www.esmo.org/guidelines/esmo-clinical-practice-guidelines-haematological-malignancies	24.10.2025	n.a. (hand-searching)	Excluded: Guidelines for relapsed/refractory multiple myeloma only	1
Website European Hematology Association (EHA) https://ehaweb.org/clinical-practice/guidelines-by-areas-of-disease	24.10.2025	n.a. (hand-searching)	Excluded: Guidelines for relapsed/refractory multiple myeloma only	1

Full text screening

Publisher (Year)	Link	Suitable for data extraction? [a]	Decision
Society for Immunotherapy of Cancer (2020)	https://jitc.bmj.com/content/8/2/e000734	No: No detailed data to inform the FAQs	Excluded
ASTRO/ASCO (2020)	The Treatment of Metastatic Carcinoma and Myeloma of the Femur: Clinical Practice Guideline no longer online available	No	Excluded
ESMO (2021)	https://www.annalsofoncology.org/article/S0923-7534(20)43169-2/fulltext	No: Probably no systematic search, no detailed data to inform the FAQs.	Excluded
AWMF/OL (2022)	https://www.leitlinienprogramm-onkologie.de/leitlinien/multiples-myelom	No: Systematic search, but too old (2018).	Excluded
EHA-EMN (2025)	https://www.nature.com/articles/s41571-025-01041-x	No: Unclear if a systematic search has been conducted. No detailed data to inform the FAQs.	Excluded

HTA reports

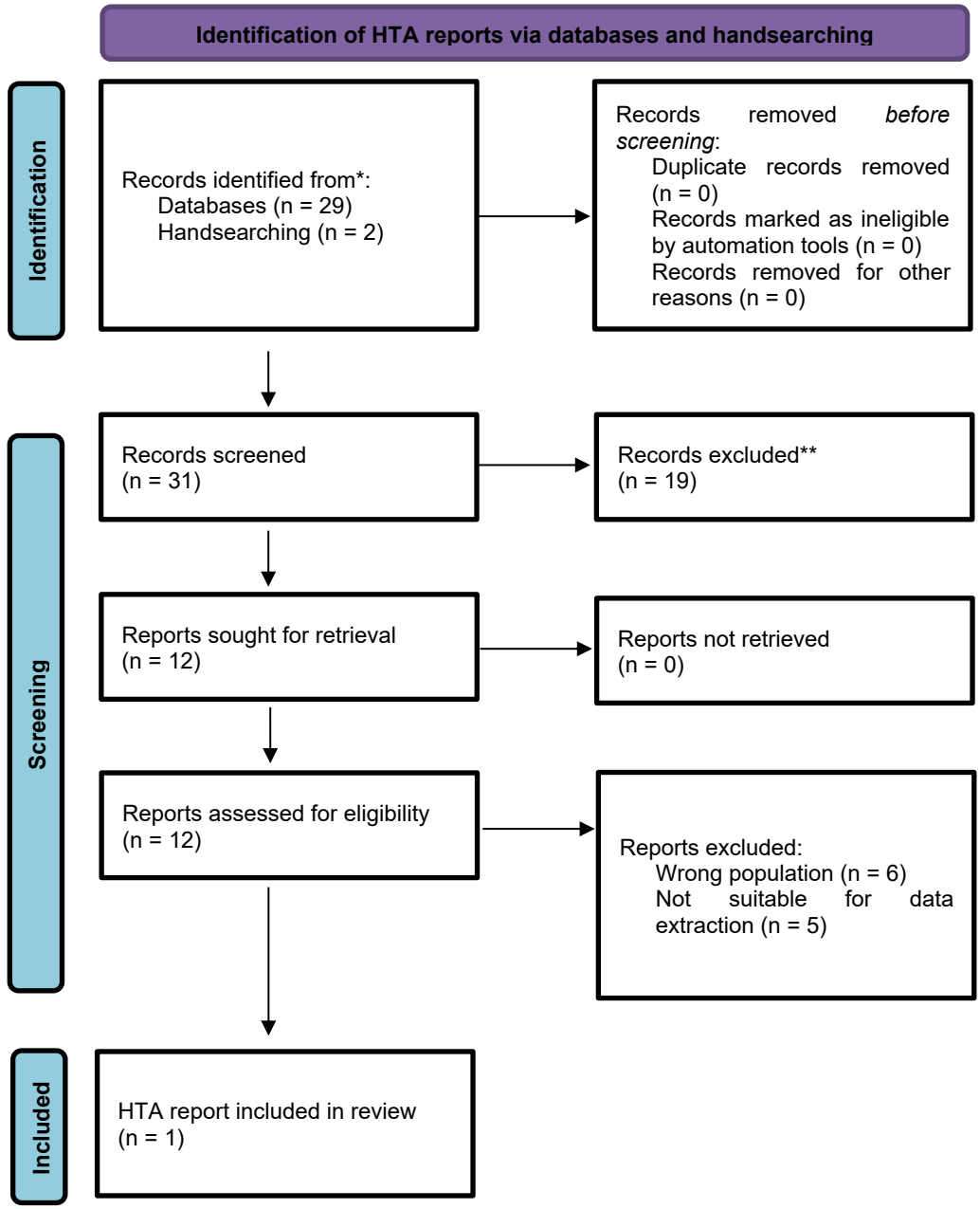
Search strategy

Source	Search date	Search term	Filters or exclusion criteria	Retrieval
INAHTA database https://database.inahta.org/	27.10.2025	myeloma AND (daratumumab OR isatuximab)	2020-2025	29 hits
IQWiG website https://iqwig.de/projekte/projekte-und-ergebnisse	17.11.2025	Handsearching	Newer HTA reports on daratumumab or isatuximab not yet in the INAHTA database	2 hits: IsaVRd, DaraVRd

Full-text screening

Publisher (year)	Link	Suitable for PICO?	Suitable for data extraction?	Decision
NICE (2022)	https://www.nice.org.uk/guidance/ta763	Yes (DaraVTd)	No, heavily redacted	Excluded
ACE (2022)	https://www.ace-hta.gov.sg/healthcare-professionals/ace-technology-guidances/drug-guidance/daratumumab-based-regimens-for-newly-diagnosed-multiple-myeloma/	No (mixed populations)	n.a.	Excluded
IQWiG (2025)	https://www.iqwig.de/download/a25-108_daratumumab_nutzenbewertung-35a-sgb-v_v1-0.pdf	Yes (DaraVRd, transplant-deferred subpopulation)	Suitable for calculation of transplant-deferred subpopulation together with trial publication	Included
IQWiG (2025)	https://www.iqwig.de/download/a25-105_isatuximab_nutzenbewertung-35a-sgb-v_v1-0.pdf	Yes (IsaVRd)	IQWiG report and AMNOG dossier do not contain trial data for data extraction.	Excluded
IQWiG (2025)	https://www.iqwig.de/download/a25-20_isatuximab_nutzenbewertung-35a-sgb-v_v1-1.pdf	No (Tx not suitable, wrong population)	n.a.	Excluded
IQWiG (2024)	https://www.iqwig.de/download/a24-114_daratumumab_nutzenbewertung-35a-sgb-v_v-0.pdf	Yes (DaraVRd)	IQWiG report does not contain trial data because no appropriate comparator therapy was used; only suitable for risk of bias	AMNOG dossier included for data extraction; IQWiG

			assessment. AMNOG dossier suitable for data extraction	dossier only for risk of bias assessment
IQWiG (2023)	https://www.iqwig.de/download/a23-127_daratumumab_nutzenbewertung-35a-sgb-v_v1-0.pdf	No (Tx not suitable, wrong population)	n.a.	Excluded
IQWiG (2022)	https://www.iqwig.de/download/a22-40_daratumumab_nutzenbewertung-35a-sgb-v_v1-0.pdf	No (relapsed myeloma, wrong population)	n.a.	Excluded
IQWiG (2021)	https://www.iqwig.de/download/a21-101_daratumumab_nutzenbewertung-35a-sgb-v_v1-0.pdf	No (relapsed myeloma, wrong population)	n.a	Excluded
IQWiG (2021)	https://www.iqwig.de/download/a21-170_daratumumab_addendum-zum-auftrag-a21-101_v1-0.pdf	No (relapsed myeloma, wrong population)	n.a.	Excluded
IQWiG (2020)	https://www.iqwig.de/download/a20-15_daratumumab_nutzenbewertung-35a-sgb-v_v1-0.pdf	Yes (DaraVTd)	No, report does not contain trial data because, according to IQWiG, no appropriate comparator therapy was used	Excluded
IQWiG (2020)	https://www.iqwig.de/download/a20-50_daratumumab_addendum-zum-auftrag-a20-15_v1-0.pdf	Yes (DaraVTd)	Yes, but newer data cut-off available in journal publication	Excluded



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

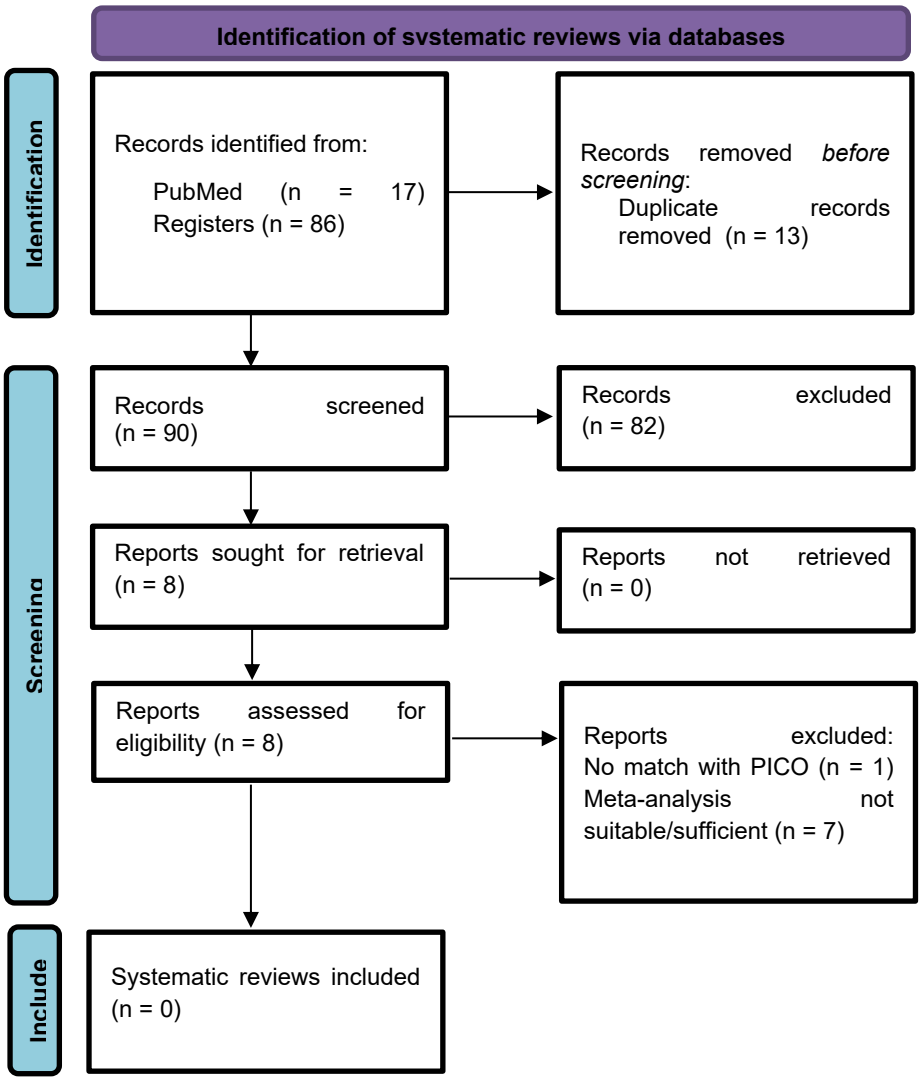
Systematic Reviews

Search strategy

Source (date)	Search term	Filters	Retrieval
Epistemonikos (28.10.2025)	(title:(myelom* OR myelomatos* OR plasm*cytom* OR "plasma cytoma*" OR (("plasma" OR "plasma cell" OR "plasma cells" OR plasma-cell*) AND (neoplasm* OR leukaem* OR leukem* OR tumor* OR tumour*))) OR abstract:(myelom* OR myelomatos* OR plasm*cytom* OR "plasma cytoma*" OR (("plasma" OR "plasma cell" OR "plasma cells" OR plasma-cell*) AND (neoplasm* OR leukaem* OR leukem* OR tumor* OR tumour*)))) AND (title:(daratumumab* OR darzalex* OR isatuximab* OR sarclisa OR CD38 OR anti-CD38 OR "CD 38" OR quadruple* OR triple* OR (lenalidomide* AND bortezomib*)) OR abstract:(daratumumab* OR darzalex* OR isatuximab* OR sarclisa OR CD38 OR anti-CD38 OR "CD 38" OR quadruple* OR triple* OR (lenalidomide* AND bortezomib*))) AND (title:(transplant* OR HSCT OR ASCT) OR abstract:(transplant* OR HSCT OR ASCT)) NOT title:(relapse* OR refract* OR ineligible OR transplant-ineligible)	Publication year: 2020-2025 Publication type: Systematic review	86 hits
PubMed (28.10.2025)	#1: "multiple myeloma"[MeSH Terms] OR "plasmacytoma"[MeSH Terms] #2: "myelom*"[Title/Abstract] OR "myelomatos*"[Title/Abstract] OR "plasm*cytom*"[Title/Abstract] OR "plasma cytoma*"[Title/Abstract] OR (("plasma"[Title/Abstract] OR "plasma cell"[Title/Abstract] OR "plasma cells"[Title/Abstract] OR "plasma cell*"[Title/Abstract]) AND ("neoplasm*"[Title/Abstract] OR "leukaem*"[Title/Abstract] OR "leukem*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract])) #3: "relapse*"[Title] OR "refract*"[Title] OR "ineligible"[Title] OR "transplant-ineligible"[Title] #4: (#1 OR #2) NOT #3 #5: "daratumumab*"[Title/Abstract] OR "darzalex*"[Title/Abstract] OR "isatuximab*"[Title/Abstract] OR "sarclisa"[Title/Abstract] OR "CD38"[Title/Abstract] OR "anti-CD38"[Title/Abstract] OR "CD 38"[Title/Abstract] OR "quadruple*"[Title/Abstract] OR "triple*"[Title/Abstract] OR ("lenalidomide*"[Title/Abstract] AND "bortezomib*"[Title/Abstract]) #6: "transplant*"[Title/Abstract] OR "HSCT"[Title/Abstract] OR "ASCT"[Title/Abstract] #7: #4 AND #5 AND #6	20202025; Systematic Review-2025; Systematic Review	17 hits

Full-text screening

Reference	Agreement with PICO/ Included trials	Decision
Zhou 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC12106411/	Quadruplet; high cytogenetic risk only	Excluded because of insufficient agreement for population
Filho 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC11906644/	Quadruplets, only daratumumab trials: GRIFFIN (not relevant[a]), CASSIOPEIA, PERSEUS; also, non-randomised study included in meta-analysis	Excluded because of inclusion of non-relevant data in the meta-analysis
Martins 2025 https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(25)00159-4/fulltext	Quadruplets, only daratumumab trials: GRIFFIN (not relevant[a]), CASSIOPEIA, PERSEUS; non-randomized studies included but reported separately	Excluded because of inclusion of non-relevant data in the meta-analysis
Channar 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC11965703/	Quadruplets, trials with daratumumab and isatuximab: CASSIOPEIA, GRIFFIN (not relevant[a]), PERSEUS, GMMG-HD7, ISKIA (not relevant[b])	Excluded because of inclusion of non-relevant data in the meta-analysis
Osama 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC11770704	Quadruplets, trials with daratumumab and isatuximab: CASSIOPEIA, GRIFFIN (not relevant[a]), PERSEUS, GMMG-HD7, ISKIA (not relevant[b])	Excluded because of inclusion of non-relevant data in the meta-analysis
Ebraheem 2024 https://pmc.ncbi.nlm.nih.gov/articles/PMC11629212/	Quadruplets, meta-analysis pools trials with transplant-eligible and non-eligible populations	Excluded because of inclusion of non-relevant data in the meta-analysis
Chong 2021 https://www.sciencedirect.com/science/article/pii/S1040842820303474	Quadruplets, only includes CASSIOPEIA and GRIFFIN (not relevant[a])	Excluded because of too little data and non-relevant data in the meta-analysis
Amitai 2025 https://karger.com/aha/article-abstract/148/4/468/913310/Role-of-Autologous-Transplant-in-Newly-Diagnosed	Triplet vs triplet plus ASCT: includes IFM 2009, DETERMINATION, FORTE (not relevant[c])	Excluded because of inclusion of non-relevant data in the meta-analysis
[a]GRIFFIN: phase 2 trial; different dosage than in the marketing authorisation. [b]ISKIA: IsaKRd. [c]FORTE: KRd		



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

RCTs

Search strategy

Source (date)	Search term	Filters	Retrieval
PubMed 29.10.2025	#1: "multiple myeloma"[MeSH Terms] OR "plasmacytoma"[MeSH Terms] #2: "myelom*"[Title/Abstract] OR "myelomatos*"[Title/Abstract] OR "plasm*cytom*"[Title/Abstract] OR "plasma cytoma*"[Title/Abstract] OR (("plasma"[Title/Abstract] OR "plasma cell"[Title/Abstract] OR "plasma cells"[Title/Abstract] OR "plasma cell*"[Title/Abstract]) AND ("neoplasm*"[Title/Abstract] OR "leukaem*"[Title/Abstract] OR "leukem*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract])) #3: "relapse*"[Title] OR "refract*"[Title] OR "ineligible"[Title] OR "transplant-ineligible"[Title] #4: (#1 OR #2) NOT #3 #5: "daratumumab*"[Title/Abstract] OR "darzalex*"[Title/Abstract] OR "isatuximab*"[Title/Abstract] OR "sarclisa"[Title/Abstract] OR "CD38"[Title/Abstract] OR "anti-CD38"[Title/Abstract] OR "CD 38"[Title/Abstract] OR "quadruple*"[Title/Abstract] OR "triple*"[Title/Abstract] OR ("lenalidomide*"[Title/Abstract] AND "bortezomib*"[Title/Abstract]) #6: "transplant*"[Title/Abstract] OR "HSCT"[Title/Abstract] OR "ASCT"[Title/Abstract] #7: "randomized controlled trial"[Publication Type] OR "random*"[Title/Abstract] #8: #4 AND #5 AND #6 AND #7 #9: "carfilzomib*"[Title/Abstract] OR "elotuzumab*"[Title/Abstract] OR "ixazomib*"[Title/Abstract] OR "amyloidosis"[Title/Abstract] OR "cilta-cel"[Title/Abstract] OR "ide-cel"[Title/Abstract] OR "selinexor"[Title/Abstract] OR "auriga"[Title/Abstract] OR "teclistamab"[Title/Abstract] OR "vorinostat"[Title/Abstract] OR "belantamab"[Title/Abstract] OR "pomalidomide"[Title/Abstract] #10: #8 NOT #9 #11: "systematic review"[Publication Type] OR "review"[Publication Type] #12: #10 NOT #11	n.a.	93

CENTRAL 29.10.2025	#1: MeSH descriptor: [Multiple Myeloma] explode all trees #2: MeSH descriptor: [Plasmacytoma] explode all trees #3: (myelom* OR myelomatos* OR plasm*cytom*):ti,ab #4: (plasma NEXT cytoma*):ti,ab #5: ((“plasma” OR “plasma cell” OR “plasma cells” OR plasma-cell*) AND (neoplasm* OR leukaem* OR leukem* OR tumor* OR tumour*)):ti,ab #6: #1 OR #2 OR #3 OR #4 OR #5 #7: (relapse* OR refract* OR ineligible OR transplant-ineligible):ti #8: #6 NOT #7 #9: (daratumumab* OR darzalex* OR isatuximab* OR sarclisa OR CD38 OR anti-CD38 OR “CD 38” OR quadruple* OR triple* OR (lenalidomide* AND bortezomib*)):ti,ab #10: (transplant* OR HSCT OR ASCT):ti,ab #11: #8 AND #9 AND #10 #12: (carfilzomib* OR elotuzumab* OR ixazomib* OR amyloidosis OR melphalan* OR cilta-cel OR ide-cel OR selinexor OR auriga OR teclistamab OR vorinostat OR belantamab OR pomalidomide):ti,ab #13: #11 NOT #12 #14: (conference or trial):pt #15: #13 NOT #14	Embase	55

Full-text screening

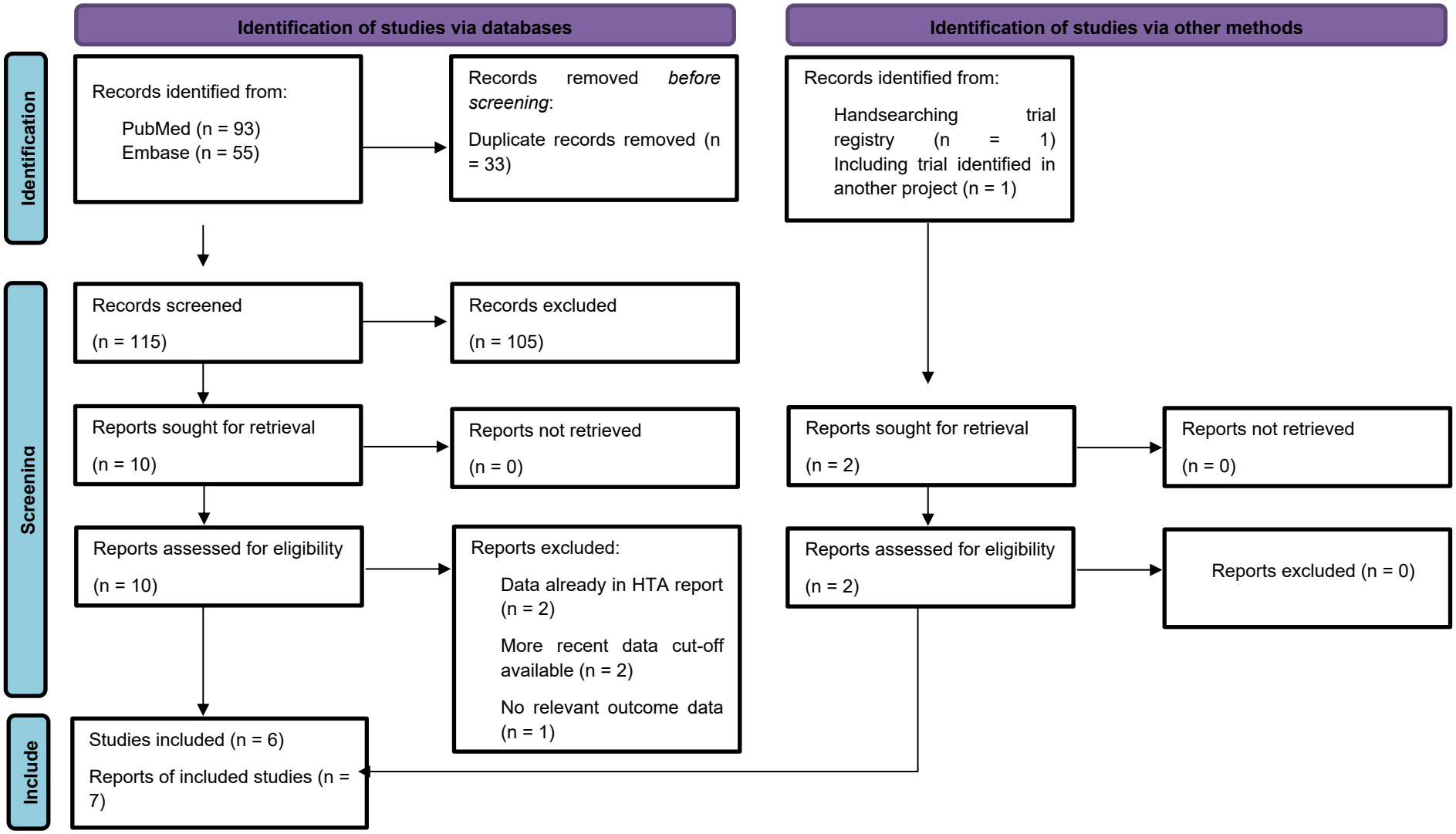
Reference	Agreement with PICO (Trial, data cut-off or follow-up)	Decision
Moreau 2024 https://pmc.ncbi.nlm.nih.gov/articles/PMC12375812/	DaraVTd + ASCT vs VTd + ASCT (CASSIOPEIA, final analysis, 01.09.2023)	Included
Corre 2025 https://www.sciencedirect.com/science/article/pii/S0006497125007189	DaraVTd + ASCT vs VTd + ASCT (CASSIOPEIA, 01.09.2023) MRD, PFS	Excluded, no relevant outcomes
Moreau 2021 https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00428-9/fulltext	DaraVTd + ASCT vs VTd + ASCT (CASSIOPEIA, part 2, follow-up 35.4 months from second randomization)	Excluded, more recent data cut-off available
Roussel 2020 https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(20)30356-2/fulltext	DaraVTd + ASCT vs VTd + ASCT (CASSIOPEIA, part 1, follow-up 18.8 months) HrQoL data	Excluded, data available in IQWiG report/AMNOG dossier
Moreau 2019 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31240-1/fulltext	DaraVTd + ASCT vs VTd + ASCT (CASSIOPEIA, part 1, 19.06.2018)	Excluded, data available in IQWiG report/AMNOG dossier
Sonneveld 2024 https://www.nejm.org/doi/10.1056/NEJMoa2312054	DaraVRd + ASCT vs VRd + ASCT PERSEUS, 01.08.2023	Included
Mai 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC11974620/	IsaVRd + ASCT vs VRd + ASCT (GMMG-HD7, 31.01.2024)	Included
Goldschmidt 2022 https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(22)00263-0/fulltext	IsaVRd + ASCT vs VRd + ASCT (GMMG-HD7, 04.11.2021)	Excluded, more recent data cut-off available
Richardson 2022 https://pmc.ncbi.nlm.nih.gov/articles/PMC10040899/	VRd + ASCT vs VRd DETERMINATION data cut-off 10.12.2021	Included
Attal 2017 https://pmc.ncbi.nlm.nih.gov/articles/PMC6201242/	VRd + ASCT vs VRd IFM 2009, Data cut-off 01.09.2015	Included

Check of study registry entries

Trial	Results in registry	Additional relevant publications in registry (handsearching)
CASSIOPEIA NCT02541383	Corresponding to Moreau 2024	none
PERSEUS NCT03710603	Corresponding Sonneveld 2024	none
GMMG-HD7 NCT03617731	No results posted	none
DETERMINATION NCT01208662	Corresponding to Richardson 2022	none
IFM 2009 NCT01191060	No results posted	Roussel 2020 https://www.tandfonline.com/doi/10.1080/10428194.2020.1719091 (HrQoL) relevant, included

Handsearching

CEPHEUS NCT03652064 included for the calculation of results for the transplant-deferred population Usmani 2025 https://www.nature.com/articles/s41591-024-03485-7



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

APPENDIX 2: RISK OF BIAS ASSESSMENT

Trial	Overall survival	Progression	Symptoms, HrQoL	Adverse events
CASSIOPEIA	High [a]	High [a]	High [b]	High [b]
PERSEUS	Low	Low [e]	High [b]	High [b]
GMMG-HD7	Low	High [f]	High [b]	High [b]
CEPHEUS	High [14] [d]	Low [e]	High [14] [b,c]	High [14] [b,c]
DETERMINATION	High [d]	High [f]	High [b]	High [b]
IFM 2009	High [c]	High [f]	High [b]	High [b]

HrQoL: Health-related quality of life

[a] inadequate maintenance therapy

[b] open-label trial

[c] incomplete outcome data

[d] inadequate second-line therapy

[e] Progression assessed via validated computer algorithm

[f] Progression assessed by investigators aware of the group assignment

The IQWiG report for CASSIOPEIA [31] contains no formal risk of bias assessment. Ratings were, however, derived from aspects discussed in the IQWiG report.

APPENDIX 3: CALCULATIONS FOR CEPHEUS TRANSPLANT-DEFERRED SUBGROUP

	Full study population				Transplant-ineligible				Transplant-deferred					
	Quadruplet		Triplet		Quadruplet		Triplet		Quadruplet			Triplet		
Outcome	**Events**	**n**	**Events**	**n**	**Events**	**n**	**Events**	**n**	**Events**	**n**	**per 100**	**Events**	**n**	**per 100**
Overall mortality [a]	51	197	60	195	33	144	47	145	18	53	34	13	50	26
Overall mortality without COVID deaths [aa]	36	197	51	195	26	144	44	145	10	53	19	7	50	14
PFS [b]	63	197	91	195	44	144	69	145	19	53	36	22	50	44
Serious AE [c]	142	197	131	195	104	144	99	142	38	53	72	32	53	60
Severe AE (CTCAE ≥ 3) [d]	182	197	167	195	134	144	126	142	48	53	91	41	53	77
Severe neuropathy (CTCAE ≥ 3) [e]	n.r.	197	n.r.	195	18	144	16	142	4	53	8	5	53	9
Severe infections (CTCAE ≥ 3) [f]	79	197	62	195	57	144	45	142	22	53	42	17	53	32
MRD negativity (10^{-5}) any time [g]	120	197	77	195	87	144	57	145	33	53	62	20	53	37
Sustained MRD negativity (10^{-5}) at12 months [h]	96	197	51	195	67	144	40	145	29	53	55	11	53	21

FSP: full study population; MRD: minimal residual disease n.r.: not reported, TIE: transplant-ineligible

[a] TIE: [14] Table 15

[aa] FSP: [17], TIE [16] Table 4-24

[b] TIE: [16] Table 4-36

[c] FSP: [17] Extended Table 4; TIE: [14] Table 15

[d] FSP: [30] Table 21; TIE: [14] Table 15

[e] [30] Table 30 (separately for transplant-ineligible and transplant-deferred)

[f] FSP [17] Table 2 Infection; TIE: AMNOG Table 4-88 full system organ class

[g] FSP [17]: DaraVRd 60,9%, VRd 39,4%; TIE: [16] Table 4-27

[h] FSP [17]: DaraVRd 48,7%, VRd 26,3%; TIE: [16] Table 4-30

Data for the transplant-deferred subgroup (TD) have been calculated as the difference between the full study population and the transplant-ineligible subgroup. For some outcomes, the EMA report [30] supplied data for FSP, TIE and/or TD. For the other outcomes, no data are reported which allow calculations for the transplant-deferred subgroup.