Evidence report

Multiple myeloma (newly diagnosed, ASCT not suitable)

Intensive or less intensive therapy?

Version 1

SHARE TO CARE
Gemeinsam entscheiden.

SHARE TO CARE. Patientenzentrierte Versorgung GmbH

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LIST OF ABBREVIATIONS

AMNOG: Pharmaceuticals Market Reorganisation Act
ASCT: autologous stem cell transplantation
C: Cyclophosphamide
CI: confidence interval
d: Dexamethasone
DA: Decision aid
Dara: Daratumumab
EORTC: European Organisation for Research and Treatment of Cancer, European Organisation for Research and Treatment of Cancer
EQ-5D-3L: EuroQol Five Dimension Three Level Questionnaire
EQ-5D-5L: EuroQol Five Dimension Five Level Questionnaire
FAQs: Frequently asked questions
FS: Frailty score
HR: Hazard ratio
HrQoL: Health-related quality of life
IMWG: International Myeloma Working Group
IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Institute for Quality and Efficiency in Health Care
Isa: Isatuximab
M: Melphalan
MM: Multiple myeloma
OIS: Optimal information size
P: Prednisone
PFS: Progression-free survival
PICOS: Participants, intervention, comparators, outcomes, and study design
QLQ: Quality of Life Questionnaire, Quality of Life Questionnaire
R: Lenalidomide
RD: Risk difference
RR: Risk ratio
SDM: Shared decision making
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 an autologous stem cell transplantation (ASCT) is not considered suitable. The report relies on teamwork with clinical experts from two German university medical centres and patients from a patient organization.

INFORMATION ON 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 number of healthy cells in the bone marrow decreases. 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 decompression, 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

When ASCT is not suitable, options for the first-line treatment of multiple myeloma are either more intensive options (a quadruplet containing a CD38 antibody) or less intensive options (triplets or a doublet). More intensive options have the chance for more benefit, but also the risk of more harm. At the same time, there is some uncertainty for both benefit and harm.

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 not considered a suitable treatment option for them. This is mainly the case if patients are above a certain age and/or comorbidities are present. The exact age cut-off, however, is a matter of clinical debate. Many trials only include patients which 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 ASCT is considered medically suitable, but who decline this treatment option, are not the target group of this DA. For them, a separate DA is planned.

The inclusion and exclusion criteria, according to PICOS, are described in Table 1.

Table 1: Inclusion criteria

	Included	**Excluded**
Population	Patients with newly diagnosed multiple myeloma for whom stem cell transplantation (ASCT) is not suitable	Relapsed/refractory multiple myeloma; patients for whom ASCT is suitable; very frail patients; 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: mainly DaraVRd, IsaVRd, in special situations DaraVMP, DaraVCd	Other combinations
Comparator	Less intensive therapy: DaraRd, DaraR, VRd	Other combinations
Outcomes	Overall survival, symptoms, progression, quality of life, adverse events	Other outcomes
Study design	Stepwise approach: Guidelines, systematic reviews, randomised controlled trials	Other study designs
n.a.= not applicable. ASCT: autologous stem cell transplantation; Dara: daratumumab; Isa: isatuximab; V: bortezomib; R: lenalidomide; d: dexamethasone; M: mephalane; P: prednisone; C: cyclophosphamide.		

The decision aid is not intended to guide the decision between the different options of intensive therapy and less intensive therapy, respectively. This decision is usually based on patients' characteristics as age, frailty or co-morbidities at the clinician's discretion.

Frequently asked questions

The frequently asked questions (FAQs) underpinning the literature searches were developed in collaboration with the patients and clinical experts. 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 2021 to 2025.

- 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 (including 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, we additionally searched for recent publications of randomised controlled trials.
- When journal publications of a trial did not provide enough details, we additionally checked trial registry entries for results.
- We completed the systematic searches by handsearching where 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 (RoB) 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 both IQWiG reports. We adopted the risk of bias assessment of these reports for the included trials.

Certainty of the identified evidence is presented using the GRADE approach which assesses risk of bias, publication bias, imprecision, inconsistency, indirectness, magnitude of effect, dose response gradient and the effects of any confounding according to the assessment criteria published by the GRADE working group [7].

The certainty of 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

Details of the search strategy and the retrieval are described in Appendix 1. The search for guidelines did not identify suitable evidence syntheses to inform the FAQs. We included three HTA reports [8–10] and three AMNOG dossiers [11–13]. As journal publications for the MAIA trial [14,15] included more recent data cut-offs than the corresponding AMNOG dossier, we included the relevant IQWiG report [16] only for the risk of bias assessments.

As a new relevant report by the Institute for Quality and Efficiency in Health Care (IQWiG) and an AMNOG dossier became available on 17 November 2025, between conducting the systematic searches and finalising the decision aid, we added these references manually to the reference pool [10,12].

We also included nine journal publications for eight clinical trials [14,15,17–23]. One of the journal publications was identified by handsearching as it had been published after the systematic searches in which we found the preprint of the respective trial.

For the description of the treatments, we included information from Myeloma UK [24–31] and from the patient guideline of the German programme for oncological guidelines [2].

Risk of bias assessment

Results of the assessments can be found in Appendix 2. For most outcomes and comparisons, the risk of bias was assessed as high.

Overview of the evidence

This report aims to discuss the evidence for the comparison of intensive (DaraVRd, IsaVRd; in special situations DaraVMP, DaraVCd) or less intensive therapy (DaraRd, DaraR, VRd) for the treatment of newly diagnosed multiple myeloma in patients for which ASCT is not suitable. However, direct evidence is only available for few of the relevant comparisons (Figure 1).

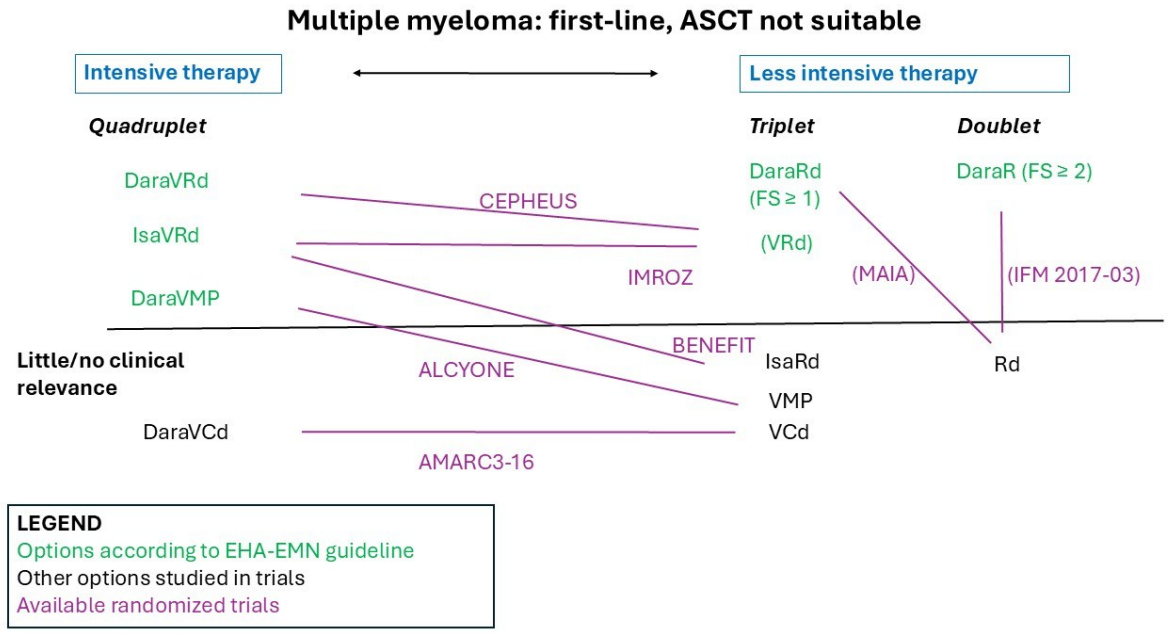

Figure 1: Available evidence

RCTs comparing quadruplets with a CD38 antibody and a triplet without a CD38 antibody are available for DaraVMP vs. VMP (ALCYONE and OCTANS), DaraVRd vs. VRd (CEPHEUS), IsaVRd vs. VRd (IMROZ) and DaraVCd vs. VCd (AMaRC3-16).

However, only VRd is mentioned as a triplet treatment option without CD38 antibody in the current European guideline [4]. Additionally, as the trials comparing the quadruplets to VRd are still ongoing, the most mature data for the added benefit for the CD38 antibody to a triplet without CD38 antibody comes to date from the trials comparing DaraVMP to VMP. However, the triplet VMP has no clinical relevance nowadays. More data from the IMROZ and CEPHEUS trials might be become available within the next two years. So far, there are no trials comparing directly quadruplets with daratumumab and isatuximab, respectively.

The added benefit of bortezomib to a triplet containing a CD38 antibody has only been tested in the BENEFIT trial comparing IsaVRd and IsaRd. In the EU, however, IsaRd, other than DaraRd, has no marketing authorisation. For the triplet DaraRd, no direct comparison to DaraVRd is available, only to the nowadays less relevant combination Rd (MAIA). The same applies to the doublet DaraR (IFM 2017-03).

Therefore, we can only roughly estimate the outcomes of the treatment with DaraRd and DaraR derived from the respective treatment arms of the MAIA and IFM 2017-03 trials. These indirect comparisons, however, have to be interpreted with caution.

Details of the trials

Except the tested interventions, there are some other differences between the trials (Table 2). One of the main differences concerns inclusion and exclusion criteria.

For ALCYONE, OCTANS, IMROZ, AMaRC 03-16 and MAIA, transplant-ineligible (TIE) was defined as age 65 or older or important comorbidities for subjects younger than 65.

However, in clinical practice only patients age 70 or above would be considered TIE, patients under age 70 only if important comorbidities are present. Therefore, the IQWiG reports [8,9] discuss the impact based on subgroup analyses of the study populations. As no subgroup effect was detected for DaraVMP, the base of the analysis was the full study population. For IsaVRd, however, subgroup effects were detectable and therefore the analysis is based on the subpopulation which was either 70 years and above or below 70 years with important comorbidities. All results for IsaVRd in this report rely on this subpopulation. For AMaRC 03-16 and MAIA, no subgroup analyses of this kind are available.

For CEPHEUS, the age cut-off for TIE was set at 65 years, but patients between 65 and 70 years received a medical check for suitability on a case-by-case base. Other than the other trials, CEPHEUS also allowed inclusion of subjects who were medically eligible for ASCT but rejected this treatment option (transplant deferred). This subgroup (<70 years and transplant deferred) comprises about 27 % of the study population. The IQWiG report relies on a subpopulation including patients 70 years and older as well as patients below the age of 70 for whom a transplant is not suitable due to medical reasons. Data from this subpopulation (called “ASZT-ungeeignet” in the IQWiG report) is used in this evidence report.

BENEFIT and IFM 2017-03 included patients 65 years of age or older for whom an ASCT was not considered suitable. The detailed criteria for suitability, however, are not reported in the journal publications and study protocols are not available, either.

Subjects older than 80 years were explicitly excluded in IMROZ, CEPHEUS and BENEFIT, but not in the other trials. For CEPHEUS and BENEFIT, a frailty index of 2 or above was an additional exclusion criterion. The IFM 2017-03 trial only included patients with a frailty index of 2 or above. As a consequence, the populations in MAIA and IFM 2017-03 were frailer than in the trials testing quadruplets. Only AMaRC 03-16 explicitly allowed any degree of renal impairment, including need for dialysis. Other differences concern the length of the induction therapy which lasted between 24 and 72 weeks. In all trials, there was some kind of continuous therapy until disease progression or unacceptable toxicity. In ALCYONE, OCTANS and AMaRC 03-16, however, continuous therapy was only available to the intervention group.

Three of the trials (IMROZ, CEPHEUS and BENEFIT) are still ongoing.

Table 2: Included trials for the comparison intensive (quadruplet) therapy vs. less intensive therapy

Trial Identifier study registry Status	Population	Interventions		
		Induction therapy	**Continuous therapy**	**Median treatment duration**
With or without CD38 antibody				
ALCYONE [8,11,17] NCT02195479 completed	TIE[a] n = 706 Mean age: 71	DaraVMP vs. VMP 54 weeks (9x 6 weeks)	Dara vs. none	33 vs. 12 months
OCTANS [8,11,19] NCT03217812 completed	TIE[a] n = 220[b] Median age: 69	DaraVMP vs. VMP 54 weeks (9x 6 weeks)	Dara vs. none	34 vs. 12 months
CEPHEUS [10,12,18] NCT03652064 ongoing	TIE[c] and TD n = 395 Median age: 70	DaraVRd vs. VRd 24 weeks (8x 3 weeks)	DaraRd vs. Rd	56 vs. 34 months
IMROZ [13,21] NCT03319667 ongoing	TIE[a] n = 446 Median age: 72	IsaVRd vs. VRd 24 weeks (4x 6 weeks)	IsaRd vs. Rd	51 vs. 29 months
AMaRC 03-16 [20] ACTRN12617000202369 completed	TIE[a] n = 129[d] Mean age: 75	DaraVCd vs. VCD 54weeks (9x 6 weeks)	Dara vs. none	Not reported
Without bortezomib				
BENEFIT [22] NCT04751877 ongoing	TIE[e] n = 270 Mean age: 73-74	IsaVRd vs. IsaRd 72 weeks (18x 4 weeks)[f]	IsaR (both arms)	16 months (both arms)
MAIA [14,15] NCT02252172 completed	TIE[a] n = 737 Mean age: 73-74	DaraRd (vs. Rd) 4-week cycles, continuously	n.a.	48 vs. 23 months

Without bortezomib and dexamethasone				
IFM 2017-03 [23] NCT03993912 completed	TIE[e] n = 295 Mean age: 81	DaraR (vs. Rd)[g] 4-week cycles, continuously	n.a.	32 months vs. 14 months

[a]important comorbidities or age ≥ 65
[b]asian patients only
[c]important comorbidities or age ≥ 70; individual assessment for ages 65-70
[d]In trials/arms with continuous therapy, treatment was continued until disease progression or unacceptable toxicity.
[e]age ≥ 65 and ASCT not considered suitable
[f]Dexamethasone discontinued after cycle 12
[g]Dexamethasone is only added for the first two cycles
TIE: transplant-ineligible; TD: transplant-deferred; n.a. not applicable

Overview of the evidence sources

Although some IQWiG reports are available, we also had to rely on additional sources to obtain comprehensive results from the trials (Table 3):

The IQWiG report for DaraVMP includes data from the trials ALCYONE and OCTANS [8], the report for IsaVRd data from the IMROZ trial [9] and the report for DaraVRd data from CEPHEUS [10]. As the IQWiG reports did not assess data for the outcome progression and only a limited operationalisation for symptoms and health-related quality of life (HrQoL), we also included journal publications of the trials ALCYONE [17], OCTANS [19], IMROZ [21] and CEPHEUS [18] as well as the AMNOG dossiers for the comparisons DaraVMP vs. VMP [11], IsaVRd vs. VRd [13] and DaraVRd vs. VRd [12].

For the MAIA trial, journal publications with more recent data cut-off [14,15] than the corresponding IQWiG report were available and therefore included instead.

For the AMaRC 03-16 [20], BENEFIT [22] and the IFM 2017-03 trial [23], only journal publications are available.

Table 3 summarises the sources of evidence used to answer the FAQs. FAQs 7 and 8 have not been included in the table as the answers will be derived from data on the reduction of symptoms (FAQ 3) and description of the treatments (FAQ 1).

Table 3: Evidence sources

Trial	Interventions	FAQ1: Treatment modalities	FAQ2: Survival	FAQ 3: Symptoms	FAQ4: Progression	FAQ5: Quality of life	FAQ6: Side effects
IQWiG report DaraVMP [8]	DaraVMP vs. VMP		✓	✓		✓	✓
AMNOG dossier DaraVMP [11]	DaraVMP vs. VMP			✓	✓	✓	
Mateos 2025 (ALCYONE) [17]	DaraVMP vs. VMP				✓		
Fu 2024 (OCTANS) [19]	DaraVMP vs. VMP				✓		
Usmani 2025 (CEPHEUS) [18]	DaraVRd vs. VRd		✓			✓	✓
IQWiG report DaraVRd [10]	DaraVRd vs. VRd		✓	✓		✓	✓
AMNOG dossier DaraVRd [12]	DaraVRd vs. VRd		✓	✓		✓	✓
IQWiG report IsaVRd [9]	IsaVRd vs. VRd		✓	✓		✓	✓
AMNOG dossier IsaVRd [13]	IsaVRd vs. VRd			✓	✓	✓	
Facon 2024 (IMROZ) [21]	IsaVRd vs. VRd				✓		
Mollee 2024 (AMaRC 03-16) [20]	DaraVCd vs. VCD		✓				✓
Facon 2025 (MAIA) [14]	DaraRd vs. Rd		✓		✓		✓
Perrot 2025 (MAIA) [15]	DaraRd vs. Rd			✓		✓	

Leleu 2024 (BENEFIT) [22]	IsaVRd vs. IsaRd		✓		✓		✓
Manier 2025 (IFM 2017-03) [23]	DaraR vs. Rd		✓	(✓)	✓	(✓)	✓
Myeloma UK Treatment Guides [24–31]	all	✓					✓
Patient guideline Multiple Myeloma [2]	all	✓					✓

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. This supportive therapy includes (as needed) medicines and other treatments [2]:

- 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)

Myeloma-specific therapy

For the specific treatment of myeloma for the target group of this decision aid, there are two general options: intensive therapy or less intensive therapy.

Intensive therapy

For intensive therapy, the myeloma-specific treatment is a combination of four different medicines (quadruplet therapy) which includes a CD38 antibody (daratumumab, short dara, or isatuximab, short isa).

The EHA-EMN guideline [32] prefers the combinations DaraVRd (including the proteasome inhibitor bortezomib (V), the immunomodulator lenalidomide (R) and the corticosteroid ("cortisone") dexamethasone (d)) and IsaVRd for patients with a Frailty score (FS) of <2 according to the International Myeloma Working Group (IMWG) and <80 years old. Other combinations are mentioned as well:

- DaraVMP: Daratumumab, bortezomib, melphalan (M), prednisone (P); if DaraVRd or IsaVRd are not available
- DaraVCd: Daratumumab, bortezomib, cyclophosphamide (C), dexamethasone; for patients with renal insufficiency. This combination therapy has no marketing authorisation in the EU and is used off label.

Less intensive therapy

The EHA-EMN guideline [32] mentions several options of combinations with fewer drugs and the situations they are recommended for:

- DaraRd especially for patients with IMWG FS ≥1
- DaraR for patients with IMWG FS ≥2 (with dexamethasone added only for the first two cycles)
- VRd, when DaraVRd or IsaVRd are not available

Treatment modalities

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). Usually, therapy is given until the disease progresses or the toxicity becomes unacceptable. Depending on the drug combination, continuous therapy may include all or only some of the drugs used for induction therapy.

For daratumumab and isatuximab, additional medicines are required at every treatment to prevent infusion/injection reactions. For melphalan and cyclophosphamide, medicines for the prevention of nausea and vomiting as well as for the prevention of toxic cystitis may be necessary. 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 (granulocyte colony-stimulating factor, G-CSF).

Which drug combination is offered, depends mainly on patients' characteristics. The EHA-EMN guideline prefers DaraVRd or IsaVRd as first options. DaraVMP is listed as therapy of choice if first options are not available. DaraVCd is recommended for patients with renal insufficiency [4].

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

The different medicines and their treatment modalities are described in Table 4.

Table 4: Overview of the medicines [2,24–31]

Medicine	Drug class	Mode of action	Mode of application	Place of treatment	Typical frequency
Daratumumab	Anti-CD38 antibodies	The drug binds to specific proteins on the surface of the myeloma cells which leads to the death of myeloma cells.	By injection under the skin or by infusion	At doctor's office	Infusions over several hours. Injections are quicker. Induction therapy: weekly at the start, followed by every 3 weeks. Continuous therapy: every 4 weeks.
Isatuximab			By infusion		Infusions over several hours. Induction therapy: weekly at the start, followed by every 2 weeks. Continuous therapy: every 4 weeks.
Bortezomib	Proteasome inhibitors	The drug inhibits a complex of enzymes (the "proteasome") which clean the cells of protein waste. As myeloma cells produce more proteins as healthy cells, they are more susceptible to proteasome inhibition.	By injection under the skin	At doctor's office	Depending on treatment regime and treatment cycle, once or twice per week. Induction therapy only.

Lenalidomide	Immuno-modulators	The drug activates the immune system which helps to destroy myeloma cells.	By mouth (as capsule)	At home	Depending on treatment regime, e.g. daily for three weeks in a 4-weeks treatment cycle
Melphalan	Cytostatic drugs (alkylating agents)	The drug crosslinks the DNA of myeloma cells and blocks cell division.	Mostly by mouth (as tablet), sometimes by infusion	At home (tablet) or at doctor's office (infusion)	Daily for 4 days (tablet) in a 6-weeks-cycle. Induction therapy only.
Cyclo-phosphamide					Depending on treatment regime, mostly once a week (tablet) in a treatment cycle of several weeks. Induction therapy only.
Dexamethasone, prednisone	Corticosteroids	The drug enhances the ability of other medicines to destroy myeloma cells.	Mostly by mouth (as tablet), sometimes by infusion	At home (tablet) or at doctor's office (infusion)	On several days per week of a treatment cycle or once weekly, depending on therapy regime and treatment cycle

Conclusion for the decision aid

- The decision aid should describe the two general options (intensive vs. less intensive therapy) and the usual combinations as well as the information for the individual medicines in Table 4.
- The decision which intensive or less intensive therapy should be used, is beyond the scope of this decision aid and is usually made by the physician on a case-by-case basis depending on comorbidities and local preferences.
- As the details of treatment cycles, days without treatment and components of induction and continuous treatments vary, only the main principles should be summarized.

FAQ 2: WILL I LIVE LONGER?

Overall mortality has been assessed in all included trials (Table 5).

Direct evidence

Direct evidence is only available for the comparison of quadruplets with triplets without a CD38 antibody (DaraVMP vs. VMP, DaraVCd vs. VCd, DaraVRd vs. VRd, IsaVRd vs. VRd) and for the comparison of a quadruplet with a triplet without bortezomib (IsaVRd vs. IsaRd). The point estimates are quite similar for DaraVMP and DaraVRd, but the hazard ratio (HR) indicates a smaller effect for IsaVRd. For BENEFIT and AMaRC 3-16, no HR is reported.

In ALCYONE, with a median follow-up of 87 months (approximately 7 years), the addition of daratumumab to VMP results in 12 per 100 people more being alive. With the more intensive therapy, the median survival is 29 months (approximately 2.5 years) longer than in the comparison group.

In the ongoing trials IMROZ, CEPHEUS and BENEFIT, there is no difference in overall survival yet between intensive and less intensive therapy, and median survival is not reached.

Indirect evidence

In the absence of direct comparisons, it is difficult to reliably estimate if the overall survival is shorter with DaraRd and DaraR than with more intensive therapy. Apart from the general difficulty of cross-trial comparisons, especially with the differences in the mean population ages (older in MAIA and IFM 2017-03), also the different lengths of follow-up do not allow to compare absolute risks at the reported data cut-off.

A triangulation on the basis of median survival is also difficult, as in most trials, median survival has not been reached yet. Based on the median survival in the respective comparison groups, median survival with DaraRd is more than 65.5 months and with DaraR more than 47.3 months. For DaraRd, this might be longer than with VMP although shorter than with DaraVMP. For DaraR, median survival is seemingly shorter than with DaraVMP. However, the population in the IFM 2017-03 trial is about 10 years older than in the ALCYONE trial. For both

DaraRd and DaraR, comparisons to DaraVRd are not possible as median survival has not been reached yet in the CEPHEUS trial. It is noted that the median survival in MAIA is in the same order of magnitude as with less intensive therapy in ALCYONE, although the median age of the population is higher. This could indicate a benefit of the CD38 antibody. However, this finding should be interpreted with care as the ALCYONE trial took place some years earlier and it is not clear if and how much changes in care and subsequent therapy contribute to the seemingly better result.

Table 5: Overall mortality

Trial	Intervention/ Comparison	Median follow-up (months)	Intensive therapy Proportion Median time to event (months)	Less intensive therapy Proportion Median time to event (months)	Notes
With or without CD38 antibody					
ALCYONE [8][a]	DaraVMP vs. VMP	87	49 per 100 83	61 per 100 54	HR 0.65 (0.53; 0.80), Difference: 12 per 100[e] 29 months
OCTANS [8][a]	DaraVMP vs. VMP	41	23 per 100 n.r.	31 per 100 n.r.	n.s. HR 0.60 (0.35; 1.03)
CEPHEUS[b] [10]	DaraVRd vs. VRd	59	23 per 100 n.r.	32 per 100 n.r.	n.s. HR 0.66 (0.42; 1.03)
IMROZ [9][c]	IsaVRd vs. VRd	57	29 per 100 n.r.	35 per 100 n.r.	n.s. HR 0.80 (0.55; 1.18)
AMaRC 03-16 [20][d]	DaraVCd vs. VCd	45	9 per 100 n.r.	8 per 100 59	n.s. HR not reported

Without bortezomib					
BENEFIT [22][f]	IsaVRd vs. IsaRd	23.5	8 per 100 n.r.	7 per 100 n.r.	n.s. HR not reported
MAIA [14][g]	DaraRd (this arm only)	64.5	n.a.	67 per 100 n.r. (> 65.5 months)	n.a.
Without bortezomib, dexamethasone-sparing					
IFM 2017-03 [23][h]	DaraR (this arm only)	46.3	n.a.	30 per 100 n.r. (> 47.3 months)	n.a.

[a]Table 15, final analysis. Median follow-up Table 10.
[b]Table 15, data for subpopulation "ASZT ungeeignet
[c]Table 14. Median follow-up Table 10.
[d]Figure 1: 5/63 with VCd, 6/66 with DaraVCd.
[e]If the numbers are calculated from the HR and the baseline of the comparator group, the intervention risk is 46 per 100 and the difference 15 per 100 (95% CI 822 per 100).
[f]Extended Data Table 2
[g]Estimated 60-month overall survival rate, Fig. 1b
[h]overall survival, Figure 2b
n.s.: not significant; n.r.: not reached; n.a.: not applicable; HR: hazard ratio. Effect sizes are reported as point estimate and 95% confidence interval (CI).

Summary

Only for DaraVMP vs. VMP, the superiority of the more intensive therapy is shown in terms of overall survival. For the other comparisons with direct evidence, this is unclear due to lack of mature data for this outcome. Triangulation of indirect evidence for DaraRd and DaraR (in comparison to more intensive therapy) is not possible.

Table 6: GRADE rating for outcome: overall mortality

Domain	Downgrading	Certainty	Notes
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	↓		OS data is immature for most trials. In ALCYONE, CI does not include null or unimportant effect; HR 0.65 is marginally implausibly large. However, the ratio of upper and lower confidence intervals for the effect size of both trials is < 3 and the OIS has been reached.[a]
Indirectness	↓		Many comparisons rely on indirect evidence.
Inconsistency	n.a.		Not enough data to assess inconsistency
Publication bias	n.a.		No concerns due to IQWiG report
Overall	↓↓↓	**very low**	

[a]For ALCYONE, an effect size HR 0.73 for overall survival has been hypothesized, requiring 382 death events [17]. At final data cut-off, there were 172+217 = 389 events. Therefore, OIS has been reached.
HR: hazard ratio; OIS: optimal information size, CI: confidence interval

Conclusion for the decision aid

- There is an indication that intensive therapy with a quadruplet improves overall survival compared with a less intensive therapy option.
- However, this conclusion relies only on the data for the comparison DaraVMP vs. VMP. For other comparisons, there is a lack of evidence, either because of immature overall survival data or because there are no direct comparisons and triangulation is not possible.
- The certainty of the evidence for this outcome is very low (Table 6).
- In the face of the uncertainty, the decision aid should not communicate effect estimates.

FAQ 3: Will the treatment help my symptoms?

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.

Effects of the myeloma-specific therapies on symptoms have been assessed in the trials comparing quadruplets and triplets without an CD38 antibody, ALCYONE, OCTANS, IMROZ and CEPHEUS.

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 and the EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L) Visual Analogue Scale (VAS) for the assessment of health status. The IMROZ and CEPHEUS trials additionally used the myeloma-specific questionnaire EORTC QLQ-MY20 for the assessment of disease symptoms and side effects.

The BENEFIT trial [22] did not assess symptoms. In the IFM 2017-03 trial [23], the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) instrument as well as the EuroQol Five Dimension Three Level Questionnaire (EQ-5D-3L) were used. The journal publication, however, reports the results only as sum scales and does not distinguish between symptom items and quality of life items. Therefore, the results are reported in the FAQ for quality of life.

The MAIA trial used the EORTC QLQ-C30 instrument. In the journal publication with long-term results [15], only the data for the symptoms pain and fatigue are reported.

It should be noted that the follow-up time for morbidity endpoints had been defined differently in the trials, and for some trials, also according to the outcomes:

- In ALCYONE, OCTANS and MAIA, patients were followed until 16 weeks after progression.
- In IMROZ, patients were followed for 90 days after the last treatment.
- In 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.
- IFM 2017-03: Symptoms were assessed regularly until the end of the trial.

When the duration of treatment differed between intervention and control groups, so did the follow-up time.

In the AMNOG process, the minimal important (“relevant”) difference has been defined as 10 points (10 %) for the respective items of EORTC QLQ-C30 and EORTC QLQ-MY20 and 15

points (15 %) for EQ-5D VAS. This definition is adopted for this evidence report. The respective responder analyses can be found below.

Delaying relevant worsening of symptoms

Direct evidence

As myeloma is a progressing disease, the IQWiG reports [8–10] only assessed the time to first relevant worsening of symptoms (Table 7), i.e. how quadruplet and triplet therapies without a CD38 antibody compare in regard to delaying relevant worsening of symptoms. It should be noted that this operationalization does not mean sustained delay.

Table 7: First relevant worsening of symptoms

Domain	Trial	Intensive therapy Proportion Median time to event (months)	Less intensive therapy Proportion Median time to event (months)	Notes
With or without CD38 antibody				
Fatigue	ALCYONE[a] [8]	39 per 100 46	38 per 100 17	1 to 5 per 100[d,e] HR 0.76 (0.61; 0.94)
	OCTANS[b] [8]	51 per 100 18	46 per 100 9	
	IMROZ[c] [9]	73 per 100 3	78 per 100 3	n.s.
	CEPHEUS[f] [10]	73 per 100 2	75 per 100 2	n.s.
Nausea/ vomiting	ALCYONE[a] [8]	31 per 100 77	27 per 100 n.r.	n.s.
	OCTANS[b] [8]	34 per 100 51	22 per 100 n.c.	
	IMROZ[c] [9]	54 per 100 18	57 per 100 9	3 per 100 HR 0.72 (0.54; 0.97)
	CEPHEUS[f] [10]	60 per 100 6	50 per 100 11	n.s.
Pain	ALCYONE[a] [8]	34 per 100 79	33 per 100 33	n.s.[d] For ALCYONE: 1 per 100[e]
	OCTANS[b] [8]	43 per 100 44	34 per 100 27	

				HR 0.75 (0.57; 0.98)
	IMROZ[c] [9]	64 per 100 6	67 per 100 4	n.s.
	CEPHEUS[f] [10]	57 per 100 4	64 per 100 4	n.s.
Dyspnoea	ALCYONE[a] [8]	36 per 100 58	26 per 100 n.r.	n.s.[d]
	OCTANS[b] [8]	35 per 100 n.r.	24 per 100 n.c.	
	IMROZ[c] [9]	58 per 100 11	67 per 100 4	9 per 100 HR 0.61 (0.46; 0.80)
	CEPHEUS[f] [10]	73 per 100 3	64 per 100 5	n.s.
Insomnia	ALCYONE[a] [8]	38 per 100 44	31 per 100 46	n.s.
	OCTANS[b] [8]	40 per 100 n.r.	39 per 100 18	
	IMROZ[c] [9]	62 per 100 4	63 per 100 3	n.s.
	CEPHEUS[f] [10]	73 per 100 3	68 per 100 3	n.s.
Loss of appetite	ALCYONE[a] [8]	33 per 100 n.r.	26 per 100 55	n.s.
	OCTANS[b] [8]	35 per 100 50	31 per 100 n.r.	
	IMROZ[c] [9]	61 per 100 7	68 per 100 6	7 per 100 HR 0.75 (0.57; 0.99)
	CEPHEUS[f] [10]	73 per 100 4	70 per 100 4	n.s.
Obstipation	ALCYONE[a] [8]	31 per 100 n.c.	26 per 100 n.r.	n.s.
	OCTANS[b] [8]	33 per 100 n.r.	28 per 100 24	

	IMROZ[c] [9]	58 per 100 6	60 per 100 3	n.s.
	CEPHEUS[f] [10]	67 per 100 3	77 per 100 2	10 per 100 HR 0.69 (0.51;0.92)
Diarrhoea	ALCYONE[a] [8]	30 per 100 n.r.	23 per 100 n.r.	n.s.
	OCTANS[b] [8]	32 per 100 n.r.	20 per 100 n.r.	
	IMROZ[c] [9]	67 per 100 9	70 per 100 6	n.s.
	CEPHEUS[f] [10]	82 per 100 5	78 per 100 4	n.s.
Health status	ALCYONE[a] [8]	21 per 100 n.r.	19 per 100 n.r.	n.s.
	OCTANS[b] [8]	25 per 100 n.r.	18 per 100 n.r.	
	IMROZ[c] [9]	50 per 100 17	55 per 100 7	n.s.
	CEPHEUS[f] [10]	59 per 100 4	56 per 100 7	n.s.
Disease symptoms	IMROZ[c] [9]	57 per 100 11	56 per 100 12	n.s.
	CEPHEUS[f] [10]	52 per 100 12	55 per 100 14	n.s.
Side effects	IMROZ[c] [9]	65 per 100 5	70 per 100 4	n.s.
	CEPHEUS[f] [10]	71 per 100 2	67 per 100 3	n.s.

[a]Table 15. Median follow-up time for quadruplet 34 months, for triplet 19 months (Table 10)
[b]Table 15. Median follow-up time for quadruplet 32 months, for triplet 14 months (Table 10)
[c]Table 14. Median follow-up time for quadruplet 53 months, for triplet 29 months (Table 10).
[d]The statistical significance is reported for the meta-analysis of ALCYONE and OCTANS as in the IQWiG report.
[e]The difference is statistically significant for the results from ALCYONE alone.
[f]Table 15. Median follow-up for outcomes measured with EORTC QLQ-C30 and EORTC QLQ-MY20 for quadruplet 53 months, for triplet 38 months. For outcomes measured with EQ-5D VAS for quadruplet 54 months, for triplet 52 months (Table 10).

n.s. not significant; n.r. not reached, n.c. not calculable. Effect sizes are reported as point estimate and 95% confidence interval.

For most symptoms, there is no statistically significant difference between quadruplet and triplet (without a CD38 antibody) therapy. Although there are some exceptions, there is, however, no consistency in the symptoms for which the quadruplets show a statistically significant superiority:

- DaraVMP vs. VMP: Fatigue, pain (only in ALCYONE)
- IsaVRd vs. VRd: Nausea/vomiting, dyspnoea, loss of appetite
- DaraVRd vs. VRd: Obstipation

The IQWiG report for IsaVRd only acknowledges the benefit for the outcome dyspnoea (small effect size, more than marginally clinically relevant), but not for nausea/vomiting and loss of appetite due to the marginally clinically relevant effect size in relation to the low severeness of the symptoms [9]. The same applies to the quadruplet DaraVRd and the outcome obstipation [10].

For the quadruplet DaraVMP, the IQWiG report refers only to the meta-analytical results for ALCYONE and OCTANS. In the meta-analysis, other than in ALCYONE alone, there is no added benefit of the quadruplet for the outcome pain. As OCTANS only included patients from Asia, there is room for debate whether the results of ALCYONE are more relevant for the target group of the decision aid. Although the meta-analysis shows a statistically significant difference for the outcome fatigue, the IQWiG does not acknowledge a benefit due to the marginally clinically relevant effect size in relation to the low severeness of the symptoms [8].

Indirect evidence

In the MAIA trial, there are data on time to worsening, both for pain and fatigue. However, the operationalisation of worsening does not rely on clinically meaningful worsening (difference ≥ 10 points) but used change of at least a half a standard deviation in comparison to baseline. Therefore, these data are not reported here.

Relevant improvement of symptoms

For patients, not only delay of relevant symptom worsening is important, but also relevant improvement of symptoms.

Direct evidence

Some details can be found in the AMNOG dossiers. The dossier for the quadruplet DaraVMP [8] reports the proportion of patients with first relevant improvement of symptoms at data

cut-off and time to event (Table 8). It should be noted that this operationalization does not mean sustained relevant improvement of symptoms.

Table 8: First relevant improvement of symptoms [11]

Outcome	Trial	Intensive therapy Proportion Median time to event (months)	Less intensive therapy Proportion Median time to event (months)	Difference
With or without CD38 antibody				
Pain	ALCYONE[a]	61 per 100 4	58 per 100 6	n.s.
	OCTANS[b]	58 per 100 7	60 per 100 6	n.s.
Fatigue	ALCYONE[a]	66 per 100 6	58 per 100 6	RR, RD sign., HR n.s. RR 0.88 (0.78-0.98)[c]
	OCTANS[b]	62 per 100 6	53 per 100 6	n.s.
Nausea/ vomiting	ALCYONE[a]	15 per 100 n.r.	15 per 100 n.r.	n.s.
	OCTANS[b]	15 per 100 n.r.	20 per 100 n.r.	n.s.
Dyspnoea	ALCYONE[a]	31 per 100 n.r.	29 per 100 61	n.s.
	OCTANS[b]	32 per 100 n.r.	27 per 100 n.r.	n.s.
Insomnia	ALCYONE[a]	43 per 100 17	36 per 100 20	n.s.
	OCTANS[b]	30 per 100 n.r.	34 per 100 n.r.	n.s.

Loss of appetite	ALCYONE[a]	36 per 100 n.r.	33 per 100 n.r.	n.s.
	OCTANS[b]	32 per 100 n.r.	28 per 100 n.r.	n.s.
Obstipation	ALCYONE[a]	32 per 100 91	27 per 100 n.r.	n.s.
	OCTANS[b]	32 per 100 n.r.	31 per 100 n.r.	n.s.
Diarrhoea	ALCYONE[a]	11 per 100 n.r.	11 per 100 n.r.	n.s.
	OCTANS[b]	12 per 100 n.r.	14 per 100 n.r.	n.s.

[a][11] Table 4-86
[b][11] Table 4-88
[c]In the AMNOG dossier, the risk ratio is calculated for an increase of a positive event: RR 1.14 [1.02; 1.28]. IQWiG methods for assessing the magnitude of benefit, however, assume a reduction of negative events. Therefore, the numbers have been calculated as 1/RR and for the lower and upper boundary of the confidence interval accordingly.
n.r. not reached; n.s. not significant. HR: hazard ratio; RR: risk ratio; RD: risk difference. Effect sizes are reported as point estimate and 95% confidence interval.

Other than in the IQWiG report, the AMNOG dossier for DaraVMP assesses the results of ALCYONE and OCTANS separately. As OCTANS only included patients from Asia, there is room for debate whether the results of ALCYONE are more relevant for the target group of the decision aid.

In the OCTANS trial, there are no differences between quadruplet and triplet therapy regarding at least temporary relevant improvement of symptoms. In the ALCYONE trial, there are statistically significant differences in the proportions of responders for fatigue, but not for the other symptoms and not for the time to event.

If the results from the AMNOG dossier for first relevant improvement of symptoms would be assessed by standard IQWiG methods and other judgments in the IQWiG report were adopted (fatigue no severe symptom), the magnitude of the added benefit for the quadruplet would be judged as marginally clinically relevant (upper boundary of the confidence interval > 0.90). If fatigue was judged as severe symptom, this would result in a small added benefit (upper boundary of the confidence interval < 1.00).

For the quadruplet IsaVRd, no corresponding analysis is available in the AMNOG dossier [13]. The same applies to the AMNOG dossier of DaraVRd [12].

Indirect evidence

For the MAIA trial, there are no data on proportions of patients with clinically relevant improvement of pain. The proportion of patients with clinically relevant improvement of fatigue with DRd was 45.4% at about 3 years (cycle 36) and 45.6% at 5 years (cycle 60) [15] which is somehow lower than with the quadruplets in the other trials. However, it should be taken into account that the population in MAIA was older and frailer than in the quadruplet trials which could also influence the level of fatigue.

Course of symptoms

For patients, it is also relevant to know how symptoms improve due to treatment overall. The data from ALCYONE show that depending on the symptom, the experience of relevant improvement can be quite different: Whereas about 60 per 100 patients experience at least temporarily relevant improvement of pain and fatigue, for gastrointestinal symptoms as nausea or diarrhoea, the numbers are much smaller (around 10 to 20 per 100).

Median time to relevant improvement of symptoms can be as short as 4 to 6 months (e.g. for pain and fatigue) or as long as 91 months (for obstipation).

For IsaVRd, the dossier [13] does not contain detailed analyses, only graphs for changes in least square means (appendix to module 4). For pain, a relevant improvement is noted as early as cycle 3 (p. 2947), for insomnia only at the very end of the treatment (p. 3057). No relevant improvement is noted for fatigue (p. 2837), nausea/vomiting (p. 2892), dyspnoea (p. 3002), diarrhoea (p. 3222, rather continuous worsening), whereas the means for loss of appetite (p. 3112) and constipation (p. 3167) fluctuate. In most symptoms, there is no difference between quadruplet and triplet therapy. For a short period at the beginning of the therapy, fatigue was worse with the triplet than with the quadruplet, but the difference is probably not clinically relevant.

Graphs for changes are also available for DaraVRd in the AMNOG dossier (module 4) [12] which report the mean of scores over time. For nausea/vomiting (p. 186) and dyspnoea (p. 189), symptom scores remain nearly constant over the trial. Pain (p. 188) is reduced slightly, but in a clinically relevant magnitude. Diarrhoea (p. 195) increases, also in a clinically relevant magnitude. Marginally clinically relevant differences between start and end of therapy are noted loss of appetite (p. 192, slight improvement) and disease symptoms (p. 210, slight improvement at start of therapy). No clinically relevant change is noted for fatigue (p. 185), insomnia (p. 191), obstipation (p. 194) and side effects (p. 212).

In the MAIA trial, the mean improvement for pain in comparison to baseline in the DaraRd arm is consistently above the threshold for a clinically meaningful effect. Otherwise, the mean changes for fatigue were below the threshold for clinical relevance [15].

Summary

Overall, there are some indications that the quadruplets might better than the triplets without a CD 38 antibody improve symptoms and delay relevant worsening.

However, the additional benefit in delaying relevant worsening of symptoms is shown for DaraVMP only for the outcomes fatigue and pain, for DaraVRd only for the outcome obstipation and for IsaVRd only for the outcomes nausea/vomiting, dyspnoea and loss of appetite. Only for IsaVRd and dyspnoea, there is a small effect whereas the effect size is marginally clinically relevant for the other outcomes.

The cause of the heterogeneity between the quadruplets cannot be explored with the available data.

An additional benefit in relevant improvement of symptoms is only shown for the quadruplet DaraVMP in the ALCYONE trial and only for the outcome fatigue. The effect size is probably marginally clinically relevant or small. The respective analyses for IsaVRd and DaraVRd are not available.

For the other less intensive treatments, data on symptoms are only available for DaraRd from the MAIA trial, not for DaraR. Due to differences in the operationalisation, it is not possible to interpret the data for time to relevant worsening pain unequivocally in the context of the other trials. However, the mean change of pain scores shows clinically relevant improvement. For fatigue, the mean change is not meaningful. However, about 45% of patients experience clinically relevant improvement of fatigue. This is lower than in both arms of the ALCYONE trial. This indirect comparison, however, should be regarded with caution as there are some indications of different patients' characteristics.

Table 9: GRADE rating for outcome: symptoms

Aspect	**Downgrading**	**Certainty**	**Notes**
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	n.a.		Not enough data to assess imprecision.
Indirectness	↓		Many comparisons rely on indirect evidence.
Inconsistency	↓		The quadruplets do not show a consistent benefit for the same symptoms; there is no consistency for all symptoms.
Publication bias	n.a.		No concern
Overall	↓↓↓	**Very low**	

Conclusion for the decision aid

- There are some indications that intensive therapy with a quadruplet might improve symptoms and delay worsening of symptoms better than a less intensive therapy option.
- It should be noted that the results are not consistent for all symptoms and not for all quadruplets and that the effect sizes are mostly marginally clinically relevant.
- However, this conclusion relies only on the data for the comparisons of quadruplets and triplets without CD38 antibody. For other comparisons, there is a lack of evidence, because there are no direct comparisons and triangulation is not possible.
- The certainty of the evidence for a relevant difference between intensive therapy and less intensive therapy in improving symptoms or preventing symptom worsening is very low (Table 9).
- In the face of the uncertainty, the decision aid should not communicate effect estimates.
- The decision aid should point out that not only myeloma-specific treatments, but also supportive therapies can improve symptoms of the disease.

FAQ 4: Will the treatment help that my disease does not progress?

In all trials, progression has been defined according to the IMWG based on biochemical and/or radiological markers [33] and progression-free survival (PFS) as time to progression or death, whatever comes first. It should be noted that this definition of progression is not necessarily directly linked to patient experience (e.g. worsening of symptoms).

PFS

PFS has been assessed as outcome in all trials (Table 10).

Direct evidence

Based on the hazard ratios, PFS was significantly longer in most trials which compared a quadruplet and the triplet without an CD38 antibody. For BENEFIT [22], no hazard ratio is reported due to immature data, and in AMaRC 03-16 [20] no difference was found.

It is, however, difficult to estimate a common effect size over all trials: In the trials testing DaraVMP vs. VMP, PFS was 17 to 24 months longer with the quadruplet. Median PFS has not been reached yet in the quadruplet arms with DaraVRd and IsaVRd [17–19,21].

Additionally, in the triplet arms of the trials IMROZ and CEPHEUS, median PFS was much longer (49 and 50 months, respectively) than in the respective arms of ALCYONE and OCTANS (15 and 19 months, respectively). The reasons for these differences are not clear.

Indirect evidence

In the MAIA trial [14], median PFS was 62 months with DaraRd. This is seemingly longer than in the triplet arms (VRd) of IMROZ and CEPHEUS (49 and 50 months, respectively) although the population in MAIA was older and frailer. In the IFM 2017-03 trial, patients in the DaraR group had a median PFS of 53 months. This is in the same order of magnitude as in the triplet arms (VRd) of IMROZ and CEPHEUS, although the population in IFM 2017-03 was much older and frailer. This indicates that the CD38 antibody might at least partially compensate for the lack of bortezomib. However, these cross-trial comparisons should be interpreted with caution.

For both DaraRd and DaraR, it is, however, unclear, if the median PFS is shorter than it would have been with DaraVRd (median PFS not reached yet).

Table 10: Progression-free survival

Trial	Intervention/ Comparison	Median follow-up (months)	Intensive therapy Time to event (months)	Less intensive therapy Time to event (months)	Notes
With or without CD38 antibody					
ALCYONE [11][a]	DaraVMP vs. VMP	87	36	19	HR 0.43 (0.36; 0.52)
OCTANS [11][b]	DaraVMP vs. VMP	41	39	19	HR 0.35 (0.23; 0.52)
IMROZ [13][c]	IsaVRd vs. VRd	60	n.r.	49	HR 0.65 (0.45; 0.93)
CEPHEUS [12][d]	DaraVRd vs. VRd	58	n.r.	50	HR 0.51 (0.35; 0.74)
AMaRC 03-16 [20]	DaraVCd vs. VCd	45	26	17	HR 0.67 (CI not reported)
Without bortezomib					
BENEFIT [22]	IsaVRd vs. IsaRd	24	n.r.	n.r.	Not reported
MAIA [14]	DaraRd (this arm only)	65	n.e.	62	n.a.

Without bortezomib, dexamethasone-sparing					
IFM 2017-03 [23]	DaraR (this arm only	46	n.e.	53	n.a.

Effect sizes are reported as point estimate and 95% confidence interval.
n.r.: not reached; n.a.: not applicable, n.e. not extracted; HR: hazard ratio; CI: confidence interval
[a]Table 4-28, data cut-off 31.05.2023
[b]Table 4-29, data cut-off 23.12.2022
[c]Table 4-23, data cut-off 26.09.2023, data for subpopulation, progression assessed by independent review committee (IRC).
[d]Table 4-36

Time to progression

However, as PFS is a composite outcome, it is not easy to interpret. Therefore, we decided to also use progression events as reported in the outcome time to progression. However, this outcome is only available from the trials IMROZ and ALCYONE (Table 11).

Time to progression is longer with the quadruplet as with the triplet without CD38 antibody Due to the different lengths of follow-up time, there are more events in the ALCYONE trial as in the IMROZ trial. In both trials, however, there are fewer patients with disease progression in the quadruplet arms than in the triplet arms. The difference is 15 to 19 per 100 patients.

Table 11: Time to progression

Trial	Intervention/ Comparison	Median follow-up (months)	Intensive therapy Proportion Time to event (months)	Less intensive therapy Proportion Time to event (months)	Notes
With or without CD38 antibody					
ALCYONE [11][a]	DaraVMP vs. VMP	87	54 per 100 46	73 per 100 20	HR 0.37 (0.30; 0.45) Difference: 19 per 100 26 months
IMROZ [13][b]	IsaVRd vs. VRd	60	19 per 100 n.r.	34 per 100 n.r.	HR 0.45 (0.29; 0.69) 15 per 100

Event rates have been extracted from the outcome time to progression (TTP). Effect sizes are reported as point estimate and 95% confidence interval.
[a]Table 4-32, data cut-off 31.05.2023
[b]Table 4-26, data cut-off 26.09.2023, data for subpopulation
n.r.: not reached; HR: hazard ratio; CI: confidence interval

In the BENEFIT trial, progression events are reported as 10 per 100 with IsaVRd and 16 per 100 with IsaRd at a follow-up of 23.5 months. However, no HR is available and the median time to event is not reached [22].

Another measure for progression is the need for subsequent therapy:

- In the ALCYONE trial for daratumumab, 43 per 100 patients with the quadruplet as first-line therapy needed subsequent therapy, with the triplet (without CD38 antibody) 69 per 100 patients (difference: 26 per 100). The median time to subsequent antimyeloma therapy was longer in the group with quadruplet as first-line therapy than in the triplet group: 67 months vs. 26 months [17].
- The journal publication of the OCTANS trial only reports the composite of time to subsequent therapy or death which is statistically significantly longer with the quadruplet than with the triplet (without CD38 antibody): 47 versus 21 months [19].
- In the IMROZ trial, 20 per 100 patients with the quadruplet as first-line therapy needed subsequent therapy, with the triplet (without CD38 antibody) 44 per 100 patients (difference: 24 per 100) [21].
- In the CEPHEUS trial, 13 per 100 patients with the quadruplet as first line therapy needed subsequent therapy, with the triplet (without CD38 antibody) 37 per 100 patients (difference: 24 per 100) [12].
- In MAIA, 35 per 100 patients in the DRd arm had subsequent therapy [14]. This is in the same order of magnitude as with the less intensive treatment arm in IMROZ and CEPHEUS (similar length of follow-up). In IFM 2017-03, 29 per 100 patients had subsequent therapy [23]. As the lengths of follow-up differed between the quadruplet trials and IFM 2017-03, it is difficult to estimate if the proportions are different. Also, as the population was substantially older than in the other trials, it is unclear whether the proportions reflect the real need for or rather the inclination to subsequent therapy.
- In BENEFIT, no data on need for subsequent therapy is reported.

These results are consistent with the data on progression and confirm the added benefit of the quadruplets in comparison to the triplets (without CD38 antibody). The difference of the effect sizes is similar for both DaraVMP and IsaVRd, although the effect sizes differ.

It should be noted that the numbers for need of subsequent therapy are higher than the numbers for progression, probably because they also include patients who change therapy due to inacceptable toxicity.

Summary

The probable superiority for progression has been shown for the quadruplets DaraVMP, DaraVRd, IsaVRd in comparison to the triplets without a CD38 antibody. For the comparison of IsaVRd to a triplet without bortezomib, the data is not mature yet.

Especially for DaraRd, based on a rather long median PFS in the MAIA trial, there is not enough evidence available to assess whether the treatment is really inferior to the quadruplets.

Table 12: GRADE rating for outcome: disease progression

Aspect	**Downgrading**	**Certainty**	**Notes**
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	n.a.		For most of the trials comparing quadruplets and triplets without CD38 antibody, CIs for PFS and progression do not include null or unimportant effect. HRs indicate a rather large effect size. However, the ratio of upper and lower confidence intervals for the effect size of the trials is < 3 and the OIS has been reached.
Indirectness	(↓)		No downgrading for the comparison of options with and without CD38 antibody; downgrading for the comparison of quadruplets vs. less intensive options with CD38 antibody (indirect evidence)
Inconsistency	(↓)		In comparison to triplets without CD38 antibody, quadruplets are more effective (no downgrading for this comparison). It cannot, however, be ruled out that the efficacy of DaraRd might be close to a quadruplet. (downgrading for comparison of all options)
Publication bias	n.a.		No concern
Overall	↓(↓↓)	**Very low** **Moderate**	**for all comparisons of intensive and less intensive therapy** **for the comparison with or without CD38 antibody**
Optimal information size (OIS) has been calculated by https://sample-size.net/ (Survival analysis), with α = 0.05 and β = 0.8 for IMROZ. For IMROZ with 3:2 randomisation, an effect size HR 0.64 [21] has been			

hypothesized, requiring n = 165 events. For ALCYONE, an effect size of HR 0.724 has been hypothesized, requiring n = 360 events [17]. In total, n = 525 events are required. Events from IMROZ are 37 (intervention) and 46 (control) [13] and from ALCYONE 188 (intervention) and 259 (control) [11], in total n = 530.
HR: hazard ratio; OIS: optimal information size; CI: confidence interval

Conclusion for the decision aid

- In the trials comparing quadruplets and triplets without a CD38 antibody, the quadruplets resulted in delayed progression (measured as PFS or time to progression).
- It cannot be reliably assessed if the other options (DaraRd and DaraR) are inferior to DaraVRd. For DaraRd, we cannot rule out that the effectiveness might be close to a quadruplet.
- The certainty of the evidence for the general comparison of intense and less intense therapy has been rated as very low. For the comparison of treatment options with or without CD38 antibody, the certainty of the evidence is moderate (Table 12). In the face of the uncertainty, the decision aid should not communicate effect estimates.

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

HrQoL has been assessed in all trials except BENEFIT. All trials used the EORTC QLQ-C30 instrument, IMROZ and CEPHEUS also the EORTC QLQ-MY20 instrument. For the IFM 2017-03 trial, results obtained by the application of the EQ-5D-3L instrument are reported as HrQoL data and therefore summarised in this FAQ.

HrQoL has been assessed in different domains:

- 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.

It should be noted that in ALCYONE, OCTANS and MAIA, the follow-up time for HrQoL had been defined as 16 weeks after progression, in IMROZ as 90 days after the last treatment and in CEPHEUS as 30 days after the last treatment. Where the duration of treatment differed between intervention and control groups, so did the follow-up time.

In the AMNOG process, the minimal important ("relevant") difference has been defined as 10 points (10 %) for the respective items of EORTC QLQ-C30 and EORTC QLQ-MY20. This definition is adopted for this evidence report. The respective responder analyses can be found below.

Results for HrQoL from AMaRC 03-16 are neither reported in the journal publication [20] nor the study registry.

Delaying relevant worsening of HrQoL

Data for the comparisons of DaraVMP vs. VMP, IsaVRd vs. VRd and DaraVRd vs. VRd is available from IQWiG reports [8–10] and AMNOG dossiers [11–13].

As myeloma is a progressing disease, the IQWiG reports [8–10] only assessed the time to first relevant worsening of HrQoL, i.e. how quadruplet and triplet therapies without a CD38 antibody compare in regard to delaying worsening of HrQoL (Table 13). It should be noted that this operationalization does not mean sustained delay. The same operationalisation is not available from the MAIA or the IFM 2017-03 trial. In MAIA, there is data on time to worsening. However, the operationalisation does not rely on meaningful worsening (difference ≥ 10 points) but used change of at least a half a standard deviation in comparison to baseline. Therefore, this data is not reported here.

Table 13: First relevant worsening of HrQoL

Domain	Trial	Intensive therapy Proportion Median time to event (months)	Less intensive therapy Proportion Median time to event (months)	Notes
With or without CD38 antibody				
Global health status	ALCYONE[a] [8]	30 per 100 86	30 per 100 44	Significant[d]; 16 to 42 months HR 0.73 (0.58; 0.93)
	OCTANS[b] [8]	35 per 100 44	30 per 100 28	
	IMROZ[c] [9]	61 per 100	65 per 100	n.s.

		7	4	
	CEPHEUS[e] [10]	62 per 100 2	60 per 100 3	n.s.
Physical functioning	ALCYONE[a] [8]	29 per 100 n.r.	28 per 100 40	n.s.
	OCTANS[b] [8]	35 per 100 44	26 per 100 n.r.	n.s.
	IMROZ[c] [9]	63 per 100 6	69 per 100 4	n.s.
	CEPHEUS[e] [10]	65 per 100 3	67 per 100 4	n.s.
Role functioning	ALCYONE[a] [8]	38 per 100 46	35 per 100 25	n.s.
	OCTANS[b] [8]	37 per 100 n.r.	37 per 100 27	n.s.
	IMROZ[c] [9]	64 per 100 4	68 per 100 3	4 per 100 1 month HR 0.76 (0.58; 0.99)
	CEPHEUS[e] [10]	65 per 100 2	66 per 100 3	n.s.
Emotional functioning	ALCYONE[a] [8]	29 per 100 n.c.	22 per 100 56	n.s.
	OCTANS[b] [8]	31 per 100 n.r.	20 per 100 n.r.	n.s.
	IMROZ[c] [9]	58 per 100 10	55 per 100 8	n.s.
	CEPHEUS[e] [10]	54 per 100 9	60 per 100 5	n.s.
Cognitive functioning	ALCYONE[a] [8]	47 per 100 23	38 per 100 23	n.s.
	OCTANS[b] [8]	52 per 100 17	39 per 100 20	n.s.

	IMROZ[c] [9]	70 per 100 6	74 per 100 5	n.s.
	CEPHEUS[e] [10]	75 per 100 3	75 per 100 4	n.s.
Social functioning	ALCYONE[a] [8]	37 per 100 60	32 per 100 34	n.s.
	OCTANS[b] [8]	49 per 100 22	38 per 100 22	n.s.
	IMROZ[c] [9]	72 per 100 4	71 per 100 3	n.s.
	CEPHEUS[e] [10]	67 per 100 3	69 per 100 3	n.s.
Future perspective	IMROZ[c] [9]	56 per 100 8	64 per 100 3	8 per 1005 months HR 0.74 (0.56; 0.99)
	CEPHEUS[e] [10]	50 per 100 8	53 per 100 14	n.s.
Body image	IMROZ[c] [9]	60 per 100 7	68 per 100 4	n.s.
	CEPHEUS[e] [10]	57 per 100 9	49 per 100 12	n.s.

[a]Table 15. Median follow-up time for quadruplet 34 months, for triplet 19 months (Table 10)
[b]Table 15. Median follow-up time for quadruplet 32 months, for triplet 14 months (Table 10)
[c]Table 14. Median follow-up time for quadruplet 53 months, for triplet 29 months (Table 10).
[d]for the meta-analysis of ALCYONE/OCTANS and ALCYONE alone, but not for OCTANS alone
[e]Table 15. Median follow-up for outcomes measured with EORTC QLQ-C30 and EORTC QLQ-MY20 for quadruplet 53 months, for triplet 38 months (Table 10).
n.r. not reached; n.c. not calculable; n.s. not significant. HR: hazard ratio. Effect sizes are reported as point estimate and 95% confidence interval.

However, in most domains there is no statistically significant difference between quadruplet and triplet therapy. Notable exceptions are global health status (in the ALCYONE trial only) and role functioning and future perspective (in the IMROZ trial only).

The median time to relevant worsening of quality of life is longer with the quadruplet than with the triplet therapy (without CD38 antibody): 16 to 24 months longer with DaraVMP for

global health status, 1 month longer with IsaVRd for role function and 5 months longer with IsaVRd for future perspective.

The magnitude of the effect size is considered small, but clinically relevant for the three outcomes [8,9].

However, there is some heterogeneity regarding the proportion of patients with first worsening of HrQoL: Whereas there is no nominal difference for global health status in ALCYONE, in IMROZ the difference in role function is 4 per 100 and in future perspective 8 per 100. However, there is a clear added benefit for the quadruplet in ALCYONE in terms of length of time to event. This might mean: The quadruplets may delay relevant worsening of HrQoL but not prevent it in the long term.

Improving HrQoL

For patients, not only delay of HrQoL worsening is important, but also relevant improvement of HrQoL. Some details can be found in the AMNOG dossiers. The dossier for the DaraVMP [8] reports the proportion of patients with first relevant improvement of HrQoL at data cut-off and time to event (Table 14). It should be noted that this operationalisation does not mean sustained relevant improvement of HrQoL. From the MAIA trial, this operationalisation is only available for the outcome physical function: With DaraRd, 46 per 100 patient experience relevant improvement of physical function at cycle 60 (about 60 months).

Although there is data available on the outcome "meaningful improvement of global health status", the operationalisation for this domain in the MAIA trial uses a threshold of 8 points instead of 10 points as in the AMNOG dossiers. Therefore, these data are not reported here.

Table 14: First relevant improvement of HrQoL [11]

Domain	**Trial**	**Intensive therapy** **Proportion** **Median time to event (months)**	**Less intensive therapy** **Proportion** **Median time to event (months)**	**Notes**[c]
With or without CD38 antibody				
Global health status	ALCYONE[a]	64 per 100 6	53 per 100 6	RR/RD sign., HR n.s. 11 per 100 RR 0.83 (0.74-0.94)
	OCTANS[b]	62 per 100 6	50 per 100 8	n.s.

Physical functioning	ALCYONE[a]	59 per 100 6	48 per 100 7	RR/RD sign., HR n.s. 11 per 100 RR 0.81 (0.70-0.93)
	OCTANS[b]	45 per 100 18	47 per 100 8	n.s.
Role functioning	ALCYONE[a]	55 per 100 6	48 per 100 8	RR/RD sign., HR n.s. 8 per 100 RR 0.86 (0.75-1.00)
	OCTANS[b]	52 per 100 9	47 per 100 8	n.s.
Emotional functioning	ALCYONE[a]	50 per 100 9	48 per 100 8	n.s.
	OCTANS[b]	41 per 100 39	35 per 100 n.r.	n.s.
Cognitive functioning	ALCYONE[a]	40 per 100 36	31 per 100 n.r.	RR/RD sign., HR n.s. 9 per 100 RR 0.78 (0.64-0.96)
	OCTANS[b]	41 per 100 39	50 per 100 9	RR/RD n.s., HR sign.
Social functioning	ALCYONE[a]	51 per 100 7	43 per 100 9	RR/RD sign., HR n.s. 8 per 100 RR 0.85 (0.72-0.99)
	OCTANS[b]	53 per 100 9	46 per 100 16	n.s.

[a]Table 4-104. Median follow-up time for quadruplet 34 months, for triplet 19 months.
[b]Table 4-105. Median follow-up time for quadruplet 32 months, for triplet 14 months.
[c]In the AMNOG dossier, the risk ratio is calculated for an increase of a positive event. IQWIG methods for assessing the magnitude of benefit, however, assume a reduction of negative events. Therefore, the numbers have been calculated as 1/RR and for the lower and upper boundary of the confidence interval accordingly.

n.r. not reached; n.s. not significant; sign.: significant; RR: risk ratio; RD: risk difference; HR: hazard ratio
Effect sizes are reported as point estimate and 95% confidence interval.

However, relevant improvement is not found for all domains and there are differences between the trials as well as for the types of effect measures:

- In OCTANS, there is only a significant difference between quadruplet and triplet in the domain cognitive functioning and only for median time to event, not for response. Surprisingly, the median time to relevant improvement is much longer with the quadruplet than with the triplet (39 vs. 9 months) which cannot be easily explained.
- In ALCYONE, a significant difference for response was found for the domains global health status, physical functioning, role functioning, cognitive functioning and social functioning. The difference of effect size is quite consistent (8 to 11 per 100). No significant difference was found for emotional functioning.
- In ALCYONE, there was no significant difference for the median time to response in any domain.

If the results from the AMNOG dossier for first improvement of HrQoL would be assessed by standard IQWiG methods, the magnitude of the benefit for the quadruplet would be judged as small, but not marginally clinically relevant (upper boundary of the confidence interval < 1.00).

For IsaVRd and DaraVRd, no corresponding analysis is available in the AMNOG dossiers.

For patients, it is also relevant to know how HrQoL improves due to treatment overall. The data from ALCYONE show that about 50 per 100 patients experience relevant improvement in HrQoL, with the proportions being higher for global health status and physical functioning (about 60 per 100 with the quadruplet) and being lower for cognitive functioning (about 40 per 100 with the quadruplet). Median time to relevant improvement of HrQoL is about 6 to 9 months for most domain except for cognitive functioning which was about 36 months with the quadruplet (median time not reached with the triplet without a CD38 antibody).

Course of HrQoL

For IsaVRd, the dossier [13] does not contain detailed analyses, only graphs for changes in least square means in the appendix of module 4. For all domains, the scores remain relatively stable but show no relevant improvement: Global health status (p. 3332), physical functioning (p. 3387), role functioning (p. 3442), , emotional functioning (p. 3552), social functioning (p. 3607), future perspective (p. 4493, fluctuating around marginally relevant improvement). Body image is slowly but steadily worsening (p. 4437), also cognitive functioning (p. 3497). However, the exact time of reaching relevant worsening cannot be

estimated reliably from the graph. In all domains, the scales are quite similar for quadruplet and triplet therapy.

Also for DaraVRd, graphs (mean scores) are available in the AMNOG dossier [12]. Most domains show some improvements. However, the change between baseline and end of trial is only clinically relevant for role functioning (p. 223) and future perspective (p. 242). No clinically relevant improvements are noted for global health status (p. 221), emotional functioning (p. 224), physical function (p. 226), social functioning (p. 229) and body image (p. 243). Cognitive function (p. 227) remains relatively constant. There is no relevant difference between quadruplet and triplet therapy (without CD38 antibody).

In the MAIA trial, the mean scores for global health status and physical functioning improve over time in the DaraRd arm, but not in a clinically relevant magnitude [15].

In the IFM 2017-03 trial, only sum scores are reported (Fig. S8, appendix) for EORTC QLQ-C30 and EQ-5D-3L. Both scores improve over time with DaraR, but probably not in a clinically relevant magnitude [23].

Summary

Overall, there are some indications that the quadruplets might better than the triplets without CD 38 antibody improve HrQoL and delay worsening.

The additional benefit in delaying relevant worsening of HrQoL is, however, shown for DaraVMP only in the domain global health status in the ALCYONE trial and for IsaVRd only for role functioning and future perspective, not for all other domains. The effect sizes are considered small, but clinically relevant. For DaraVRd, there is no difference between quadruplet and triplet therapy in neither of the domains.

The reasons for the heterogeneity between the quadruplets cannot be explored with the available data.

At least temporary relevant improvement of HrQoL is shown for the quadruplet with DaraVMP in comparison to the triplet in the ALCYONE trial only (not in OCTANS) for all domains except emotional functioning. The effect sizes are considered small, but clinically relevant. The respective analyses are not available for IsaVRd or DaraVRd.

For DaraRd and DaraR, there is only limited data on the different domains of HrQoL. With DaraRd, about 45 of 100 patients experience relevant improvement of physical functioning. Due to differences in the trial population and probably follow-up time, it is, however, not clear how this compares to the proportion with the quadruplet in the other trials.

Table 15: GRADE rating for outcome: HrQoL

Aspect	Downgrading	Certainty	Notes
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	↓		For relevant worsening of HrQoL, the confidence intervals for the effect estimates cross the null effect but include clinically important benefit.
Indirectness	n.a.		Evidence relies mainly on direct comparisons.
Inconsistency	↓		The quadruplets do not show a consistent benefit for the same domains of HrQoL. The differences are mostly significant for most domains in relevant improvement of symptoms, but not in delaying worsening of HrQoL.
Publication bias	↓		Some results of some trials have not been published so far.
Overall	↓↓↓	**Very low**	

Conclusion for the decision aid

- There are some indications that intensive therapy with a quadruplet might improve HrQoL and delay relevant worsening of HrQoL better than a less intensive therapy option.
- It should be noted that the results are not consistent for all domains and not for all quadruplets.
- The effect sizes are considered small, but clinically relevant.
- However, this conclusion relies only on the data for the comparisons of quadruplets with and triplets without CD38 antibody. For other comparisons, there is a lack of evidence, because there are no direct comparisons and triangulation is not possible.

- The certainty of the evidence for a relevant difference between intensive therapy and less intensive therapy in improving HrQoL or preventing HrQoL worsening in a relevant magnitude is very low (Table 15).
- In the face of the uncertainty, the decision aid should not communicate effect estimates.
- The decision aid should point out that HrQoL might improve when symptoms regress. Therefore, not only myeloma-specific treatments, but also supportive therapies might improve HrQoL.

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

Adverse events (AE) have been assessed in all trials. We report qualitative data on the most important AE (e.g. very common AE) and quantitative data on serious AE, severe AE and discontinuation due to AE as well as individual AE which might limit or delay therapy (e.g. peripheral neuropathy, severe infections). However, due to differences in operationalisation and reporting, specific adverse events outcomes are not available for all trials.

It should be noted that the follow-up time for adverse events outcomes had been defined as 30 days after the last treatment in nearly all trials. When the duration of treatment differed between intervention and control groups, so did the follow-up time for adverse events. For AMaRC 3-16, this information is not available.

Most common AE

Information on the most common AE has been extracted from the Treatment Guides for the individual medicines by Myeloma UK [24–31] and the patient guideline of the German guideline programme oncology [2]. It should be noted that the information (Table 16) 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 for infection and the risk of bleeding.

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

Table 16: Overview of most common side effects of myeloma-specific therapies

Medicine	Most important side effects
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
Melphalan Cyclophosphamide	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
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 Prednisone	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

Serious adverse events

Serious adverse events (SAEs) are defined as undesirable events in association with a medicine that lead to death or are life-threatening, require or prolong hospitalisation or result in disability or permanent damage. SAEs have been reported in all trials except BENEFIT (Table 17).

However, in none of the trials a statistically significant difference has been found for serious AE for the quadruplets compared to the triplets without a CD38 antibody. With DaraRd and DaraR, serious AE were in the same order of magnitude as with more and less intensive therapy in IMROZ and CEPHEUS, respectively.

Table 17: Serious adverse events

Trial	Intervention/ Comparison	Intensive therapy Proportion	Less intensive therapy Proportion	Notes
With or without CD38 antibody				
ALCYONE [8][a]	DaraVMP vs. VMP	54 per 100	33 per 100	n.s.
OCTANS [8][a]	DaraVMP vs. VMP	52 per 100	40 per 100	n.s.
CEPHEUS[b] [10]	DaraVRd vs. VRd	72 per 100	70 per 100	n.s.
IMROZ [9][c]	IsaVRd vs. VRd	71 per 100	74 per 100	n.s.
AMaRC 03-16 [20][d]	DaraVCd vs. VCd	30 per 100	25 per 100	Not reported
Without bortezomib				
MAIA [14]	DaraRd (this arm only)	n.a.	79 per 100	n.a.
Without bortezomib, dexamethasone-sparing				
IFM 2017-03 [23]	DaraR (this arm only)	n.a.	63 per 100	n.a.

[a]Table 15, final analysis. Median follow-up for ALCYONE is 34 months with the quadruplet and 13 months with the triplet; for OCTANS 35 months and 13 months, respectively (Table 10). ALCYONE: HR 1.17 (0.91; 1.50), OCTANS HR 1.12 (0.72; 1.75)
[b]Table 15. Median follow-up 56 months with the quadruplet and 35 months with the triplet. HR 0.93 (0.70; 1.23)
[c]Table 14. Median follow-up is 51 months with the quadruplet and 29 months with the triplet (Table 10). HR 0.79 (0.61; 1.03)
[d]Table 3. Median follow-up not reported.
n.s.: not significant; n.a. not applicable.

Severe adverse events

Severe adverse events are operationalised as all adverse events with a grade of 3 or higher according to the Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 refers e.g. to a medically significant event which is not immediately life-threatening but requires a (invasive) medical intervention, might include hospitalisation and impair ability to care for oneself. Grade 4 refers to life-threatening events requiring urgent care, Grade 5 refers to death.

Severe AE are reported in all trials (Table 18). The BENEFIT trial, however, does not report the number of all AE grade 3 and higher, only for haematologic AEs and separately for the different AEs. For the MAIA trial, only the sum of AE Grade 3 and 4 is available. In none of the trials comparing a quadruplet with a triplet without CD38 antibody, a statistically

significant difference has been found. How the proportions of severe AE with DaraRd and DaraR compare to the quadruplet, cannot be reliably estimated due to differences in follow-up and older populations.

Table 18: Severe adverse events (CTCAE grade ≥ 3)

Trial	Intervention/ Comparison	Intensive therapy Proportion	Less intensive therapy Proportion	Notes
With or without CD38 antibody				
ALCYONE [8][a]	DaraVMP vs. VMP	84 per 100	78 per 100	n.s.
OCTANS [8][a]	DaraVMP vs. VMP	92 per 100	86 per 100	n.s.
CEPHEUS[b] [10]	DaraVRd vs. VRd	93 per 100	89 per 100	n.s.
IMROZ [9][c]	IsaVRd vs. VRd	90 per 100	86 per 100	n.s.
AMaRC 03-16 [20][d]	DaraVCd vs. VCd	50 per 100	40 per 100	Not reported
Without bortezomib				
MAIA [14][e]	DaraRd arm only	n.a.	96 per 100	n.a.
Without bortezomib, dexamethasone-sparing				
IFM 2017-03 [23][f]	DaraR arm only	n.a.	90 per 100	n.a.

[a]Table 15, final analysis. Median follow-up for ALCYONE is 34 months with the quadruplet and 13 months with the triplet; for OCTANS 35 months and 13 months, respectively (Table 10). ALCYONE: HR 1.07 (0.90; 1.27), OCTANS HR 1.32 (0.96; 1.82)

[b] Table 15. Median follow-up for quadruplet 56 months, for triplet 35 months (Table 10). HR 1.05 (0.82; 1.36]

[c]Table 14. Median follow-up is 51 months with the quadruplet and 29 months with the triplet (Table 10). HR 0.95 (0.75; 1.20)

[d]Table 3. Median follow-up not reported.

[e]Grade 3 and 4 only

[f]Table 3, sum of Grade 3, 4 and 5. Median follow-up for AE not reported.

n.s.: not significant; n.a. not applicable

Discontinuation due to adverse events

For the BENEFIT trial, no data on discontinuation due to adverse events is available. In the MAIA trial, data has not been operationalised in a way that it can be compared to the other trials.

In the IQWiG reports, discontinuation due to adverse events (AE) is operationalised as discontinuing at least one medicine of the quadruplet or triplet therapy. Results for this operationalisation, however, are only available for the trials ALCYONE and OCTANS [8] and CEPHEUS [10] as well as from IFM 2017-03 (Table 19). For IsaVRd, the data is reported in an additional analysis provided by the manufacturer during the consultation process [34]. The operationalisation "discontinuation of at least one medicine", however, is not available for the other trials.

Regarding discontinuation of at least one medicine due to AE, there was no statistically significant difference between quadruplet and triplet without CD38 antibody in neither of the trials. The proportion of patients with discontinuation of at least one medicine with DaraR seems to be somewhat lower than in both arms of the CEPHEUS and IMROZ trials, indicating a possibly better tolerability. However, cross-trail comparisons should be interpreted with cautions.

Table 19: Discontinuation of at least one medicine due to AE

Trial	Intervention/ Comparison	Intensive therapy Proportion	Less intensive therapy Proportion	Notes
With or without CD38 antibody				
ALCYONE [8][a]	DaraVMP vs. VMP	13 per 100	11 per 100	n.s.
OCTANS [8][a]	DaraVMP vs. VMP	14 per 100	9 per 100	n.s.
CEPHEUS [10][b]	DaraVRd vs. VRd	44 per 100	48 per 100	n.s.
IMROZ [34][c]	IsaVRd vs. VRd	45 per 100	44 per 100	n.s.
Without bortezomib, dexamethasone-sparing				
IFM 2017-03 [23][d]	DaraR (this trial arm only)	n.a.	30 per 100	n.a.

[a]Table 15, final analysis. Median follow-up for ALCYONE is 34 months with the quadruplet and 13 months with the triplet; for OCTANS 35 months and 13 months, respectively (Table 10). ALCYONE: HR 0.81 (0.51; 1.29), OCTANS HR 1.38 (0.55; 3.51)
[b]Table 15. Median follow-up for quadruplet 56 months, for triplet 35 months (Table 10). HR 0.76 (0.54;1.07)
[c]p. 77, subpopulation "ASZT Nicht-Eignung gemäß EMA-Definition". HR 0.90 (0.65; 1.26)
[d]Median follow-up not reported.
n.s.: not significant; n.a.: not applicable

For discontinuation of all medicines due to AE, data is available from some of the trials (Table 20). In ALCYONE, the hazard ratio indicates that the time to event was significantly shorter with the quadruplet than with the triplet. However, median time to event was not reached in neither of both treatment arms. The proportion of patients who discontinued all medicines due to AE was not significantly different for quadruplet and triplet. This is probably due to the different lengths of follow-up in the trial arms. In the other trials except CEPHEUS, there was a no significant difference between quadruplet and triplet without CD38 antibody. For AMaRC 03-16, however, it is not reported if the differences are statistically significant. In CEPHEUS, the proportions were lower with the quadruplet, time to event, however, was not significantly different. In the IFM 2017-03, the proportion was in the same order of magnitude as in IMROZ and CEPHEUS.

Table 20: Discontinuation of all medicines due to AE

Trial	Intervention/ Comparison	Intensive therapy Proportion	Less intensive therapy Proportion	Notes
With or without CD38 antibody				
ALCYONE [11][a]	DaraVMP vs. VMP	9 per 100	9 per 100	HR 0.48 (0.26; 0.86) RR 0.96 (0.61; 1.53)
OCTANS [11][a]	DaraVMP vs. VMP	4 per 100	6 per 100	n.s. RR 0.71 (0.20; 2.60)
CEPHEUS [12][b]	DaraVRd vs. VRd	8 per 100 n.r.	19 per 100 n.r.	RR 0.40 (0.21; 0.78) HR 0.76 (0.54; 1.07)
IMROZ [13][c]	IsaVRd vs. VRd	23 per 100	27 per 100	n.s. HR 0.73 (0.47; 1.13)
AMaRC 03-16 [20][d]	DaraVCd vs. VCd	3 per 100	7 per 100	not reported

Without bortezomib, dexamethasone-sparing				
IFM 2017-03 [23][e]	DaraR (this trial arm only)	n.a.	18 per 100	n.a.

[a]Table 4-109 (ALCYONE) and Table 4-110 (OCTANS). Median follow-up for ALCYONE is 34 months with the quadruplet and 13 months with the triplet; for OCTANS 35 months and 13 months, respectively. Median time to event not reached.
[b]Table 4-86. Median follow-up 56 month with quadruplet, 35 months with triplet.
[c]Table 4-62, subpopulation transplant-ineligible. Median follow-up 51 months with quadruplet and 29 months with triplet.
[d]Table 3, "permanent discontinuation" (not explicitly operationalised). Median follow-up not reported.
[e]Median follow-up for AE not reported.
n.s.: not significant; n.r. not reached. Effect sizes are reported as point estimate and 95% confidence interval.

Severe peripheral neuropathy

The outcome severe (CTCAE grade ≥ 3) peripheral neuropathy has been assessed for all trials comparing quadruplets with triplets (without CD38 antibody), except AMaRC 03-16 (Table 21).

In the BENEFIT trial, peripheral neuropathy is only reported as all grades or grade ≥ 2. Therefore, the results are not reported in the table, but separately: For both operationalisations, the incidence is higher with IsaVRd than with IsaRd (52 per 100 vs. 28 per 100 for all grades, 27 per 100 vs. 10 per 100 for grade ≥ 2). There is, however, no information on the statistical significance of the difference [22]. Whether neuropathy grade ≥ 3 is more frequent with the quadruplet than with the less intensive therapy cannot be reliably assessed from the available data.

Table 21: Severe peripheral neuropathy (CTCAE grade ≥ 3)

Trial	Intervention/ Comparison	Intensive therapy Proportion	Less intensive therapy Proportion	Notes
With or without CD38 antibody				
ALCYONE [8][a]	DaraVMP vs. VMP	3 per 100	5 per 100	n.s.
OCTANS [8][a]	DaraVMP vs. VMP	4 per 100	3 per 100	n.s.
CEPHEUS [10][b]	DaraVRd vs. VRd	13 per 100	11 per 100	n.s.
IMROZ [34][c]	IsaVRd vs. VRd	9 per 100	7 per 100	n.s.
AMaRC 03-16 [20][d]	DaraVCd vs. VCd	0 per 100	Not reported	Not reported

Without bortezomib				
MAIA [14][e]	DaraRd (this arm only)	n.a.	3 per 100	n.a.
Without bortezomib, dexamethasone-sparing				
IFM 2017-03 [23][f]	DaraR (this arm only)	n.a.	2 per 100	n.a.

[a]Table 15. Median follow-up for ALCYONE is 34 months with the quadruplet and 13 months with the triplet; for OCTANS 35 months and 13 months, respectively. ALCYONE: HR 0.55 (0.25; 1.19], OCTANS HR 1.09 (0.21; 5.66)
[b] Table 15. Median follow-up for quadruplet 56 months, for triplet 35 months (Table 10). HR 1.12 (0.57; 2.21)
[c]p. 79, subpopulation "ASZT-Nicht-Eignung gemäß EMA-Definition"; HR 1.19 (0.54; 2.60)
[d]Table 3, "permanent discontinuation" (not explicitly operationalised). Median follow-up not reported.
[e]Grade 3 or 4
[f]Median follow-up for AE not reported.
n.s.: not significant; n.a. not applicable

There is no significant difference between the quadruplets and the triplets without CD38 antibody in any of the trials.

In the MAIA trial, peripheral sensory neuropathy grade 3 or 4 occurred in 3 per 100 patients with DaraRd [14]. In IFM 2017-03 trial, peripheral neuropathy of at least grade 3 was noted for 2 per 100 of the patients [23].

Given the slightly different operationalisations, this might be a similar order of magnitude as with IsaRd. It might be reasonable to assume that peripheral neuropathy occurs more often with a quadruplet containing bortezomib than with a triplet without bortezomib. However, if this also applies to severe neuropathy, cannot be reliably assessed from the available data.

Severe infections

The proportion of patients with severe infections (CTCAE grade ≥ 3) are reported in all trials comparing a quadruplet and a triplet without CD38 antibody except AMaRC 03-16 and OCTANS (Table 22).

In BENEFIT, infections are only reported as all grades or grade ≥ 2. Infections grade ≥ 2 affected 71 per 100 patients with IsaVRd and 68 per 100 patients with IsaRd (sum of infections of the respiratory system and infections of other types). It is unknown if the difference is statistically different and if this would also apply to infections grade ≥ 3 [22].

In the MAIA trial, there is no summary statistics for infections. However, grade 3 or 4 bronchitis or pneumonia affected about 23 per 100 patients with DaraRd [14]. Also due to

the differences in operationalisation, these results cannot easily be compared to the trials involving a quadruplet.

For most trials, there is no statistically significant difference between the quadruplet and the triplet without CD38 antibody. In ALCYONE, however, with the quadruplet 16 per 100 patients more experienced severe infections than with the triplet. The difference is statistically significant. Although nominally not statistically significant, the relative risk reported in the CEPHEUS trial is compatible with an increased risk.

In the IFM 2017-03 trial, the infection risk with DaraR is seemingly lower than in both arms of IMROZ and CEPHEUS and in the same order of magnitude as in the triplet arm of the ALCYONE trial. As there is lack of information regarding the comparability of median follow-up, these data cannot be easily interpreted.

The risk of infection in the trial arms with less intensive therapy was seemingly lower in ALCYONE as in CEPHEUS and IMROZ. This might be at least partially attributable to lenalidomide which was part of combination therapy in CEPHEUS and IMROZ, but not in ALCYONE. As all of the relevant options of less intensive therapy contain lenalidomide and two of them also an CD38 antibody, it is questionable if there is a significantly increased risk of severe infections when comparing intensive and less intensive therapy.

Table 22: Severe infections (CTCAE grade ≥ 3)

Trial	Intervention/ Comparison	Intensive therapy Proportion	Less intensive therapy Proportion	Notes
With or without CD38 antibody				
ALCYONE [8] [a]	DaraVMP vs. VMP	31 per 100	15 per 100	Difference 16 per 100
OCTANS [8] [a]	DaraVMP vs. VMP	Not reported	Not reported	Not reported
CEPHEUS [12][b]	DaraVRd vs. VRd	40 per 100	32 per 100	n.s.
IMROZ[c] [13]	IsaVRd vs. VRd	44 per 100	40 per 100	n.s.
AMaRC 03-16 [20]	DaraVCd vs. VCd	Not reported	Not reported	Not reported
Without bortezomib, dexamethasone-sparing				
IFM 2017-03 [23][d]	DaraR (this arm only)	n.a.	20 per 100	n.a.

[a]Table 15. Median follow-up for ALCYONE is 34 months with the quadruplet and 13 months with the triplet; for OCTANS 35 months and 13 months, respectively. ALCYONE: HR 1.43 (1.002; 2.04)
[b]Table 4-88. Median follow-up 56 month with quadruplet, 35 months with triplet. RR 1.25 (0.91; 1.72), HR 1.10 (0.74; 1.64)
[c]Table 4-66. Median follow-up 51 months with the quadruplet and 29 months with the triplet. HR 0.93 (0.66; 1.31)
[d] Table 3, sums of grades 3-5: Median follow-up for AE not reported.
n.s.: not significant; n.a. not applicable; RR: relative risk,;HR: hazard ratio. Effect sizes are reported as point estimate and 95% confidence interval.

Besides severe infections, patients might also be interested in differences in the risk of infection of any grade. Direct comparisons are only available for quadruplets vs. their corresponding triplet without a CD 38 antibody. In the CEPHEUS trial, infections of any grade occurred in 93.1 % vs. 84.5 % (Table 4-87) [12], in the IMROZ trial 91.3 % vs. 86.0 % (Table 4-64) [13]. However, the difference is statistically significant only in the CEPHEUS trial.

Other adverse events

Infusion-/injection-related reactions occur almost exclusively with the quadruplets, not with the triplets without CD38 antibody, and are mitigated by pre- and post-medication. For DaraVMP, infusion-related reactions of any grade were reported for 29 per 100 patients [17]. In CEPHEUS, daratumumab was given by subcutaneous injection and the reactions affected less participants (4 per 100) [12]. For IsaVRd, infusion-related reactions of any grade were reported for 24 per 100 patients [21]. The IQWiG reports, however, considered the operationalisation of the data for DaraVMP and IsaVRd not suitable for the early benefit assessment [8,9].

For the trials MAIA [14], BENEFIT [22] and IFM 2017-03 [23], infusion-related reactions are not reported.

The IQWiG report for DaraVMP states more harm for the quadruplet in comparison to the respective triplet in terms of severe hypertension as well as severe cough, dyspnoea and bronchospasm [8,11]. For IsaVRd, the IQWiG report states a benefit for the quadruplet in comparison to the respective triplet in terms of severe metabolic diseases and severe thoracic diseases which are, however, not defined in detail [9]. For DaraVRd, no significant differences were found between quadruplet and triplet in terms of specific severe side effects [10].

Summary

For adverse events of any grade, there are some indications from the trials that more intensive therapy leads to more adverse events. However, there were no consistent indications that serious and severe adverse events, discontinuation of therapy due to adverse events (one or all medicines) and severe peripheral neuropathy or infections happened more often with intensive therapy as with the less intensive therapy. Severe

infections happened more often with the quadruplet, however, only in ALCYONE the difference is statistically significant.

Infusion-/injection-related reactions basically only occur with combinations which contain a CD38 antibody. This applies to both intensive and less intensive therapy options. The exact frequency, however, depends on the mode of application (injection or infusion) and can be mitigated by pre- and post-medication.

For adverse events overall, the certainty of the evidence is rated as very low (Table 23).

Table 23: GRADE rating for outcome: adverse events

Aspect	Downgrading	Certainty	Notes
Study type		High	RCT
ROB	↓		See Appendix 2
Imprecision	↓		Most confidence intervals include both benefit and harm.
Indirectness	-1		Many comparisons rely on indirect evidence
Inconsistency	n.a.		Not enough data to assess inconsistency
Publication bias	n.a.		No concerns
Overall	↓↓↓	**Very low**	

Conclusion for the decision aid

- With the quadruplets, infusion-/injection-related reactions are possible which can be mitigated by pre-/post-medication. In the trials, they affected between 4 per 100 (daratumumab by injection) and 24 per 100 (isatuximab by infusion) to 29 per 100 (daratumumab by infusion) patients.
- Most common side effects can be reported qualitatively according to Table 16.
- There might be no difference between intensive and less intensive therapy for serious or severe adverse effects or discontinuation of therapy due to adverse events.
- There are some indications that infections are more frequent with quadruplets than with triplets without a CD38 antibody. For severe infections, the differences are only statistically significant for DaraVMP, not for other quadruplets.

- There are some indications that neuropathy is less frequent in combinations without bortezomib compared to combinations with bortezomib. However, it is unclear if this also applies to severe peripheral neuropathy.
- Overall, for most AE outcomes there are only little comparable data due to different operationalisations and reporting in the trials.
- The certainty of the evidence for all comparisons for AE outcomes is very low (Table 23).
- In the face of the uncertainty, the decision aid should not communicate effect estimates.

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

Treatment (supportive therapy and/or myeloma-specific medicines) can improve some symptoms as pain within a few months or even earlier. Other symptoms, however, may take more time to resolve or only few people experience improvement. The treatments can also delay worsening of symptoms due to progressive disease (see FAQ 2).

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?

Both treatment options require 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, 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.

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 [31].

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 [31].

Due to the disease and the treatment, especially with the quadruplets, there is a high risk of infection. Patients should discuss with their doctor if prophylactic medication is required and which other measures they should take to prevent infections.

DISCUSSION

Summary of main findings

This evidence report compares therapy options for the first-line treatment of multiple myeloma in patients for whom ASCT is not suitable. Intensive treatment options include

quadruplets (mainly DaraVRd and IsaVRd, in special situations DaraVMP and DaraVCd). Less intensive treatment options comprise DaraRd, VCd and DaraR.

There are some indications that intensive therapy might be more effective than less intensive therapy in terms of overall survival and disease progression. Also, patients might benefit more from intensive therapy for some symptoms and some domains of HrQoL.

In the trials, there were no consistent indications that serious and severe adverse events, discontinuation of therapy due to adverse events (one or all medicines) and severe peripheral neuropathy or infections happened more often with intensive therapy as with the less intensive therapy. Infusion-/injection-related reactions are specific to combinations with a CD38 antibody only. However, the certainty of the evidence is rated as very low for all outcomes.

STRENGTH, LIMITATIONS AND UNCERTAINTIES

One strength of this report is the comprehensive evidence base: The report relies on eight randomised controlled trials which tested relevant drug combinations. For some of these trials, not only the journal publications but also additional data from IQWiG reports and AMNOG dossiers were used. This allowed to discuss several operationalisations for the outcomes progression, symptoms and HrQoL.

However, there are also some limitations of the available data:

- Direct evidence is only available for the comparisons of quadruplets to triplets without a CD 38 antibody and to a triplet without bortezomib. There is only indirect evidence to compare DaraRd and DaraR to the respective quadruplet (DaraVRd).
- Except for the comparison DaraVMP vs. VMP, only one trial is available for each quadruplet combination. There are no direct comparisons between quadruplets with daratumumab and quadruplets with isatuximab. Therefore, it is not possible to reliably assess if one of the antibodies shows more benefit than the other. It should be noted that for the target group of the decision aid, more data is available for quadruplets with daratumumab.
- For some outcomes, not all trials report data, not in sufficient depth or not in the operationalisation which would be necessary to make cross-trial comparisons.
- In many trials, data for overall survival is immature. This also applies to progression-related data in some trials. This limits our ability to draw definite conclusions.
- Most conclusions rely on evidence from direct comparisons. Triangulation of the evidence across trials was limited due to differences in operationalisation of outcomes and/or differences in follow-up. Even when triangulation was possible, the comparisons were limited due to differences in populations. Therefore, we are uncertain if the conclusions refer to all options of less intensive therapy in the same way.

- As a consequence, we could not reliably assess how much trade-off in efficacy there would be when opting for a less intensive therapy. Especially for DaraRd, based on a rather long median PFS in the MAIA trial, there is not enough evidence available to assess whether the treatment is really inferior to the quadruplets.
- There was considerable inconsistency in benefit of intensive therapy in terms of symptoms and domains of HrQoL. The cause of this heterogeneity cannot be explored with the available data.
- Although we found no convincing evidence that serious and severe adverse events (including peripheral neuropathy and infections) are more common with intensive than with less intensive therapy, we cannot rule out that there might be differences. It should be noted that the evidence for these outcomes is quite scarce and most data from the indirect comparisons is not easily interpretable.
- For most outcomes and comparisons, the risk of bias was assessed as high and the certainty of the evidence as very low. Besides risk of bias, mainly indirectness and inconsistency or imprecision contributed to this rating.
- In current guidelines, continuous therapy is recommended after induction therapy until disease progression or unacceptable toxicity. For the triplets without a CD38 antibody, this has been only realised in some, but not all trials. This is especially relevant for some outcomes as time on treatment varies between the treatment arms and patients were only followed for a certain period after treatment discontinuation, leading possibly to informative censoring. However, as more events might accumulate for both desirable and undesirable outcomes with the quadruplet than with the triplet, the respective biases might cancel each other out in the overall assessment.

Comparison with the results of early benefit assessments

In the early benefit assessments, the quadruplets DaraVMP, DaraVRd and IsaVRd have been compared to their respective triplets without a CD38 antibody (VMP and VRd, respectively). There are no assessments which compare DaraRd and DaraR to a quadruplet.

For DaraVMP, the IQWiG acknowledged an indication of a non-quantifiable added benefit [8], whereas the G-BA rated the evidence as a hint of a considerable added benefit. For IsaVRd, both institutions acknowledged an indication of a minor added benefit [9]. For DaraVRd, so far only the IQWiG report is published which does not acknowledge an added benefit [10].

The effect size for overall survival has been assessed as considerable for daratumumab in the early benefit assessment by G-BA. However, due to study limitations, the IQWiG report acknowledges only a non-quantifiable effect [8]. As survival data is not mature in the IMROZ trial, the survival benefit has not been shown for IsaVRd so far [9]. The same applies to

DaraVRd [10]. The rating in this evidence report (GRADE very low for a benefit in terms of overall survival) assumes that the survival benefit will show once more data for the other quadruplets has accrued. This is, however, an optimistic assumption.

In the early benefit assessments, benefits in terms of symptoms and HrQoL contribute to an overall acknowledgement of benefit for DaraVMP and IsaVRd. For DaraVRd, however, no benefits in these categories are acknowledged. The rating in this evidence report (GRADE very low for a benefit in terms of symptoms and HrQoL) corresponds to the ratings by IQWiG/G-BA for DaraVMP and IsaVRd. For DaraVRd, the IQWiG rating relies on the assessment that obstipation is a minor symptom and the statistically significant benefit of DaraVRd is therefore negligible. The same effect size would be considered to be more important (minor) if the symptom is severe, then contributing to an added benefit as it is the case for DaraVMP and IsaVRd. If obstipation is really only a minor symptom for patients, is, however, debatable. This evidence report therefore acknowledges this uncertainty and extends the rating also to DaraVRd.

In terms of adverse events, the early benefit assessments report more harm (more severe infections) for DaraVMP only. For IsaVRd, less harm is reported in two specific categories of severe adverse events, whereas there is no difference for DaraVRd. The ratings in this evidence report (GRADE very low for no difference in all adverse event categories) takes into account that for the most commonly used quadruplets, DaraVRd and IsaVRd, there is no evidence for more severe harm.

It should be noted that the IQWiG reports do not consider progression as a patient-relevant outcome as it is not necessarily linked with patients' experience. The G-BA ratings, however, point out that there is no agreement about the patient relevance of this outcome. Progression has been added as an item in this evidence report due to input from experts and because this topic emerged in needs assessments (evaluations of qualitative literature). Although easily interpretable data on progression is scarce, the overall evidence indicates that the quadruplets might delay progression better than the triplets without a CD38 antibody.

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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	28.08.2025	myeloma	Filters: 2021-2025; status: published	1
Website International Myeloma Working Group (IMWG) https://www.myeloma.org/imwg-publications	28.08.2025	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	28.08.2025	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	28.08.2025	n.a. (hand-searching)	Excluded: Guidelines for relapsed/refractory multiple myeloma only	1

Full text screening

Published by	Year	Link	Suitable for data extraction?[a]	Decision
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/	28.08.2025	myeloma	2021-2025	73; included for full-text screening: 10 (reasons for exclusion see RIS file)

Full-text screening

Published by	Year	Link	Suitable for PICO?	Suitable for data extraction?	Decision
CADTH	2024	https://www.cda-amc.ca/sites/default/files/DRR/2024/TR0014-MM-ESHPM-Combined-Report.pdf	Yes	No, NMA for all sorts of combinations (also duplet therapy), data for our comparisons not readily available	Excluded
NICE	2023	https://www.nice.org.uk/guidance/ta917	No, Dara-Rd vs. Rd only	N.a., data heavily redacted	Excluded
ACE	2022	https://www.ace-hta.gov.sg/healthcare-professionals/ace-technology-guidances/details/daratumumab-based-regimens-for-newly-diagnosed-multiple-myeloma	Partially	No, evidence search and detailed data not reported	Excluded
IQWiG	2025	https://www.iqwig.de/projekte/a25-20.html	Yes	Yes, for IsaVRd vs. VRd Search up to 04.12.2024 Included trials: IMROZ, Data cut-off 26.09.2023 No data on progression	Included
IQWiG	2023	https://www.iqwig.de/projekte/a23-127.html	Yes	Yes, for DaraVMP vs. VMP	Included

				Search up to 04.09.2023 Included trials: ALCYONE/OCTANS Data cut-off 31.05.2023 (both trials) No data on progression	
IQWiG	2022	https://www.iqwig.de/projekte/a22-40.html	No, relapsed myeloma	n.a.	Excluded
IQWiG	2022	https://www.iqwig.de/projekte/a22-27.html	No, addendum to A21-170 (relapsed myeloma)	n.a.	Excluded
IQWiG	2021	https://www.iqwig.de/projekte/a21-170.html	No, relapsed myeloma	n.a.	Excluded
IQWiG	2021	https://www.iqwig.de/projekte/a21-126.html	No, DaraRd vs. Rd	n.a.	Excluded (no recent data cut-off)
IQWiG	2021	https://www.iqwig.de/projekte/a21-101.html	No, relapsed myeloma	n.a.	Excluded

Search strategy for RCTs

PubMed 01.09.2025

#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: #1 OR #2

#4: "relapse*"[Title] OR "refract*"[Title]

#5: #3 NOT #4

#6: "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]

#7: #5 AND #6

#8: "randomized controlled trial"[Publication Type] OR ("random*"[Title/Abstract] AND "controlled"[Title/Abstract] AND "trial"[Title/Abstract])

#9: #7 AND #8

Filter: 2023-2025

CENTRAL 01.09.2025

#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*):ti

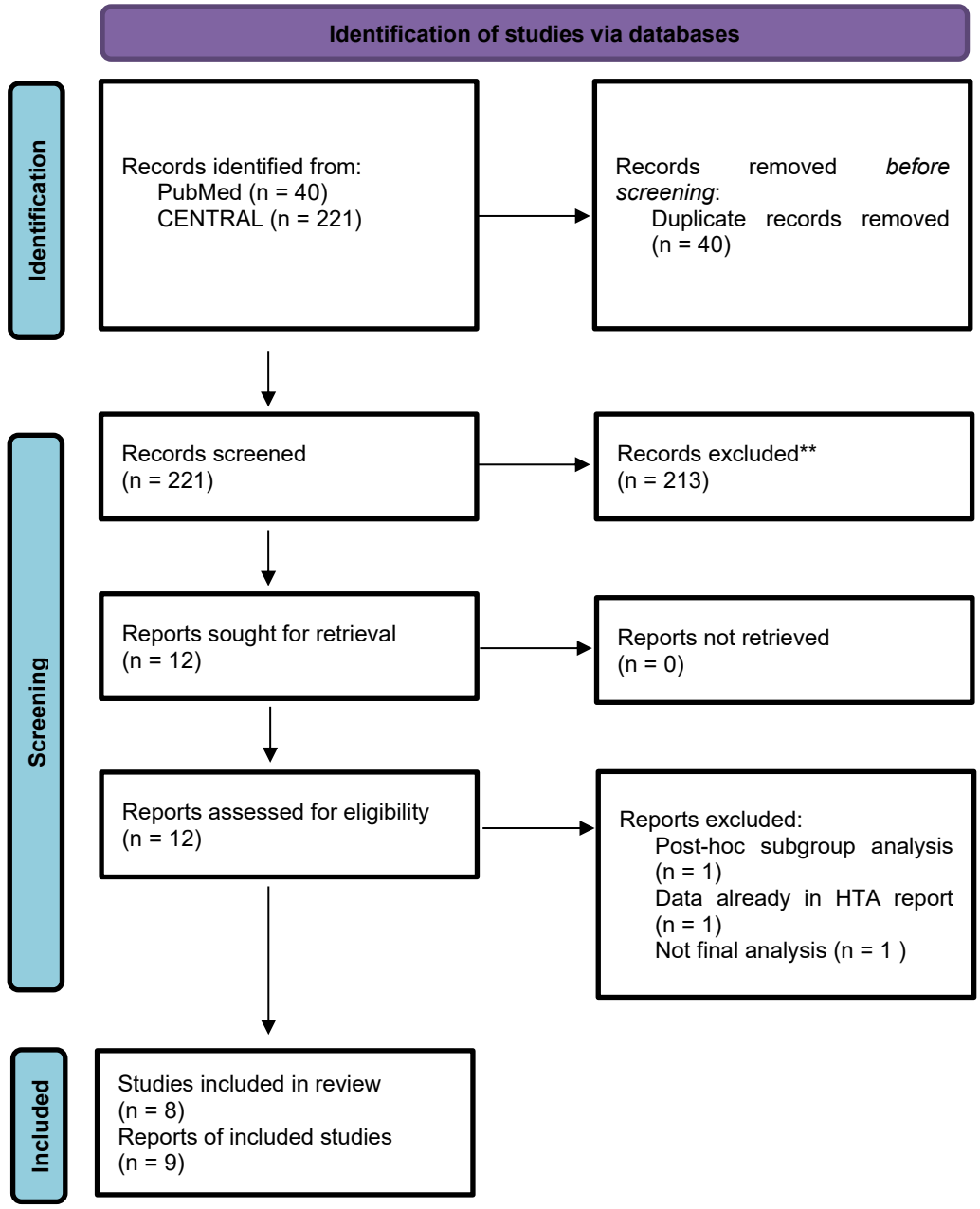
#8: #6 NOT #7

#9: (daratumumab* OR darzalex* OR isatuximab* OR sarclisa OR CD38 OR anti-CD38 OR “CD 38” OR quadruple*):ti,ab

#10: #8 AND #9

Filter: Trials 2023-2025

Retrieval



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

Full-text screening

Reference	Included	Reasons
Usmani 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC12003169/	Included	CEPHEUS DaraVRd vs. VRd
Mollee 2024 https://pmc.ncbi.nlm.nih.gov/articles/PMC11296246/	Included	AMaRC 03-16 DaraVCd vs. VCd
Facon 2024 https://www.nejm.org/doi/10.1056/NEJMoa2400712	Included	IMROZ IsaVRd vs. VRd For data on progression
Manier 2025 https://haematologica.org/article/view/11994	Excluded	IMROZ post-hoc subgroup analysis for frailty
Fu 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC12141397/	Excluded	OCTANS HrQoL data; already included in IQWiG 2023
Fu 2024 https://pmc.ncbi.nlm.nih.gov/articles/PMC11868237/	Included	OCTANS DaraVMP vs. VMP For data on progression
Fu 2023 https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(23)00073-3/fulltext	Excluded	OCTANS not final analysis
Mateos 2025 https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(25)00018-X/fulltext	Included	ALCYONE For data on progression
Facon 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC11976258/	Included	MAIA final analysis
Perrot 2025 https://pmc.ncbi.nlm.nih.gov/articles/PMC11976685/	Included	MAIA final analysis HrQoL
Leleu 2024 https://pmc.ncbi.nlm.nih.gov/articles/PMC11333283/	Included, IsaVRd vs. IsaRd (as proxy for the comparison DaraVRd vs. DaraRd)	BENEFIT
Manier 2025 https://papers.ssrn.com/sol3/papers.cfm?abstract_id=5201850	Preprint, therefore excluded, but substituted by full journal publication via handsearching	IFM2017-03

APPENDIX 2: RISK OF BIAS ASSESSMENTS

Trial	Overall survival	Progression	PRO: symptoms, quality of life	Adverse events
CEPHEUS[a]	High	High	High	High
IMROZ	Low [9]	Low[b]	High [9]	High [9]
ALCYONE	High [8][a]	High[c]	High [8]	High [8]
AMaRC 3-16[d]	High	High	n.a.	High
BENEFIT[e]	High	High	n.a.	High
MAIA	Low [16]	Low[f]	High [[16]]	High/Low [[16]]
IFM 2017-03[g]	High	High	High	High

Risk of bias assessments are adopted from published reports if a reference is given, otherwise based on own assessments.

[a]Risk of bias is high for progression, symptoms, quality of life and adverse events mainly due to unblinded outcome assessment. For the comparison DaraVMP vs. VMP, the IQWiG report assessed risk of bias as high for overall survival due to suboptimal therapy in the control group in case of progression. However, in the final assessment of the Federal Joint Committee, therapy has been rated as adequate according to guideline recommendations at the time of the treatment decisions. As of today, other treatment combinations are available which might prolong survival, therefore the IQWiG rating is adopted. As the situation is the same in the CEPHEUS trial, the assessment also applies to the comparison DaraVRd vs. VRd.

[b]Progression has been assessed by a committee unaware of the assigned treatment.

[c]Risk of bias is high for progression due to unblinded outcome assessment (some judgment is involved)

[d]Risk of bias is high for all outcomes mainly due to unclear concealment of allocation and high proportion of missing outcome data. Risk of bias for progression, patient-reported outcomes and adverse events is also high due to unblinded outcome assessment.

e Risk of bias is high for all outcomes mainly due to unclear concealment of allocation. For progression and most adverse events, also high due unblinded outcome assessments.

f Progression has been assessed by a computer algorithm validated by an independent review committee.

gRisk of bias is high for overall survival due to inadequate subsequent therapy. For the other outcomes, risk of bias is mainly high due to unblinded outcome assessments.

n.a. applicable. PRO: patient-reported outcomes