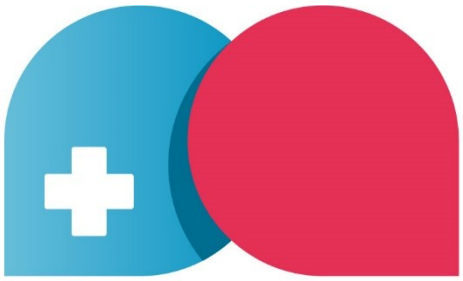
Evidence report

Relapsed/refractory multiple myeloma

Which treatment?

Version 1



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CONTENTS

LIST OF ABBREVIATIONS

ADC: Antibody drug conjugate
ASCO: American Society of Clinical Oncology
ASCT: Autologous stem-cell transplantation
BCMA: B-Cell Maturation Antigen
Bela: Belantamab mafodotin
CAR-T: Chimeric Antigen Receptor T-cell therapy
Cilta-cel: Ciltacabtagene autoleucel
d: Dexamethasone
DA: Decision aid
Dara: Daratumumab
EHA: European Hematology Association
Elo: Elotuzumab
Elra: Elranatamab
EMA: European Medicines Agency
EMN: European Myeloma Network
FAQs: Frequently asked questions
GPRC5D: G-Protein Coupled Receptor Family C Group 5 Member D
HTA: Health technology assessment
IMF: International Myeloma Foundation
IMiD: Immunomodulatory drug
IMWG: International Myeloma Working Group
Isa: Isatuximab
Ixa: Ixazomib
K: Carfilzomib
Linvo: Linvoseltamab
MGUS: Monoclonal gammopathy of undetermined significance
MM: Multiple myeloma
MRD: Minimal residual disease
NMA: Network meta-analysis
OS: Overall survival
P: Pomalidomide
PFS: Progression-free survival
PICOS: Participants, intervention, comparators, outcomes, and study design
PRESS: Peer Review of Electronic Search Strategies Checklist
R: Lenalidomide
RCT: Randomised controlled trial
RRMM: Relapsed/refractory multiple myeloma
SAE: Serious adverse events
SDM: Shared decision-making
Sel: Selinexor
SLAMF7: Signalling Lymphocyte Activation Molecule F7
SMM: Smouldering Multiple Myeloma
Tal: Talquetamab
TCRT: T-cell redirecting therapies
Tec: Teclistamab
V: Bortezomib
XPO1: Exportin 1

PROJECT OBJECTIVES

A key aim is to inform patients with relapsed/refractory multiple myeloma (RRMM) on the different therapy options as part of shared decision-making (SDM). This evidence report is prepared to form the scientific basis for an online decision aid (DA). The report was developed in cooperation with clinical experts from two German university medical centres and patient representatives from patient organizations.

Due to the fast-evolving field of multiple myeloma (MM) treatments, the DA and this evidence report are intended to be living documents. Updates are planned in case of clinically relevant changes, e.g. in the availability of treatment options or new evidence affecting the d decision-making process. The DA will be modular; thus, the evidence is presented accordingly.

INTRODUCTION TO THE DISEASE

MM is a type of blood cancer. It affects the plasma cells in the bone marrow which proliferate in an uncontrolled manner, producing unfunctional antibodies, called M-proteins or paraproteins. Before developing active MM, patients might be diagnosed with the precursor condition Smouldering Multiple Myeloma (SMM) and/or before with monoclonal gammopathy of undetermined significance (MGUS).

In MM, the functions of the haematopoietic system and the immune system are compromised, also organ damage can occur, especially in the kidneys, and bone stability decreases. Patients typically experience fatigue, bone pain, sometimes with complications like fractures and nerve compression, frequent infections, anaemia and decrease of renal function. Hypèrcalcaemia may occur as well.

So far, it is usually not possible to heal the disease. However, long-term remission occurs more frequently with newer treatments than in previous decades. Nevertheless, even with effective treatments in the first line of therapy, MM may relapse, also several times, and become non-responsive (refractory) to certain treatments. Refractory myeloma is defined as disease that is nonresponsive (failure to achieve minimal response) while on primary or salvage therapy or progresses within 60 days of last therapy. Myeloma can relapse without being refractory, can be relapsed and refractory or be primary refractory [1]. In any line of therapy, the aim of the treatment is to suppress the course of the disease, to extend life expectancy, to decrease symptoms and to preserve or even increase quality of life [2].

THE DECISION PROBLEM

The decision which treatment to choose in RRMM, depends on several aspects: From a medical point of view, the patient's age and comorbidities as well as treatment urgency and early or late relapse have to be taken into account. The choice is also influenced by which previous therapies the patient has already received and the marketing authorisation of the medicines. From the patients' point of view, the available treatments differ in efficacy, treatment burden and specific toxicity.

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

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

The DA addresses patients with RRMM. For patients with newly diagnosed MM or SMM, separate DA are available. The included interventions rely on current guideline recommendations [2,3] as well as marketing authorisations in the EU and availability in Germany.

Therefore, only Ciltacabtagene autoleucel (Cilta-cel) has been included as CAR-T cell therapy as Idecabtagene vicleucel is not available in Germany for the time being. Also, doublets have been excluded as they are not recommended as preferred therapy in current guidelines.

Table 1: Inclusion criteria

	Included	Excluded
Population	Patients with RRMM and at least one previous treatment	Newly diagnosed MM, SMM, MGUS
Intervention / Comparator */**	ADC-based triplets Other triplets CAR-T Bispecific antibodies First ASCT	Second ASCT Medicines which are not recommended, authorised or available
Outcomes	Overall survival, progression/PFS, symptoms and quality of life, adverse events	Other outcomes as MRD negativity or complete response
Study design	RCTs only. Publication type: Stepwise approach 1) evidence-based guidelines 2) HTA or systematic reviews 3) Single study journal publication	Other study designs

* According to marketing authorisation and availability in Germany (as of 15.07.2026, anticipating the marketing authorisation of TecDara in the 2nd line of therapy based on the positive CHMP opinion on 25.06.2026).
** At the time of the preparation of this evidence report, it has not been finally decided, if the decision aid presents ADC-based triplets separately or as part of all triplets.

ADC: antibody drug conjugate, ASCT: autologous stem-cell transplantation, CAR-T: Chimeric Antigen Receptor T-cell therapy, HTA: Health technology assessment; MGUS: monoclonal gammopathy of undetermined significance, MM: multiple myeloma, MRD: minimal residual disease, PFS: progression-free survival, RCT: randomised controlled trial, RRMM: relapsed/refractory multiple myeloma, SMM: smouldering multiple myeloma

Frequently asked questions

The following FAQs were identified:

- FAQ 1: What does the treatment involve?
- FAQ 2: Will I live longer?
- FAQ 3: Will the treatment delay progression of the disease?
- FAQ 4: How long will the treatment affect symptoms and my quality of life?
- FAQ 5: What are the risks or side effects?

Literature searches

For FAQ 1 and qualitative information on risks and adverse events, the summary of product characteristics for the relevant medicines as well as additional information by relevant medical societies and patient information were used. The sources were identified by handsearching the websites of the European Medicines Agency (EMA), the International Myeloma Working Group (IMWG), Myeloma UK and the International Myeloma Foundation (IMF).

The literature search for quantitative data informing FAQ 2 to FAQ 5 focussed on RCTs. We followed a stepwise approach 1) search for evidence-based guidelines

which are suitable for data extraction 2) health technology assessment (HTA) reports and systematic reviews 3) single study journal publications.

As the treatment of RRMM is a fast-evolving field, only very recent guidelines (2025-2026) were included. Guidelines were identified by hand searching the websites of relevant organisations.

As a high-quality evidence-based guideline was identified, no HTA reports and systematic reviews were sought. Additionally to the data in the guideline, we retrieved the journal publications for the trials included in the guideline via its list of references and cross-checked with the publications listed in clinicaltrials.gov which are automatically linked via the NCT identifier.

Additionally, we searched for newer RCTs not yet included in the guideline. If the drugs did not (yet) have marketing authorisation in the EU, the trials were included as "studies awaiting classification" for the next update. We also set up alerts for automatic updates of searches (monthly).

Systematic search for newer RCT was conducted in PubMed only as preliminary searches showed that this database has a sufficient coverage for RRMM treatment trials. The broad search strategy of the guideline (independent from the line of therapy) has not been adopted as this evidence report focusses on RRMM only. With this focus, the search was limited to the title/abstract field (for population) and the title/abstract plus publication type field (for RCT). The inclusion of Medical Subject Headings has been omitted as a preliminary search showed that all relevant trial publications can be found with the search strategy as detailed above. For this search, publications were excluded if they reported only on non-relevant subpopulations (e.g. Japanese patients only) or not on results of phase 3 trials.

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.

Quality assurance within the search process

One reviewer (IH) developed the search strategy, a second reviewer (JP) checked the strategy according to the Peer Review of Electronic Search Strategies Checklist (PRESS) [4].

METHODS OF 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.

Methods of data extraction and interpretation

We used the evidence profiles in the ASCO guideline [3] as primary source for the data extraction. Where necessary, additional data were extracted from journal publications, supplemented, if necessary and available, by results in clinicaltrials.gov.

For each study, data were extracted by one reviewer (IH) and checked by another (JP). Any disagreements were resolved through discussion.

For the assessment of clinically meaningful differences between treatment effects, we used the non-adjusted European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale for Haematological Malignancy in the non-curative setting [5] as a guide. Under the assumption of treatment effects with standard treatments (i.e. other triplets) for overall survival of ≥ 36 months and for progression-free survival of ≥ 12 months, a difference of at least 10 % between a new intervention and a standard treatment has to be attained to reach an at least moderately clinically meaningful effect in the case of immature data (Grade 3 for overall survival and Grade 2 for progression-free survival). It should be noted, however, that the ESMO scale in the stricter sense can only be applied to comparisons from randomised controlled trials, involves not only thresholds for absolute differences, but also for relative effect measures (hazard ratio), and does not rely on point estimates, but on the confidence intervals. These data, however, are not available for most comparisons of interest. Therefore, we applied the threshold of at least 10 % also to other comparisons (e.g. cross-trial) to identify clinically meaningful differences between treatments, acknowledging the inherent uncertainty with this approach.

Methods for appraising risk of bias and certainty of the evidence

Sufficient quality of guidelines for data extraction was assumed if details of a systematic search strategy were described (databases searched, search terms, search period), the inclusion and exclusion criteria were defined and the process described transparently, there was a formal risk of bias assessment with a suitable instrument and the certainty of the evidence was rated via GRADE.

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.

Certainty of 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 [6].

The certainty of the evidence is rated as follows:

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

Where evidence-based guidelines, systematic reviews or HTA reports present GRADE assessments, we adopt the ratings for the evidence report.

RESULTS

Literature searches and inclusion assessment

The handsearching of relevant guideline organisations retrieved two myeloma guidelines which could inform PICOS: the European Hematology Association (EHA)-European Myeloma Network (EMN) guideline (2025) [2] and the American Society of Clinical Oncology (ASCO) guideline Version 2026.1.1 [3]. However, only the ASCO guideline was suitable for data extraction.

As the literature search for the ASCO guideline was up to 27.02.2026, we ran a focussed search for newer RCTs on 16.06.2026 and retrieved three further publications [7–9]. However, as all of the medicines do not have marketing authorisation in the EU yet, we deferred the assessment and data extraction of these trials for the next update. We ran another update on 01.07.2026 which retrieved no relevant trials. During the preparation of the evidence report, an update of the ASCO guideline (2026.1.2, systematic review up to 30.04.2026) became available. However, none of the few changes were relevant for the evidence report.

Therefore, the included evidence for this version of the evidence report corresponds to the trials represented in the ASCO guideline 2026.1.1. For some details and outcomes, we supplemented the data in the guideline by the respective journal publications of the trials during data extraction. All details for searches and inclusion are described in the Appendix.

Risk of bias assessment

The assessment of the ASCO guideline showed sufficient quality and suitability for data extraction (see Appendix).

We adopted GRADE ratings where available in the summary of findings tables which included ratings on study-specific (e.g. randomisation, concealment of allocation) as well as outcome-specific items (e.g. blinding). There was, however, no GRADE assessment available for the patient-reported outcomes (PRO)

symptoms and quality of life. For these outcomes, we used additional information from the journal publications (see Appendix).

Overview of the evidence

Overview of the sources

The ASCO guideline "Treatment of Multiple Myeloma" [3] is designed as a living guideline. The version included in this evidence report is 2026.1.1, the literature search is up to date to 27.02.2026. We did not find newer trials which are relevant for this version of the evidence report.

The guideline relies on a systematic search and assessment of the literature. Details of the search as well as evidence profiles and evidence tables (including GRADE assessments) can be found in the data supplement. Therefore, the guideline is the primary source for this evidence report, supplemented by data from the journal publication of trials where necessary. This is indicated in the respective sections of the evidence report.

The guideline gives recommendations for SMM, first-line treatment of MM as well as the treatment of RRMM. The latter is the focus of this evidence report.

Overview of the trials

The guideline reports on several trials which are relevant for this evidence report. However, comparative data are only available for few treatments of interest.

Comparative data are available for CAR-T cell therapy (Cilta-cel) vs other triplets, ADC-based triplets vs other triplets and the TecDara combination of the bispecific antibody teclistamab with the CD38 antibody daratumumab. It should be noted that these comparisons are only available for selected other triplets: Cilta-cel vs DaraPd or VPd (at the physicians' discretion), BelaPd vs VPd, BelaVd vs DaraVd and TecDara vs DaraPd or DaraVd (at the physicians' discretion).

The majority of other triplets have only been tested against doublets (which are no longer standard of therapy), but not against other triplets or other therapy options. Most comparisons have been tested only in one trial with the exception of DaraVd vs Vd for which two trials are available.

A graphical overview of the comparative trials can be found in Figure 1.

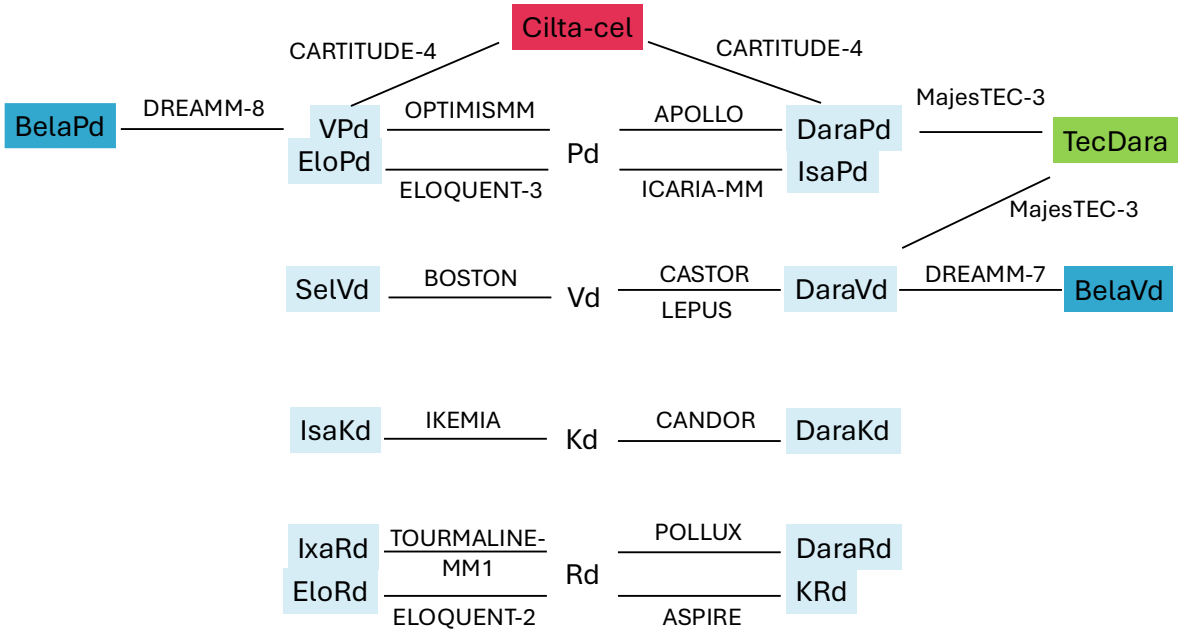

Figure 1: Graphical overview of the relevant comparative trials. Included are ADC-based triplets (blue), other triplets (light blue), CAR-T (red) and the combination of the bispecific antibody teclistamab and the CD38 antibody daratumumab (green). For bispecific antibodies as monotherapy (4th line of therapy) and ASCT (2nd line of therapy), no comparative trials are available.

For bispecific antibodies as monotherapy, only single arm trials are available and therefore no comparative evidence. The inclusion criteria for the trials were at least three previous lines of therapy, whereas for the majority of the trials for the other treatments, only one prior line of therapy was required. Therefore, patients in the trials with bispecific antibodies had on average more previous therapies and further advanced disease. This precludes comparison of efficacy data with other treatments.

There are no trials which explicitly evaluate ASCT as treatment option in the second line of therapy. In the trials IFM-2009 [10] and DETERMINATION [11], early vs delayed ASCT has been evaluated for first-line therapy and according to the protocol, ASCT was the recommended treatment in relapse. In IFM-2009, 79 % of patients in the delayed ASCT arm with subsequent therapy due to relapse received ASCT as second-line therapy. In DETERMINATION, however, only 13 % of patients with subsequent therapy received ASCT within the next line of therapy and only 28% received ASCT at any time following end of study treatment. The others received non-ASCT treatments. In both trials, second-line treatment was not randomised to ASCT or other options. In both trials first-line therapy was a triplet whereas nowadays, a quadruplet would be used which probably would affect overall survival (OS) as well as disease progression. Therefore, efficacy data from IFM-2009 and DETERMINATION cannot be applied to the decision problem.

Also data from first-line ASCT trials with quadruplet induction (PERSEUS [12] and GMMG-HD7 [13]) will not be applicable to second-line therapy: First, at least disease progression and possibly OS will be different for second-line patients; second, contemporary patients having typically received a quadruplet in the first line of therapy, will usually have other induction therapy. Additionally, for GMMG-HD7 only data from the first part of the trial (without maintenance therapy) are available. Therefore, no evidence is available for OS and disease progression on ASCT as second-line therapy.

For symptoms and quality of life, data from the ASCT trials as first-line therapy might not apply to second-line therapy, either, at least for the longer course of the disease. However, data from IFM-2009 and DETERMINATION comparing ASCT vs no ASCT might be applicable to symptoms and quality of life during and shortly after the treatment.

As the risks and side effects from ASCT might be similar in first- and second-line therapy, it might be possible to use harm data. It should be noted that induction therapy for ASCT as second-line therapy will probably be different to the first-line setting, depending on previous therapy and refractory status. In PERSEUS, induction therapy was VRd (triplet) and DaraVRd (quadruplet), respectively. Due to a lack of better data, we use the range of harm with these options as a surrogate for other induction options which might be used in clinical practice. As IFM-2009 and DETERMINATION share a common induction treatment arm with PERSEUS and are older trials, we only include the PERSEUS trial for convenience. As the ASCO guideline only reports the combined data from GRIFFIN (not relevant for this evidence report) and PERSEUS, we extracted the data from the journal publication [12].

Summary: As a consequence, there is only indirect evidence available for the majority of the comparisons. As the ASCO guideline [3] points out and Figure 1 illustrates, a network meta-analysis (NMA) would not be feasible because not all treatments are connected within the network. Additionally, it is debated if the assumption of transitivity/exchangeability (a prerequisite for NMA) holds for the RRMM trials as there are relevant differences in patient characteristics and hence potential effect modifiers between the trials [14]. Therefore, for most comparisons we can only communicate data from single treatment arms and discuss the resulting uncertainty. As the resulting DA is modular, the interpretation of the extracted data is presented in evidence matrices, separately for each outcome.

An overview of the available evidence (direct or indirect evidence) is shown in Table 2. Details on the trials can be found in Table 3.

Table 2: Overview of the available evidence

	ADC-based triplets	**Other triplets**	**CAR-T**	**Bispecific antibodies**	**ASCT**
ADC-based triplets					
Other triplets	*DREAMM-7* BelaVd vs DaraVd *DREAMM-8* BelaPd vs VPd Indirect evidence only for other comparisons				
CAR-T	Indirect evidence only	*CARTITUDE-4* Cilta-cel vs VPd or DaraPd Indirect evidence only for other comparisons			
Bispecific antibodies	Indirect evidence only [a]	*MajesTec-3* TecDara vs VPd or KD [a]	Indirect evidence only [a]		
	Indirect evidence only from single-arm trials [b]				
ASCT	No evidence for second-line therapy (efficacy), indirect evidence only for side effects				

ADC: antibody drug conjugate, ASCT: autologous stem-cell transplantation, CAR-T: Chimeric Antigen Receptor T-cell therapy
[a] 2nd line of therapy, only TecDara
[b] 4th line of therapy

Table 3: Details of the included trials

Trial Recruitment period	Comparison	Key eligibility criteria	n
ADC-based triplets			
DREAMM-7 [15–17] NCT04246047 2020–2021	BelaVd vs DaraVd	Relapsed or refractory, ≥ 1 prior treatment Excluded: prior BMCA-targeted therapy, CD38 refractory, refractory to V	494
DREAMM-8 [18,19] NCT04484623 2020–2022	BelaPd vs VPd	Relapsed or refractory, ≥ 1 prior treatment including R Excluded: Prior treatment with P, refractory to V, prior BMCA-targeted therapy	302
Other triplets			
APOLLO [20,21] NCT03180736 2017–2019	DaraPd vs Pd	Relapsed or refractory, ≥ 1 prior treatment including R and PI, progressive disease Excluded: Prior treatment with P or CD38 antibody	304
ASPIRE [22–24] NCT01080391 2010–2012	KRd vs Rd	Relapsed or refractory, 1 to 3 prior treatments Excluded: Progression on previous therapy with Rd	792
BOSTON [25] NCT03110562 2017–2019	SelVd vs Vd	Progression on or after most recent treatment; 1 to 3 prior treatments Excluded: prior exposure to Sel	402
CANDOR [26–30] NCT03158688 2017–2018	DaraKd vs Kd	Relapsed or refractory; 1 to 3 prior treatments; partial response to at least one treatment Excluded: Non-responsive to prior therapy	466
CASTOR [31,32] NCT02136134 2014–2015	DaraVd vs Vd	Relapsed or refractory; ≥ 1 prior treatment, partial response to at least one treatment Excluded: Refractory to PI	489
ELOQUENT-2 [33,34] NCT01239797 2011–2012	EloRd vs Rd	Relapsed or refractory, 1 to 3 prior treatments Limited number of patients with prior R treatment	646
ELOQUENT-3 [35,36] NCT02654132 2016–2017	EloPd vs Pd	Relapsed or refractory, ≥ 2 prior treatments including R and PI Excluded: Previous treatment with P	117
ICARIA-MM [37,38]	IsaPd vs Pd	Relapsed or refractory; ≥ 2 prior treatments; not responded to R and PI	307

Trial Recruitment period	Comparison	Key eligibility criteria	n
NCT02990338 2017–2018		Excluded: Refractory to CD38 antibody, previous treatment with P	
IKEMA [39–41] NCT03275285 2017–2019	IsaKd vs Kd	Relapsed or refractory; 1 to 3 prior treatments Excluded: Primary refractory, refractory to CD38 antibody, previous treatment with K	302
LEPUS [42,43] NCT03234972 2017–2019	DaraVd vs Vd	Relapsed or refractory; ≥1 prior treatment Excluded: Refractory to PI	211
OPTIMISMM [44] NCT01734928 2013–2017	VPd vs Vd	Relapsed or refractory; 1 to 3 prior treatments including R Excluded: Prior therapy with P	559
POLLUX [45–47] NCT02076009 2014–2015	DaraRd vs Rd	Relapsed or refractory; ≥ 1 prior treatments Excluded: Refractory to R	569
TOURMALINE-MM1 [48,49] NCT01564537 2012–2014	IxaRd vs Rd	Relapsed or refractory; 1 to 3 prior treatments Excluded: Refractory to PI or R	722
CAR-T			
CARTITUDE-4 [50–52] NCT04181827 2020–2021	Cilta-cel vs DaraPd or VPd	Refractory to R; 1 to 3 prior treatments including PI and IM Excluded: prior CAR-T or BMCA-targeted therapy	419
Bispecific antibodies			
MajesTEC-3 [53] NCT05083169 2021–2023	Teclistamab + Daratumumab vs DaraPd or DaraVd	Relapsed or refractory; 1 to 3 prior treatments including PI and R, anti-CD38 naïve or sensitive Excluded: prior BCMA-targeted therapy or CD38 refractory	587
MagnetisMM-3 [54,55] NCT04649359 2021-2022	Elranatamab single-arm trial	≥ 3 prior lines of therapy including an IMiD, a PI, and an anti-CD38 antibody and triple-class refractory Cohort A: BCMA-naïve Cohort B: prior BCMA-targeted therapies	123
LINKER-MM1 [56,57] NCT03761108 2019-2022	Linvoseltamab single-arm trial	≥ 3 prior lines of therapy including an IMiD, a PI, and an anti-CD38 antibody and triple-class refractory	117

Trial Recruitment period	Comparison	Key eligibility criteria	n
		Excluded: prior treatment with BCMA-targeted therapies except ADC triplets	
MajesTEC-1 [58–60] NCT04557098 2020-2021	Teclistamab single-arm trial	≥ 3 prior lines of therapy including an IMiD, a PI, and an anti-CD38 antibody and triple-class refractory Excluded for Cohort C: prior therapy with a BCMA-targeted therapy	165
MonumenTAL-1 [61–63] NCT03399799 2018-2021	Talquetamab single-arm trial	≥ 3 prior lines of therapy including an IMiD, a PI, and an anti-CD38 antibody and triple-class refractory Cohort A: no prior TCRT, weekly; Cohort B: no prior TCRT, every 2 weeks; Cohort C: prior TCRT	232
ASCT			
IFM-2009 [10] NCT01191060 2010–2012	VRd + ASCT vs VRd	n.a. (1st line of therapy)	700
DETERMINATION [11] NCT01208662 2010–2018	VRd + ASCT vs VRd	n.a. (1st line of therapy)	722
PERSEUS [12] NCT03710603 2019–2020	DaraVRd + ASCT vs VRd + ASCT	n.a. (1st line of therapy)	709

ADC: antibody drug conjugate, ASCT: autologous stem cell transplantation, Bela: Belantamab mafodotin, BCMA: B cell maturation antigen, CAR-T: Chimeric Antigen Receptor T-cell therapy, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, d: Dexamethasone, Elo: Elotuzumab, IMiD: immunomodulatory drug, Isa: Isatuximab, Ixa: Ixazomib, K: Carfilzomib, P: Pomalidomide, PI: proteasome inhibitor, R: Lenalidomide, Sel: Selinexor, TCRT: T-cell redirecting therapy (CAR-T or bispecific antibodies), V: Bortezomib.

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)
- 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)

Overview of myeloma-specific therapy

The myeloma-specific therapy for RRMM can be categorised into five general options:

- ADC-based triplets
- Other triplets
- CAR-T
- Bispecific antibodies
- ASCT

All options except CAR-T and ASCT consist of several possible medicines or combinations thereof. The medicines differ in the mechanism of action and the mode and frequency of application. These details are listed in Table 4. An overview of the treatment options and their marketing authorisation (line of therapy and previous treatments) and other aspects to consider is shown in Table 5.

Table 4: Details for the drugs used in the treatment of RRMM

Drug	Mechanism of action	Mode of application
ADC Belantamab mafodotin (Bela)	In the medicine an antibody is linked to a cytotoxic molecule. The antibody binds to the B-Cell Maturation Antigen (BCMA) on the surface of myeloma cells which leads to the internalisation of the cytotoxic molecule, leading to a stop of cell division and triggering apoptosis. Additionally, the medicine activates the immune system to destroy cancer cells and blocks the binding of natural growth ligands.	Infusion every 3 weeks (in the combination BelaVd) or 4 weeks (in the combination BelaPd)
CD38 antibodies	The drug binds to the CD 38 protein on the surface of the myeloma cells which leads to the death of myeloma cells.	Depending on the medicine
Daratumumab (Dara)		Injection/infusion: first weekly, then every 2 weeks, then every 4 weeks
Isatuximab (Isa)		Injection/infusion: first weekly, then every 2 weeks
Proteasome inhibitors	The drugs inhibit 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.	Depending on the medicine
Bortezomib (V)		Injection: depending on treatment plan, mostly once a week with scheduled treatment breaks
Carfilzomib (K)		Injection: once or twice a week with scheduled treatment breaks
Ixazomib (Ixa)		Oral: once a week with scheduled treatment breaks
Immunomodulatory drugs	The drug activates the immune system which helps to destroy myeloma cells.	Oral, daily with or without scheduled treatment breaks, depending on drug and treatment plan
Lenalidomide (R)		
Pomalidomide (P)		
Elotuzumab (Elo)	The drug, a monoclonal antibody, binds to the protein Signaling Lymphocyte Activation Molecule F7 (SLAMF7) which is present on immune cells as well as on	Infusion: first weekly, then every 2 weeks, then every 4 weeks

Drug	Mechanism of action	Mode of application
	myeloma cells. It activates the immune cell to attack the myeloma cells and at the same time, it makes the myeloma cells more vulnerable to attacks by the immune cells.	
Selinexor (Sel)	The drug blocks the action of a protein called exportin 1 (XPO1) on myeloma cells. The blocking leads to the death of the cancer cells.	Oral: once or twice a week, depending on the treatment plan
CAR-T cells Ciltacabtagene autoleucel (Cilta-cel)	Genetically modified T-cells bind to BCMA protein on the surface of myeloma cells and kill them.	Infusion: once (but other medication required)
Bispecific antibodies	The drugs attach to two targets simultaneously: one on myeloma cells and one (CD3) on T cells. This way, the T cells are activated and kill the myeloma cells.	Depending on the drug
Elranatamab (Elra)	Target on myeloma cells: BCMA	Injection: after dose step-up (several times per week) first every week, later every 2 weeks
Linvoseltamab (Linvo)	Target on myeloma cells: BCMA	Infusion: every 2 weeks after dose step-up
Teclistamab (Tec)	Target on myeloma cells: BCMA	Injection
		Monotherapy: once a week after dose step-up (several times per week)
		TecDara: 28-days cycles: dose step-up for Tec; then for both drugs weekly (up to Cycle 2), then every second week (up to Cycle 6), then every 4 weeks
Talquetamab (Tal)	Target on myeloma cells: G-Protein Coupled Receptor Family C Group 5 Member D (GPRC5D)	Injection: every 1 or 2 weeks after dose step-up (several times per week)
Dexamethasone (d)	The drug enhances the ability of other medicines to destroy myeloma cells.	Oral: mostly daily with scheduled therapy breaks or less often depending on the treatment plan
ADC: antibody drug conjugate, BCMA: B cell maturation antigen, CAR-T: Chimeric Antigen Receptor T-cell therapy		

Table 5: Overview of treatment options in RRMM

Treatment option	Medication	Line of therapy	Other limitations
ADC-based triplets (all including Belantamab)	ADC + PI: BelaVd ADC + IM: BelaPd	2+	BelaPd only after previous treatment with R
Other triplets (all including dexamethasone)	CD38 + PI: DaraKd, DaraVd, IsaKd CD38 + IM: DaraRd, DaraPd PI + IM: KRd, IxaRd, VPd Elo + IM: EloRd Sel + PI: SelVd	2+	DaraPd: after previous treatment with PI and R VPd: after previous treatment with R IsaKd, EloRd, KRd, IxaRd, SelVd: none
	EloPd, IsaPd	3+	IsaPd, EloPd: after previous treatment with R and PI and with disease progression during previous therapy
CAR-T	Ciltacabtagene autoleucel (Cilta-cel) plus several others (see text)	2+	After previous therapy with IMiD +PI and with disease progression during previous therapy and R-refractory Fitness required to tolerate side effects Not suitable for patients with urgent treatment needs
Bispecific antibodies	Teclistamab, Elranatamab, Linvoseltamab or Talquetamab as monotherapy	4+	Previous therapy with CD38, PI + IMiD; relapsed and refractory and with disease progression during previous therapy
	Teclistamab + Daratumumab [a]	2+	At least one prior therapy
ASCT	Several (see text) including chemotherapy	In clinical practice, 2nd line only	Fitness required

Treatment option	Medication	Line of therapy	Other limitations
ADC: antibody drug conjugate, ASCT: autologous stem-cell transplantation, CAR-T: Chimeric Antigen Receptor T-cell therapy, CD38: CD38 antibody, IMiD: immunomodulatory drugs, PI: proteasome inhibitor. For the abbreviations of the individual drugs see Table 3. [a] The combination received a positive CHMP opinion in June 2026. The EC decision was pending at the editorial deadline of the decision aid but is expected by 31.08.2026.			

ADC-based triplets

The ADC-based triplets BelaPd and BelaVd combine the antibody-drug-conjugate belantamab mafodotin (Bela), dexamethasone (d) and either the immunomodulator pomalidomide (P) or the protease inhibitor bortezomib (V).

ADC-based triplets are usually given in cycles with scheduled treatment breaks. Patients receive a therapy scheme which varies according to the medicines used. Therapy is usually continuous until disease progression or unacceptable toxicity.

Belantamab and bortezomib are given at the oncologist's office; the other drugs are taken orally at home.

Other triplets

Other triplets combine dexamethasone and either

- a CD38 antibody and a proteasome inhibitor
- a CD38 antibody and an immunomodulator
- a proteasome inhibitor and an immunomodulator
- the monoclonal antibody elotuzumab and an immunomodulator
- the exportin-1 (XPO1) inhibitor selinexor and a proteasome inhibitor

The combinations which have a marketing authorisation can be found in Table 5. It should be noted that EloPd and IsaPd can only be used after two previous therapies.

The monoclonal antibodies, i.e. CD38 antibodies and elotuzumab, require additional anti-inflammatory medication to prevent infusion/injection-related reactions. They are usually given at the oncologist's office, the same applies to the other drugs which are given as injection or infusion. The oral drugs can be taken at home. Patients receive a therapy scheme which varies according to the medicines used.

Other triplets are usually given in cycles with scheduled treatment breaks. Therapy is usually continuous until disease progression or unacceptable toxicity.

CAR-T

CAR-T cell therapy is usually a single-dose therapy which involves several steps. First, patients undergo apheresis of lymphocytes. T-cells are subsequently genetically modified resulting in CAR-T cells. Patients received these cells back

after a short course (3 days) of lymphodepleting chemotherapy, typically with fludarabine and cyclophosphamide. Pre-medication is required immediately before the infusion of CAR-T cells to reduce the risk of cytokine release syndrome. Patients usually receive infection prophylaxis medications for some time during and after therapy [64].

Maintenance with myeloma-specific medicines is not standard of care for the time being. However, regular administration of immunoglobulins may be required as supportive therapy in the first year to prevent infection.

Before apheresis, there is usually a washout phase where no myeloma-specific therapy is given. Because of the manufacturing process, there is usually also a delay of several weeks between apheresis and lymphodepletion. For patients with an urgent need for treatment, CAR-T cell therapy might therefore not be suitable. During the time of manufacturing, patients usually receive bridging therapy.

Before CAR-T cell therapy, frailty and cardiovascular fitness of the patients should be considered as patients need to be able to tolerate the side effects of the treatment. However, there is no absolute age limit. CAR-T cell therapy is not suitable for patients with active infections such as chronic viral infections, e.g. hepatitis.

There are also some considerations for T-cell fitness: Ongoing severe cytopenia might limit the ability to safely undergo apheresis and successfully produce CAR T cells. Exposure to high doses of alkylator few months before can negatively affect peripheral blood lymphocyte counts and T-cell fitness for CAR T-cell manufacturing. Also previous therapy might affect the manufacturing of CAR-T cells (see section "Sequencing of treatment") [65].

CAR-T cell therapy can only be administered in specialised treatment centres. The treatment usually requires a hospital stay of about two weeks. Afterwards, frequent checks at the treatment centre are required for about four weeks. Patients should discuss vaccinations before and after the treatment with their doctors.

Bispecific antibodies

Bispecific antibodies are given by infusion or injection. Due to the risk of cytokine release syndrome, a dose step-up is required. For the dose step-up, a hospital stay of a few days may be required as close monitoring is necessary. Afterwards, the treatment can be administered at the oncologist's office.

Before the treatments, pre-medication is required to reduce the risk of cytokine release syndrome. During treatment, infection prophylaxis medication might be required [66].

Bispecific antibodies as monotherapy and the combination of teclistamab and daratumumab are usually administered as continuous therapy until disease progression or unacceptable toxicity.

As of 15.06.2026, bispecific antibodies only had marketing authorisation as monotherapy after three previous therapies including a PI, an IMiD and a CD38 antibody. On 25.06.2026, the EMA Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for a new indication for teclistamab in combination with daratumumab for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior therapy (2nd line therapy). The final EC decision is expected by 31.08.2026.

ASCT

In RRMM, a second ASCT (after ASCT in the first line of therapy) is used less frequently than in previous decades as effective alternative therapy options have become available. ASCT is usually discussed in RRMM when the patient did not receive ASCT in the first line of therapy [3]. In clinical practice, ASCT is usually not administered later than in the second line of therapy due to a lack of evidence and eligibility of the patients. Therefore, we restrict the discussion to ASCT as a first-time treatment in the second line of therapy.

Before ASCT, eligibility has to be established. Criteria are usually age 70 years or younger and no important comorbidities.

ASCT consists of several steps: First, there will be induction therapy over several cycles. For the choice of medicines for induction therapy, especially first-line therapy and refractoriness have to be considered. Second, there will be stem cell mobilisation and collection. Usually, G-CSF with or without one cycle of chemotherapy (cyclophosphamide) will be used. In the case of insufficient mobilisation, also plerixafor is an option. Third, patients receive high-dose chemotherapy (HDT), mostly with melphalan, and subsequently their previously collected stem cells. After these treatment steps, usually maintenance therapy follows.

After the treatment, the infection risk is high. Additional infection prophylaxis medication might be required. Patients should discuss vaccinations after ASCT with their doctors.

ASCT can only be administered in specialised treatment centres and usually requires a hospital stay of several weeks.

Sequencing of treatments

Recommendations on the sequencing of treatments in RRMM can be found in a IMWG guideline [64], in the ASCO guideline [3] and in an EMN guideline [67]. It should be noted, however, that many of these recommendations are only

supported by scarce evidence and not all mechanisms of reduced efficacy for certain sequences are fully understood.

T-cell redirecting therapies (TCRT) refer to BCMA-targeted CAR-T and bispecific antibodies (BCMA-targeted or GPRC5D). BCMA-targeted therapies include CAR-T (Cilta-cel), bispecific antibodies (not talquetamab) and ADC (belantamab).

- **In general:** As relapse on a treatment usually indicates refractory disease, patients should be offered other agents than in prior therapies. CD38 antibodies should not be reintroduced for at least six months after the last exposure [3]. This also applies to induction therapy of ASCT.
- **Other triplets:** There are no concerns about TCRT in patients after having received a PI, IMiD, monoclonal antibody (CD38 or elotuzumab), a corticosteroid or any combination of these classes.
- **BCMA-directed ADC (belantamab):** Efficacy of BCMA-targeted TCRT (CAR-T and bispecific antibodies) may be lower after prior BCMA-targeted ADC. CAR-T should be used earlier in the disease course than belantamab. Alternatively, therapies with other modes of action might be used to extend the duration (> 6 months) between belantamab and CAR-T. Regarding bispecific antibodies, there should be an BCMA-free interval > 9 months or a target switch after belantamab (i.e. GPRC5D-targeted bispecific antibody) [67].
- **BCMA-directed CAR-T:** As CAR-T cell therapy often leads to long remission and BCMA loss after BCMA-directed CAR-T cell therapy seems to not happen frequently, the reduction in efficacy when using BCMA-directed bispecific antibodies subsequently seems to be only modest. When this sequence is intended, there should be a BCMA-free interval of more than 9 months [67]. An alternative strategy is to switch the target and to use a GPRC5D-targeted bispecific antibody for which the efficacy is not affected by prior BCMA-directed CAR-T cell therapy. For belantamab after BCMA-directed CAR-T cell therapy, there is contradicting evidence for a loss of efficacy.
- **Bispecific antibodies:** The medicines can lead to profound lymphopenia and/or T-cell dysfunction, resulting in manufacturing failure and/or response in subsequent CAR-T cell therapy. Therefore, CAR-T cell therapy should be given preferably before bispecific antibodies (both targets). GPRC5D-targeting bispecific antibodies can be considered as bridging therapy after T-cell apheresis. There is only limited evidence available for belantamab after a GPRC5D-targeted bispecific antibody, however, it seems to have no negative impact on response. For belantamab after BCMA-directed bispecific antibodies, there is contradicting evidence for a

loss of efficacy, a target switch is preferred. The sequential use of bispecific antibodies targeting alternative antigens is feasible, but the efficacy of the second medicine is usually lower than the first due to detrimental effects on T-cells. If this sequence is intended, there should be a bispecific antibody-free interval of at least six months.

Conclusion for the decision aid

- The decision aid should describe the treatment options as detailed above.
- Unless the respective treatment options (or its variations) have no marketing authorisation for all lines of RRMM therapy, this should be reflected in the text.
- The wording of the information on the consequences for later lines of therapy should reflect the scarce evidence and the reliance on clinical judgment.

FAQ 2: Will I live longer?

Principles of data extraction

In the ASCO guideline [3], the data have been extracted for all triplet (ACD-based and other) trials at a follow-up of 24 months, for CAR-T (Cilta-cel) at 12 months and for TecDara at 36 months. However, the differences in the follow-ups complicate the indirect comparisons further. Also, data with longer follow-up are available for some trials and might lead to different conclusions than shorter follow-up regarding the comparison of treatment options. As a compromise between comprehensiveness and efficiency of data extraction, we decided to follow a stepwise approach:

- Primarily, we adopted the data as reported in the guideline for convenience and comparability and selectively extracted further data as detailed below.
- For ADC-based triplets, we additionally extracted overall survival (OS) data for BelaVd at 36 months and visually estimated OS at 30 months for BelaVd and BelaPd from the Kaplan-Meier curves in the journal publications [15,16,19] to facilitate the comparison with CAR-T and TecDara, respectively. 36-month follow-up data for BelaPd is not available.
- Because of the multitude of trials for other triplets, we only extracted long-term data for DaraKd (CANDOR trial) [28] at 30 and 36 months for a sensitivity analysis. This triplet seems to be one of the apparently more effective triplet options. This would also be true for IsaKd; however, most comparative trials used a daratumumab-based triplet. Additionally, the trial population is more representative for the target group of the decision aid than DaraRd in which only a minority of patients were refractory to lenalidomide.

- For CARTITUDE-4 (Cilta-cel vs VPd or DaraPd), the guideline references an update of the CARTITUDE-4 trial [50] which reports mortality data for 30 months. However, results for the longer follow-up have not been added to the evidence profile, probably due to consistency with another CAR-T trials (which is not relevant for this evidence report). We extracted these data for mortality at 30 months from the journal publication as the follow-up is closer to the follow-up reported for the triplet trials and the TecDara trial. Additionally, we estimated the follow-up at 36 months from the Kaplan-Meier curve in the journal publication to facilitate the comparison with Cilta-cel.
- For the MajesTEC-3 trial (TecDara vs DaraVd or DaraPd), we visually estimated data for a follow-up at 30 months from the Kaplan-Meier curve in the journal publication [53] to facilitate the comparison with Cilta-cel.
- For bispecific antibodies, the ASCO guideline did not provide overall mortality data in the relevant format. Therefore, these data were extracted from the journal publications [55,56,60,63] at comparable timepoints.

For ASCT, no evidence is available for overall mortality (see Overview of the evidence).

Results

Data on overall mortality are shown in Table 6 (direct evidence) and Table 7 (indirect evidence). It should be noted that overall mortality data are not mature in some trials.

Table 6: Direct evidence for overall mortality

Treatment (trial)	Proportion with intervention	Proportion with comparator	Follow-up (median, months)	GRADE	Source
Cilta-cel vs DaraPd or VPd (CARTITUDE-4)	9 per 100	16 per 100	12	Moderate	EP 4.1
	24 per 100	36 per 100	30		[50] [a]
	25 per 100	42 per 100	36		
BelaVd vs DaraVd (DREAMM-7)	21 per 100	33 per 100	24	High	EP 4.17
	24 per 100	37 per 100	30		[15] [b]
	26 per 100	40 per 100	36		[15] [c]
BelaPd vs VPd (DREAMM-8)	33 per 100	40 per 100	24	Low	EP 4.18*
	35 per 100	42 per 100	30		[19] [d]
TecDara vs DaraPd or DaraVd (MajesTEC-3)	15 per 100	30 per 100	30	Low	[53] [e]
	18 per 100	35 per 100	36		EP 4.19

If not otherwise indicated, all results have been extracted from the evidence profiles (EP) in the data supplement of the ASCO guideline [3]. Bela: Belantamab mafodotin, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, d: Dexamethasone, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib.

*The difference between intervention and comparator is not (yet) statistically significant.

[a] 30-months overall survival was 76.4% with Cilta-cel and 63.8% with the triplet options. 36 months data visually estimated from Fig. 2, overall survival approximately 75% with Cilta-cel and 58% with the triplet options.

[b] Visually estimated from Fig. 2, overall survival approximately 76% with Cilta-cel and 63% with the triplet options.

[c] The overall survival rate at 36 months was 74% in the BelaVd group versus 60% in the DaraVd group.

[d] Visually estimated from Fig. 2, overall survival approximately 65% with BelaPd and 58% with VPd.

[e] Visually estimated from Fig. 2, overall survival approximately 85% with TecDara and 70% with DaraPd or DaraVd.

Table 7: Indirect evidence for overall mortality

Treatment	Comparator	Proportion with intervention	Follow-up (median, months)	Source
Other triplets				
VPd	Vd	35 per 100	24	EP 4.3*
DaraVd	Vd	29 per 100	24	EP 4.4
SelVd	Vd	32 per 100	24	EP 4.5*
DaraPd	Pd	45 per 100	24	EP 4.7*
EloPd [a]	Pd	35 per 100	24	EP 4.8
IsaPd [a]	Pd	44 per 100	24	EP 4.9*
DaraKd	Kd	24 per 100	24	EP 4.11*
		30 per 100	30	[28] [f]
		37 per 100	36	
IsaKd	Kd	24 per 100	24	EP 4.12*
KRd	Rd	25 per 100	24	EP 4.13
EloRd	Rd	25 per 100	24	EP 4.14
DaraRd	Rd	23 per 100	24	EP 4.15
IxaRd	Rd	29 per 100	24	EP 4.16*
Bispecific antibodies				
Elranatamab	none	43 per 100	15	[55] [b]
Linvoseltamab	none	25 per 100	12	[56] [c]
Talquetamab	none	23 to 26 per 100	12	[63] [d]
Teclistamab	none	41 per 100	14	[58] [e]

If not otherwise indicated, all results have been extracted from the evidence profiles (EP) in the data supplement of the ASCO guideline. Dara: Daratumumab, d: Dexamethasone, Elo: Elotuzumab, Isa: Isatuximab, Ixa: Ixazomib, K: Carfilzomib, P: Pomalidomide, R: Lenalidomide, Sel: Selinexor, V: Bortezomib.
*The difference between intervention and comparator is not (yet) statistically significant.
[a] ≥ 2 prior lines of therapy
[b] Overall survival at 15 months 56.7% Fig. 3c
[c] For the approved 200 mg dose, the probability of survival at 12 months was 75.3%. Fig. 2c
[d] 12-month overall survival rates were 76%, 77%, and 74%, in the three cohorts respectively.
[e] Suppl. S9
[f] Visually estimated from Fig. 2: Overall survival approximately 70% at 30 months and 63% at 36 months.

Interpretation of the data

This section presents the interpretation of the results for the treatment comparisons. Identical evaluations which differ only in the direction of the comparison (e.g. CAR-T vs ADC-based triplets or ADC-based triplets vs CAR-T) are only reported once. Other triplets are only referred to as comparison for the other treatment options as they served as control in the comparative trials.

Where applicable, interpretation has been adopted from the evidence profiles in the ASCO guideline.

ASCT

Due to the lack of evidence, it is not possible to estimate the direction of the effect in comparison to the other treatment options.

Bispecific antibodies

Monotherapy, 4th line/3 prior therapies

Only single-arm trials are available for this treatment option. Additionally, the populations in the trials differ fundamentally from those in the trials with the other therapy options as patients are heavily pretreated and have a substantially higher number of prior lines of therapy. This precludes the comparison with the other treatments. Therefore, only the results for bispecific antibodies (4th line) should be communicated.

It cannot be reliably estimated if there are differences in the efficacy of the different options within the drug class of bispecific antibodies as there are no comparative trials. Additionally, the bispecific antibodies for which an apparently higher mortality is noted, have a longer follow-up than the options with lower mortality. Although the difference is only 2 to 3 months, this might be relevant in a heavily pre-treated population in the fourth line of therapy. Therefore, a range for all bispecific antibodies (monotherapy) will be communicated.

TecDara

- Compared to CAR-T (Cilta-cel): There is only indirect evidence.
    - At 30 months, overall mortality is 15 per 100 with TecDara and 24 per 100 with Cilta-cel.
    - At 36 months, overall mortality is 18 per 100 with TecDara and 25 per 100 with Cilta-cel.
    - Direction of the treatment effect: Based on the relatively small difference between the treatment effects, it is not known if overall mortality is lower with TecDara or Cilta-cel.
    - Overall mortality at 36 months with any of the treatment options is 18 to 25 per 100.
- Compared to ADC-based triplets: There is only indirect evidence.
    - At 30 months, overall mortality is 15 per 100 with TecDara, 24 per 100 with BelaVd and 35 per 100 with BelaPd.
    - At 36 months, overall mortality is 18 per 100 with TecDara and 26 per 100 with BelaVd.
    - Direction of the treatment effect: Due to the heterogeneity between the ADC-based triplets and the rather small difference between

TecDara and BelaVd at 36 months, it cannot be reliably estimated if overall mortality is lower with TecDara or an ADC-based triplet. It is also not clear if this might be different for BelaPd and BelaVd, respectively.

  - Overall mortality at 30 months with any of the treatment options is 15 to 35 per 100.

- Compared to other triplets:
  - There is direct evidence in comparison to the other triplets DaraVd or DaraPd at 36 months. Overall mortality is 18 per 100 with TecDara and 35 per 100 with DaraVd or DaraPd. The difference is statistically significant. Therefore, in comparison to the two other triplets, TecDara may decrease the risk of death (GRADE: low).
    It should be noted that the Kaplan-Meier curves for overall survival cross at about 10 months: Before, overall mortality is slightly higher with TecDara; beyond 10 months, however, there is a clear overall survival benefit for TecDara. The apparent higher early mortality is due to the increased risk of infection, according to the journal publication [53]. This issue will be discussed in the context of serious adverse events (see FAQ 5).
  - For the comparison to any other triplet, there is only indirect evidence. For the very effective other triplet DaraKd, overall mortality at 36 months is approximately 37 per 100. This is in the same order of magnitude as the other triplets in the comparative trial. The difference compared to TecDara is probably clinically meaningful (≥ 10 %).
  - Direction of the treatment effect: It might be reasonable to assume that overall mortality with TecDara may be lower than with any other triplet. Therefore, the GRADE wording of the direct comparison can be applied to other triplets in general.
  - Figures, however, should only be communicated for the direct comparison at 36 months. It can be mentioned that there are no comparative trials for other triplet options, but the figures might be in the same order of magnitude or slightly worse.

CAR-T

- Compared to ADC-based triplets: There is only indirect evidence.
    - At 30 months, overall mortality is 24 per 100 with Cilta-cel, 24 per 100 with BelaVd and 35 per 100 with BelaPd.
    - At 36 months, overall mortality is 25 per 100 with Cilta-cel and 26 per 100 with BelaVd.
    - Direction of the treatment effect: Due to the heterogeneity between the ADC-based triplets and the rather small difference between Cilta-cel and BelaVd at 36 months, it cannot be reliably estimated if overall mortality is lower with CAR-T or an ADC-based triplet. It is also not clear if this might be different for BelaPd and BelaVd, respectively.
    - Overall mortality at 30 months with any of the treatment options is 24 to 35 per 100.
- Compared to other triplets:
    - There is direct evidence for the comparison to the other triplets DaraPd or VPd. At 30 months, overall mortality is 24 per 100 with Cilta-cel and 36 per 100 with DaraPd or VPd. The difference is statistically significant.
      It should be noted that the Kaplan-Meier curves for overall survival cross at about 12 months: Before, overall survival is lower with Cilta-cel; beyond 12 months, however, there is a clear overall survival benefit for Cilta-cel. As the journal publication [50] points out, the apparent higher early mortality can be attributed to patients who progressed and died before receiving Cilta-cel and to deaths due to infection (Covid-19). These issues will be discussed a) explaining the (non-)suitability of CAR-T cell therapy in fast-progressing disease and b) in the context of serious adverse events (see FAQ 5).
    - For the comparison to any other triplet, there is only indirect evidence. For the very effective other triplet DaraKd, overall mortality at 30 months is approximately 30 per 100. This is slightly better than the other triplets in the comparative trial. At 36 months, overall mortality is 25 per 100 with Cilta-cel and 37 per 100 with DaraKd. The difference is probably clinically meaningful (≥ 10 %).
    - Direction of the treatment effect: It might be reasonable to assume that overall mortality with Cilta-cel is probably lower than with any other triplet.

- Overall mortality with Cilta-cel is probably lower than with the other triplets DaraPd or VPd (GRADE: moderate). The GRADE wording of the direct comparison can be applied to other triplets in general.
- Figures, however, should only be communicated for the direct comparison at 30 months. It can be mentioned that there are no comparative trials for other triplet options, but the figures might be in the same order of magnitude or slightly worse.

ADC-based triplets

The data for the two ADC-based triplets BelaVd and BelaPd appear heterogenous. It should be noted, however, that the trial populations differ in terms of prior therapies and/or refractory status and that longer follow-up is available for BelaVd than for BelaPd.

BelaPd compared to other triplets

- There is direct evidence in comparison to the other triplet VPd. At 24 months, overall mortality is 33 per 100 with BelaPd and 40 per 100 with VPd. However, the difference is not statistically significant. The confidence interval for the effect size includes a relevant effect.
- For the comparison to any other triplet, there is only indirect evidence. Overall mortality with BelaPd at 30 months is approximately 35 per 100, with the very effective other triplet DaraKd approximately 30 per 100. This is better as with the other triplet VPd in the comparative trial (approximately 42 per 100 at 30 months).
- Direction of the treatment effect: In comparison to VPd, BelaPd may have little effect on overall mortality (GRADE: low). It is not known if overall mortality with BelaPd is lower than with any other triplet.
- Overall mortality at 24 months with any of the treatment options is 33 to 40 per 100.

BelaVd compared to other triplets

- There is direct evidence in comparison to the other triplet DaraVd. At 36 months, overall mortality is 26 per 100 with BelaVd and 40 per 100 with DaraVd. The difference is statistically significant.
- For the comparison to any other triplet, there is only indirect evidence. Overall mortality at 36 months with the very effective other triplet DaraKd is approximately 37 per 100. This is in the same order of magnitude as with the other triplet DaraVd in the comparative trial. The difference to BelaVd is probably clinically meaningful (≥ 10 %).

- Direction of the treatment effect: It might be reasonable to assume that overall mortality with BelaVd is probably lower than with any other triplet.
- In comparison to the other triplet DaraVd, BelaVd decreases the risk of death (GRADE: high). The GRADE wording of the direct comparison can be applied to other triplets in general.
- For this comparison, the figures from the DREAMM-7 trial at 36 months can be communicated. It can be mentioned that there are no comparative trials for other triplet options, but the figures might be in the same order of magnitude or slightly worse.

Conclusion for the decision aid

For each treatment comparison, a text module should be developed according to the module matrix (Table 8).

Table 8: Module matrix for overall mortality

	ADC-based triplets	**Other triplets**	**CAR-T**	**Bispecific antibodies**	**ASCT**
ADC-based triplets					
Other triplets	OS1.1 [a] OS1.2 [b]				
CAR-T	OS2.1	OS2.2			
Bispecific antibodies	OS3.1 [c]				
	OS3.2 [d]	OS3.3 [d]	OS3.4 [d]		
ASCT	OS4				

ADC: antibody drug conjugate, ASCT: autologous stem-cell transplantation, Bela: Belantamab, CAR-T: Chimeric Antigen Receptor T-cell therapy, Dara: Daratumumab, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib
[a] for BelaPd
[b] for BelaVd
[c] for monotherapy 4th line
[d] for TecDara

Separate text modules should be prepared for the comparison of other triplets vs the ADC-based triplets BelaVd and BelaPd, respectively, to account for the direct comparisons available from the DREAMM-7 and DREAMM-8 trials.

As no data are available for ASCT as second-line treatment, the same text module can be used for all comparisons.

The text modules should reflect the interpretation of the data (Table 9). The communication as overall survival might be more appropriate than overall mortality.

Table 9: Interpretation of the data for overall mortality

Module	Interpretation
OS1.1	It is not known if overall mortality is lower with the ADC-based triplet BelaPd or with any other triplet. There are no trials which compared all treatment options directly. Direct comparisons are only available for one other triplet. *What we know from clinical trials* In comparison to the other triplet VPd, BelaPd may have little effect on overall mortality. It is not known if this also applies to all other triplets. Approximately, within 24 months 33 to 40 per 100 people die with either treatment option.
OS1.2	Overall mortality is lower with the ADC-based triplet BelaVd than with other triplets. Direct comparisons are, however, only available for one other triplet. *What we know from clinical trials* Overall mortality is lower with BelaVd than with the other triplet DaraVd. Approximately, within 36 months • 26 per 100 people die with BelaVd • 40 per 100 people die with DaraVd To our best guess, overall mortality with other triplets is in the same order of magnitude or slightly worse than with DaraVd. However, this has not been tested in comparative trials.
OS2.1	It is not known if overall mortality is lower with an ADC-based triplet (BelaPd or BelaVd) or CAR-T cell therapy. There are no trials which compared both treatments directly. *What we know from clinical trials* Approximately, within 30 months 24 to 35 per 100 people die with either treatment option.
OS2.2	Overall mortality with Cilta-cel is probably lower than with other triplets. Direct comparisons are, however, only available for two other triplets. *What we know from clinical trials* Overall mortality with Cilta-cel is probably lower than with the other triplets DaraPd or VPd Within 30 months, approximately • 24 per 100 people die with the CAR-T cell therapy Cilta-cel.

Module	Interpretation
	• 36 people per 100 die with DaraPd or VPd. To our best guess, overall mortality with other triplets is in the same order of magnitude or slightly lower as with DaraPd and VPd. However, this has not been tested in comparative trials.
OS3.1	It is not known if overall mortality is lower with bispecific antibodies or the other treatment options. There are no trials which compared both treatments directly. *What we know from clinical trials* Within 12 to 15 months, approximately 23 to 43 per 100 people die with a bispecific antibody. These figures apply to patients after three or more previous lines of therapy and with triple-class refractory disease. In the trials with bispecific antibodies, patients had on average more relapses and more lines of therapy than patients in the trials with the other treatments. Therefore, the figures cannot be compared.
OS3.2	It is not known if overall mortality is lower with TecDara than with an ADC-based triplet (BelaVd or BelaPd). There are no trials which compared both treatments directly. *What we know from clinical trials* Approximately, within 30 months 15 to 35 per 100 people with either treatment option.
OS3.3	Overall mortality with TecDara might be lower than with any other triplet. Direct comparisons are, however, only available for two other triplets. *What we know from clinical trials* Overall mortality might be lower with TecDara than with the other triplets DaraPd or DaraVd. Within 36 months, approximately • 35 per 100 people die with DaraPd or DaraVd. • 18 per 100 people die with TecDara. To our best guess, overall mortality with other triplets is in the same order of magnitude as with DaraPd or DaraVd. However, this has not been tested in comparative trials.
OS3.4	It is not known if overall mortality is lower with CAR-T cell therapy or with TecDara. There are no trials which compared both treatments directly. *What we know from clinical trials*

Module	Interpretation
	Approximately, within 36 months 18 to 25 per 100 people die with either treatment option.
OS4	It is not known if overall mortality is lower with ASCT or with any of the other treatment options. There are no trials which compared treatments directly.
ADC: antibody drug conjugate, ASCT: autologous stem cell transplantation, Bela: Belantamab mafodotin, CAR-T: Chimeric Antigen Receptor T-cell therapy, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, d: Dexamethasone, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib.	

FAQ 3: Will the treatment delay progression of the disease?

All trials assessed progression according to the criteria of the International Myeloma Working Group (IMWG) based on biochemical and/or radiological markers [68]. It should be noted that this definition of progression is not necessarily directly linked to patient experience (e.g. worsening of symptoms). All trials report on the composite outcome progression-free survival (PFS) which is defined as time to progression or death due to any cause, whatever comes first.

Principles of data extraction

In the ASCO guideline [3], the data have been extracted for all triplet (ACD-based and other) trials at a follow-up of 12 months for death or progression events, for CAR-T (Cilta-cel) at 12 months and for TecDara at 36 months. However, the differences in the lengths of follow-up complicates the indirect comparisons further. Also, data with longer follow-up are available for some trials and might lead to different conclusions than shorter follow-up regarding the comparison of treatment options. As a compromise between comprehensiveness and efficiency of data extraction, we decided to follow a stepwise approach as described above for overall mortality.

When trials only report proportions of patients alive and without disease progression, this has been converted to death or disease progression events.

Results

Data on death or disease progression are shown in Table 10 (direct evidence) and Table 11 (indirect evidence). It should be noted that in some of the newer trials, median PFS has not been reached yet.

Table 10: Direct evidence for death or disease progression

Treatment (trial)	Proportion with intervention	Proportion with comparator	Follow-up (median, months)	GRADE	Source
Cilta-cel vs DaraPd or VPd (CARTITUDE-4)	19 per 100	51 per 100	12	Moderate	EP 4.1
	41 per 100	74 per 100	30		[50] [a]
	45 per 100	78 per 100	36		
BelaVd vs DaraVd (DREAMM-7)	31 per 100	47 per 100	12	High	EP 4.17
	40 per 100	72 per 100.	30		[16] [b]
	50 per 100	82 per 100	36		
BelaPd vs VPd (DREAMM-8)	30 per 100	49 per 100	12	High	EP 4.18
	50 per 100	73 per 100	30		[19] [c]
TecDara vs DaraPd or DaraVd (MajesTEC-3) [b]	15 per 100	65 per 100	30		[53] [d]
	19 per 100	70 per 100	36	High	EP 4.19

If not otherwise indicated, all results have been extracted from the evidence profiles (EP) in the data supplement of the ASCO guideline [3]. Bela: Belantamab mafodotin, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, d: Dexamethasone, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib.

[a] Fig. 2A: At 30 months, PFS is 59,4 % in the Cilta-cel group and 25,7 % in the standard of care group. The PFS at 36 months of 55 % in the Cilta-cel group and 22 % in the standard of care group. has been visually estimated from Fig. 2A.

[b] The proportions have been visually estimated from Fig. 1: PFS at 30 months 60 % with BelaVd and 28% with DaraVd, PFS at 36 months 50 % with BelaVd. and 18% with DaraVd

[c] The proportions have been visually estimated from Fig. 1: PFS at 30 months 50 % with BelaPd and 27 % with VPd.

[d] PFS at 30 months of 85 % has been visually estimated from Fig.1. DaraPd or DaraVd 35%

Table 11: Indirect evidence for death or disease progression

Treatment	Comparator	Proportion with intervention	Follow-up (median, months)	Source
Other triplets				
VPd	Vd	47 per 100	12	EP 4.3
DaraVd	Vd	29 per 100		EP 4.4
SelVd	Vd	52 per 100		EP 4.5
DaraPd	Pd	56 per 100		EP 4.7
EloPd [a]	Pd	51 per 100		EP 4.8
IsaPd [a]	Pd	54 per 100		EP 4.9
DaraKd	Kd	26 per 100	12	EP 4.11
		52 per 100	30	[28] [f]
		57 per 100	36	
IsaKd	Kd	24 per 100	12	EP 4.12
KRd	Rd	30 per 100	12	EP 4.13
EloRd	Rd	31 per 100	12	EP 4.14
DaraRd	Rd	17 per 100	12	EP 4.15
IxaRd	Rd	32 per 100	12	EP 4.16
Bispecific antibodies				
Elranatamab	none	49 per 100	15	[55] [b]
Linvoseltamab	none	30 per 100	12	[56] [c]
Talquetamab	none	58 to 75 per 100	12	[63] [d]
Teclistamab	none	45 per 100	14	[58] [e]

If not otherwise indicated, all results have been extracted from the evidence profiles (EP) in the data supplement of the ASCO guideline [3]. Dara: Daratumumab, d: Dexamethasone, Elo: Elotuzumab, Isa: Isatuximab, Ixa: Ixazomib, K: Carfilzomib, P: Pomalidomide, R: Lenalidomide, Sel: Selinexor, TCRT: T-cell redirecting therapy (CAR-T or bispecific antibodies), V: Bortezomib.

[a] ≥ 2 prior lines of therapy

[b] PFS 50.9%, Fig. 3b

[c] PFS 70.0% Fig 2b

[d] 107 events in 143 patients (74.8%) in the 0·4 mg/kg once a week group, 89 events in 154 patients (57.8%) in the 0·8 mg/kg every 2 weeks group, and 47 events in 78 patients (60.3 %) in the previous TCRT group

[e] PFS 48 % estimated from Fig 2B

[f] PFS at 30 months of 48 % and PFS at 36 months of 43 months estimated from Suppl. Fig 1.

Interpretation of the data

The data for death or disease progression have been interpreted and are presented here as described for FAQ 1 (overall mortality).

ASCT

Due to the lack of evidence, it is not possible to estimate the direction of the effect in comparison to the other treatment options.

Bispecific antibodies

Monotherapy, 4th line/3 prior therapies

For the discussion of the study limitations see FAQ 1 (overall mortality).

In the absence of comparative trials, a range for all bispecific antibodies (monotherapy) will be communicated on the basis of the single-arm trials: 30 to 75 per 100. The broad range is probably a result of the heterogenous trial populations.

TecDara

- Compared to CAR-T (Cilta-cel): There is only indirect evidence.
    - At 30 months, the proportion of death or disease progression is 15 per 100 with TecDara and 41 per 100 with Cilta-cel.
    - At 36 months, the proportion of death or disease progression is 19 per 100 with TecDara and 45 per 100 with Cilta-cel.
    - Direction of the treatment effect: The difference is probably clinically meaningful (≥ 10 %). Therefore, it seems reasonable to assume that the proportion of death or disease progression is lower with TecDara than with Cilta-cel. It should be noted, however, that the population in the TecDara trial might have been less prone to disease progression (e.g. 35 % vs 60 % patients with high-risk cytogenetics and 5 % vs 25 % triple-class exposure). Therefore, the certainty of the evidence is very low.
    - The figures for 36 months can be communicated in the decision aid. It should be pointed out that there is no direct comparison and trial populations might not be comparable.
- Compared to ADC-based triplets: There is only indirect evidence.
    - At 30 months, the proportion of death or disease progression is 15 per 100 with TecDara, 40 per 100 with BelaVd and 50 per 100 with BelaPd.
    - At 36 months, the proportion of death or disease progression is 19 per 100 with TecDara and 50 per 100 with BelaVd.

    - Direction of the treatment effect: The difference compared to TecDara is probably clinically meaningful (≥ 10 %). Risk of death or disease progression seems to be lower with TecDara than with BelaVd or BelaPd. It should be noted, however, that there are heterogenous populations in the trials. Therefore, the certainty of the evidence is very low.
    - The risk of death or disease progression at 30 months is 15 per 100 with TecDara and 40 to 50 per 100 with an ADC-based triplet.
- Compared to other triplets:
    - There is direct evidence in comparison to the other triplets DaraVd or DaraPd at 36 months. The proportion of death or disease progression is 19 per 100 with TecDara and 70 per 100 with DaraVd or DaraPd. The difference is statistically significant. Therefore, in comparison to the two other triplets, TecDara decreases the proportion of death or disease progression (GRADE: high).
    - For the comparison to any other triplet, there is only indirect evidence. For the very effective other triplet DaraKd, the proportion of death or disease progression at 36 months is approximately 57 per 100. This might be slightly better than with DaraVd or DaraPd, but still the difference compared to TecDara is probably clinically meaningful (≥ 10 %).
    - Direction of the treatment effect: It might be reasonable to assume that the proportion of death or disease progression with TecDara may be lower than with any other triplet. Therefore, the GRADE wording of the direct comparison can be applied to other triplets in general.
    - Figures, however, should only be communicated for the direct comparison at 36 months. It can be mentioned that there are no comparative trials for other triplet options, but the figures might be in the same order of magnitude.

CAR-T

- Compared to ADC-based triplets: There is only indirect evidence.
    - At 30 months, the proportion of death or disease progression is 41 per 100 with Cilta-cel, 40 per 100 with BelaVd and 50 per 100 with BelaPd.
    - At 36 months, the proportion of death or disease progression is 45 per 100 with Cilta-cel and 50 per 100 with BelaVd.

- Direction of the treatment effect: The difference of effect sizes is rather small. It is not known if the proportion of death or disease progression is lower with CAR-T or an ADC-based triplet. It is also not clear if this might be different for BelaPd and BelaVd, respectively.
- The risk of death or disease progression at 30 months with any of the treatment options is 40 to 50 per 100.

- Compared to other triplets:
  - There is direct evidence for the comparison to the other triplets DaraPd or VPd. At 30 months, the proportion of death or disease progression is 41 per 100 with Cilta-cel and 74 per 100 with DaraPd or VPd. The difference is statistically significant.
    It should be noted that the Kaplan-Meier curves for PFS cross at about 3 to 4 months: Before, PFS is lower with Cilta-cel; beyond 3 to 4 months, however, there is a clear PFS benefit for Cilta-cel. As the journal publication [50] points out, the apparent higher early progression can be attributed to patients who progressed during bridging therapy before receiving Cilta-cel. This issue will be discussed in a) explaining the (non-)suitability of CAR-T cell therapy in fast-progressing disease and b) explaining bridging therapy.
  - For the comparison to any other triplet, there is only indirect evidence. For the very effective other triplet DaraKd, the proportion of death or disease progression at 30 months is approximately 52 per 100. This is better than the other triplets in the comparative trial. At 36 months, the proportion of death or disease progression is 45 per 100 with Cilta-cel and 57 per 100 with DaraKd. The difference is probably clinically meaningful (≥ 10 %).
  - Direction of the treatment effect: It might be reasonable to assume that the proportion of death or disease progression with Cilta-cel is probably lower than with any other triplet.
  - The risk of death or disease progression with Cilta-cel is probably lower than with the other triplets DaraPd or VPd (GRADE: moderate). The GRADE wording of the direct comparison can be applied to other triplets in general.
  - Figures, however, should only be communicated for the direct comparison at 30 months. It can be mentioned that there are no comparative trials for other triplet options, but the figures might be in the same order of magnitude.

-

ADC-based triplets

BelaPd compared to other triplets

- There is direct evidence in comparison to the other triplet VPd. At 30 months, the proportion of death or disease progression is 50 per 100 with BelaPd and 73 per 100 with VPd. The difference is statistically significant.
- For the comparison to any other triplet, there is only indirect evidence. the proportion of death or disease progression with BelaPd at 30 months is approximately 50 per 100, with the very effective other triplet DaraKd approximately 52 per 100. This is better as with the other triplet VPd in the comparative trial.
- Direction of the treatment effect: In comparison to VPd, the risk of death or disease progression with BelaPd is lower (GRADE: high). It is not known if the risk of death or disease progression with BelaPd is lower than with any other triplet.
- Figures should only be communicated for the direct comparison at 30 months. It can be mentioned that there are no comparative trials for other triplet options.

BelaVd compared to other triplets

- There is direct evidence in comparison to the other triplet DaraVd. At 30 months, the proportion of death or disease progression is 40 per 100 with BelaVd and 72 per 100 with DaraVd. The difference is statistically significant.
- For the comparison to any other triplet, there is only indirect evidence. The proportion of death or disease progression at 30 months with the very effective other triplet DaraKd is approximately 52 per 100. This is lower as with the other triplet DaraVd in the comparative trial. The difference to BelaVd is, however, probably still clinically meaningful (≥ 10 %).
- Direction of the treatment effect: It might be reasonable to assume that the proportion of death or disease progression with BelaVd is probably lower than with any other triplet.
- In comparison to the other triplet DaraVd, BelaVd decreases the risk of death or disease progression (GRADE: high). The GRADE wording of the direct comparison can be applied to other triplets in general.
- For this comparison, the figures at 30 months can be communicated. It can be mentioned that there are no comparative trials for other triplet options.

Conclusion for the decision aid

For each treatment comparison, a text module should be developed according to the module matrix (Table 12).

Table 12: Module matrix for death or disease progression

	ADC-based triplets	**Other triplets**	**CAR-T**	**Bispecific antibodies**	**ASCT**
ADC-based triplets					
Other triplets	P1.1 [a] P1.2 [b]				
CAR-T	P2.1	P2.2			
Bispecific antibodies	P3.1 [c]				
	P3.2 [d]	P3.3 [d]	P3.4 [d]		
ASCT	P4				

ADC: antibody drug conjugate, ASCT: autologous stem-cell transplantation, Bela: Belantamab, CAR-T: Chimeric Antigen Receptor T-cell therapy, Dara: Daratumumab, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib
[a] for BelaPd
[b] for BelaVd
[c] for monotherapy 4th line
[d] for TecDara

Separate text modules should be prepared for the comparison of other triplets vs the ADC-based triplets BelaVd and BelaPd, respectively, to account for the direct comparisons available from the DREAMM-7 and DREAMM-8 trials.

As no data are available for ASCT as second-line treatment, the same text module can be used for all comparisons.

The text modules should reflect the interpretation of the data in Table 13**Fehler! Verweisquelle konnte nicht gefunden werden.**. The communication as proportion of patients alive without progression might be more appropriate than proportion of patients with event (death or disease progression).

Table 13: Interpretation of the data for death or disease progression

Module	**Interpretation**
P1.1	It is not known if the risk for death or disease progression is lower with the ADC-based triplet BelaPd or with any other triplet. Direct comparisons are only available for one other triplet. *What we know from clinical trials* The risk of death or disease progression is lower with BelaPd than with VPd. Death or disease progression at 30 months experience approximately • 50 per 100 people with BelaPd • 73 per 100 people with VPd

Module	Interpretation
	To our best guess, the risk of death or disease progression with some other triplets is lower than with VPd. However, there are no trials which compared the other triplets directly to BelaPd.
P1.2	The risk of death or disease progression is lower with the ADC-based triplet BelaVd than with any other triplet. However, direct comparisons are only available for one other triplet. *What we know from clinical trials* The risk of death or disease progression is lower with BelaVd than with the other triplet DaraVd. Death or disease progression at 30 months experience approximately • 40 per 100 people with BelaVd • 72 per 100 people with DaraVd To our best guess, the risk of death or disease progression with other triplets is in the same order of magnitude as with DaraVd. However, there are no trials which compared the other triplets directly to BelaVd.
P2.1	It is not known if the risk of death or disease progression is lower with an ADC-based triplet (BelaPd or BelaVd) or CAR-T cell therapy Cilta-cel. There are no trials which compared both treatments directly. *What we know from clinical trials* Approximately, within 30 months 40 to 50 per 100 people experience death or disease progression with either treatment option.
P2.2	The risk of death or disease progression is probably lower with the CAR-T cell therapy Cilta-cel than with any other triplet. However, direct comparisons are only available for two other triplets. *What we know from clinical trials* The risk of death or disease progression with Cilta-cel is probably lower than with the other triplets DaraPd or VPd. Death or disease progression at 30 months experience approximately • 41 per 100 people with the CAR-T cell therapy Cilta-cel • 74 per 100 people with DaraPd or VPd To our best guess, the risk of death or disease progression with other triplets is in the same order of magnitude as with DaraPd or VPd or slightly lower. However, there are no trials which compared the other triplets directly to Cilta-Cel.

Module	Interpretation
P3.1	It is not known if the risk of death or disease progression is lower with bispecific antibodies or the other treatment options. There are no trials which compared both treatments directly. *What we know from clinical trials* Within 12 to 15 months, approximately 30 to 75 per 100 people die or have disease progression with a bispecific antibody. These figures apply to patients after three or more previous lines of therapy and with triple-class refractory disease. In the trials with bispecific antibodies, patients had on average more relapses and more lines of therapy than patients in the trials with the other treatments. Therefore, the figures cannot be compared.
P3.2	The risk of death or disease progression might be lower with TecDara than ADC-based triplets. However, there are no trials which compared both treatments directly and the certainty of the evidence is very low. *What we know from clinical trials* Death or disease progression at 30 months experience approximately • 15 per 100 people with the TecDara • 40 to 50 per 100 people with an ADC-based triplet However, these figures cannot be compared directly as they were compiled from different trials.
P3.3	The risk of death or disease progression is lower with TecDara than any other triplet. However, direct comparisons are only available for two other triplets. *What we know from clinical trials* Death or disease progression at 36 months experience approximately • 19 per 100 people with the TecDara • 70 per 100 people with an DaraVd or DaraPd. To our best guess, the risk of death or disease progression with other triplet is in the same order of magnitude as with DaraVd or DaraPd or slightly lower. However, there are no trials which compared the other triplets directly to TecDara.
P3.4	The risk of death or disease progression might be lower with TecDara than CAR-T cell therapy. However, there are no trials which compared both treatments directly and the certainty of the evidence is very low. *What we know from clinical trials*

Module	Interpretation
	Death or disease progression at 36 months experience approximately • 19 per 100 people with the TecDara • 45 per 100 people with the CAR-T cell therapy Cilta-cel However, these figures cannot be compared directly as they were compiled from different trials.
P4	It is not known if the risk of death or disease progression is lower with ASCT or with any of the other treatment options. There are no trials which compared treatments directly.
ADC: antibody drug conjugate, ASCT: autologous stem cell transplantation, Bela: Belantamab mafodotin, CAR-T: Chimeric Antigen Receptor T-cell therapy, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, d: Dexamethasone, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib.	

FAQ 4: How will the treatment affect symptoms and my quality of life?

Principles of data extraction

Without an effective treatment of multiple myeloma, symptoms will increase whereas quality of life (QoL) will decrease. The exact course, however, may be individually different. The aim of the myeloma-specific treatment (together with supportive therapy) is to improve or at least to stabilise for some time symptoms and QoL.

The ASCO guideline [3] did not extract information on symptoms and quality of life (QoL). Therefore, we extracted these data from the journal publications. For a better efficiency and comparability, we restricted data extraction to the comparative trials. Where available, we preferred publications dedicated to patient-reported outcomes (PRO). As a consequence, PRO data are mostly only available for shorter follow-up than overall mortality or PFS data.

In all trials, myeloma-specific symptoms or general symptoms as well as QoL have been assessed. However, not all results have been reported, e.g. for many trials only results for selected subscales are available in the journal publications.

In general, a multitude of instruments were used. For a better efficiency, we restricted data extraction per trial to one instrument measuring myeloma-specific symptoms and one instrument measuring QoL.

In the trials, symptoms and QoL were measured either with Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) or the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Myeloma Module (EORTC QLQ-MY20). Additionally, all trials used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30).

The MySIm-Q instrument addresses five symptom domains (pain, neuropathy, fatigue, digestive, cognitive) and three impact domains (activity, social, emotional) which we categorise as impact on QoL. The questionnaire consists of 17 items with a five-point verbal rating scale (0 to 4 points). Higher scores indicate worse symptoms or worse disease impact. The total symptom score is calculated as the average of 11 items in the symptom scales. The clinically meaningful difference of 0.32 for the total symptom scale has been derived from post-hoc trial analyses in the CARTITUDE-4 trial [52]. It should be noted, however, that this is far below the threshold of 15 % of the scale range (4 * 0.15 = 0.6) which is usually applied in the early benefit assessments of IQWiG. The clinically meaningful difference for the total impact scale is not reported. In the MajesTEC-3 trial [53], the minimally important difference was defined as the mean change on the MySIm-Q Symptom Scale associated with a 2-point increase on the Patient Global Impression of Severity symptom question between baseline and cycle 4. The resulting change on the MySIm-Q Symptom Scale, however, is not reported.

The EORTC QLQ-MY20 instrument addresses symptoms in the two domains disease symptom and side effects of treatment as well as QoL in the two domains body image and future perspectives. The EORTC QLQ-C30 instrument addresses symptoms in three symptom scales (fatigue, pain and nausea/vomiting) and QoL in five functional scales (physical, role, cognitive, emotional and social functioning) as well as in a global health status/QoL scale. All EORTC scales range from 0 to 100 with higher values representing higher QoL and higher symptom burden, respectively. In the early benefit assessments, a clinically meaningful difference of 10 points has been accepted.

For the data extraction, we focussed on the question if there are relevant differences between the intervention and the comparator. Where available, we based this assessment on data from responder analyses based on the clinically meaningful difference (with the caveat for MySIm-Q mentioned above). As there were usually no statistical tests for responder analyses, we accepted a difference of 10 % points or more (similarly as for indirect comparisons for overall mortality and PFS) as an indication for superiority while acknowledging the inherent uncertainty of this approach. When responder analyses were not available, we based the assessment on figures or data representing the course of symptoms and/or QoL and assumed superiority when the difference between intervention and comparator curves reached at least the clinically meaningful difference.

Results

Results for symptoms and QoL are presented in Table 14. Additionally, the trials IFM-2009 [10] and DETERMINATION [11] indicate that during the phase high-dose chemotherapy symptoms might increase and quality of life might decrease for ASCT compared to no ASCT (triplet therapy only).

Based on the intensity of the treatment, a similar course might be assumed for CAR-T cell treatment as well. However, there are no data to support this hypothesis as there have been no PRO measurements during chemotherapy and CAR-T infusion in the CARTITUDE-4 trial [52].

Table 14: Direct comparisons for symptoms and quality of life

	Cilta-cel vs DaraPd/VPd CARTITUDE-4 [52] [a]	**BelaVd vs DaraVd DREAMM-7 [17]** [b]	**BelaPd vs VPd DREAMM-8 [18]** [c]	**TecDara vs DaraVd/DaraPd MajesTEC-3** [53] [d]
Time of assessment (T) (months) or Follow-up (F) (median, months)	12 (T)	28.2 (F)	12 (T)	36 (T)
Symptoms				
EORTC QLQ-C30 Fatigue	⇧ for more improvement and less worsening	⇔ for improvement/ worsening	⇔ for improvement	Not reported
EORTC QLQ-C30 Pain	⇧ for more improvement, ⇔ for less worsening	Not reported	Not reported	Not reported
EORTC QLQ-C30 Nausea/vomiting	⇔ for course of symptoms	Not reported	Not reported	Not reported
MySIM-Q (symptom scores)	⇧ for more improvement and less worsening	Not assessed	Not assessed	⇧ for less worsening, more improvement not reported
EORTC-QLQ-M20 (symptom scores)	Not assessed	⇔ for improvement/ worsening	⇔ for improvement	Not assessed
Quality of life				
EORTC QLQ-C30 Global health status	⇧ for more improvement and less worsening	⇔ for improvement/ worsening	⇧ for improvement	Not reported
EORTC QLQ-C30 Physical functioning	⇧ for more improvement and less worsening	⇔ for improvement/ worsening	⇧ for improvement	Not reported
EORTC QLQ-C30 Role functioning	⇔ for course of QoL	⇔ for improvement/ worsening	⇔ for improvement	Not reported

	Cilta-cel vs DaraPd/VPd CARTITUDE-4 [52] [a]	**BelaVd vs DaraVd DREAMM-7 [17]** [b]	**BelaPd vs VPd DREAMM-8 [18]** [c]	**TecDara vs DaraVd/DaraPd MajesTEC-3** [53] [d]
EORTC QLQ-C30 Cognitive functioning	⇔ for course of QoL	Not reported	Not reported	Not reported
EORTC QLQ-C30 Social functioning	⇔ for course of QoL	Not reported	Not reported	Not reported
MySIM-Q (impact scores)	Not evaluable	Not assessed	Not assessed	Not reported
EORTC-QLQ-M20 (QoL scores)	Not assessed	Not reported	Not reported	Not assessed
GRADE [e]	Very low	Very low	Very low	Very low

QoL: quality of life. Bela: Belantamab mafodotin, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, d: Dexamethasone, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib.
⇧ Intervention better than comparator (for responder analyses: more improvement, less worsening; for course: difference at least the threshold for clinically meaningful difference), ⇔ No meaningful difference between intervention and comparator. If not otherwise noted, analysis of MySIM-Q total symptom score relies on an assumed clinically meaningful difference of 0.32 points. The clinically meaningful difference for the total impact score is not reported. Analysis of EORTC scores relies on an established clinically meaningful difference of 10 points.

[a] Cilta-cel vs comparator. The difference between intervention and comparator for proportions for meaningful improvement and worsening, respectively, is higher than 10 percentage points for total symptoms (Fig. 1E), EORTC QLQ-C30 (Fig. 2E) global health status, physical functioning: fatigue. For pain, the difference is only higher for improvement, but not for worsening. Differences at 12 months are not meaningfully different for nausea/vomiting (Suppl. Fig. 2E), role function (Suppl. Fig. 2B), cognitive function (Suppl. Fig. 2D), social function (Suppl. Fig 2C).
[b] Post-hoc responder analysis in Fig. S3 at end of treatment (EOT): The difference between intervention and comparator for proportions for meaningful improvement and worsening, respectively, is below 10 percentage points for EORTC QLQ-C30 (A) global health status/quality of life, (B) role functioning, (C) physical functioning, (D) fatigue, and (E) EORTC QLQ-MY20 disease symptoms.
[c] Suppl. Tab. 3 at 53 weeks. It is unclear, however, from the course of PRO (Fig 1A-E) if the difference persists with a longer follow-up.
[d] No worsening of symptoms at 36 months was reported in 75.6% of patients with TecDara and in 63.3% of patients with DaraPd or DaraVd group (hazard ratio, 0.50; 95% CI, 0.34 to 0.72; P<0.001). The threshold for worsening was defined as the mean change in MySIM-Q (symptom scores) associated with a 2-point increase on the Patient Global Impression of Severity symptom question. The change in MySIM-Q is not reported explicitly.
[e] see Appendix

Interpretation of the data

For symptoms and QoL, only comparative trials have been used to extract the directions of the effect. The data are interpreted accordingly.

ASCT

Due to the lack of evidence, it is not possible to estimate the direction of the effect in comparison to the other treatment options. Data indicate that symptoms might increase and QoL might decrease during high-dose chemotherapy.

Bispecific antibodies

Monotherapy, 4th line/3 prior therapies

Due to the lack of evidence, it is not possible to estimate the direction of the effect in comparison to the other treatment options.

TecDara

- Compared to CAR-T (Cilta-cel): There is no direct evidence. Therefore, it is not possible to estimate the direction of the effect.
- Compared to ADC-based triplets: There is no direct evidence. Therefore, it is not possible to estimate the direction of the effect.
- Compared to other triplets: There is direct evidence in comparison to the other triplets DaraVd or DaraPd. Within 36 months, TecDara might prevent relevant worsening of symptoms. However, the certainty of the evidence is very low. There are no data on the comparison to other triplets or for QoL.

CAR-T

- Compared to ADC-based triplets: There is no direct evidence. Therefore, it is not possible to estimate the direction of the effect.
- Compared to other triplets: There is direct evidence for the comparison to the other triplets DaraPd or VPd. Within 12 months, CAR-T might be better to improve the majority of symptoms (but not all) and prevent worsening. Also, CAR-T might be better to improve some aspects of QoL and prevent worsening. However, this does not apply to all aspects of QoL. Overall, the certainty of the evidence is very low. It should be noted that symptoms and QoL might be worse during the acute phase of the treatment.

ADC-based triplets

BelaPd compared to other triplets

There is direct evidence in comparison to the other triplet VPd, but not to other triplets. Within 12 months, BelaPd might not be better than VPd to improve

symptoms or prevent worsening. However, it might be better to improve some, but not all aspects of QoL. Overall, the certainty of the evidence is very low.

BelaVd compared to other triplets

There is direct evidence in comparison to the other triplet DaraVd, but not to other triplets. BelaVd might not be better to improve or prevent worsening of symptoms or QoL within 28 months. Overall, the certainty of the evidence is very low.

Conclusion for the decision aid

For each treatment comparison, a text module should be developed according to the module matrix (Table 15).

Table 15: Module matrix for symptoms and quality of life

	ADC-based triplets	**Other triplets**	**CAR-T**	**Bispecific antibodies**	**ASCT**
ADC-based triplets					
Other triplets	PRO 1.1 [a] PRO 1.2 [b]				
CAR-T	PRO 2.1	PRO 2.2			
Bispecific antibodies	PRO 3.1 [c]				
	PRO 3.2 [d]	PRO 3.3 [d]	PRO 3.4 [d]		
ASCT	PRO 4				

ADC: antibody drug conjugate, ASCT: autologous stem-cell transplantation, Bela: Belantamab, CAR-T: Chimeric Antigen Receptor T-cell therapy, Dara: Daratumumab, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib
[a] for BelaPd
[b] for BelaVd
[c] for monotherapy 4th line
[d] for TecDara

Separate text modules should be prepared for the comparison of other triplets vs the ADC-based triplets BelaVd and BelaPd, respectively, to account for the direct comparisons available from the DREAMM-7 and DREAMM-8 trials.

As no data are available for ASCT as second-line treatment, the same text module can be used for all comparisons.

The text modules should reflect the interpretation of the data in Table 16**Fehler! Verweisquelle konnte nicht gefunden werden.**.

Table 16: Interpretation of the data for symptoms and quality of life

Module	Interpretation
PRO1.1	We only have data on the comparison of BelaPd and VPd, not for other triplets. Within 12 months, BelaPd might have similar effects on symptoms as VPd. However, BelaPd might have more favourable effects on some, but not all aspects of quality of life. More favourable effects mean improvement and prevention of worsening. Overall, the certainty of the evidence is very low.
PRO 1.2	We only have data on the comparison of BelaVd and DaraVd, not for other triplets. Within 28 months, BelaVd might have similar effects on symptoms and quality of life as DaraVd. Overall, the certainty of the evidence is very low.
PRO 2.1	It is not known if CAR-T cell therapy or an ADC-based triplet (BelaPd or BelaVd) have more favourable effects on symptoms or quality of life in the further course of the disease. This has not been tested in comparative trials. It is possible that symptoms increase and quality of life decreases during and shortly after CAR-T cell treatment.
PRO 2.2	We only have data on the comparison of CAR-T and DaraPd/VPd, not for other triplets. Within 12 months, CAR-T might have more favourable effects on the majority of symptoms. However, this does not apply to all symptoms. Also, CAR-T might have more favourable effects on some aspects of quality of life. However, this does not apply to all aspects of QoL. More favourable effects mean improvement of symptoms and QoL, respectively, and prevention of worsening. It is possible that symptoms increase and quality of life decreases during and shortly after lymphodepletion chemotherapy and CAR-T cell therapy. Overall, the certainty of the evidence is very low.
PRO 3.1	It is not known if bispecific antibodies or other treatments have more favourable effects on symptoms and quality of life in the further course of the disease. This has not been tested in comparative trials.
PRO 3.2	It is not known if TecDara or an ADC-based triplet (BelaPd or BelaVd) have more favourable effects on symptoms or quality of life in the further course of the disease. This has not been tested in comparative trials.
PRO 3.3	We only have data on the comparison of TecDara and DaraVd/DaraPd, not for other triplets.

Module	Interpretation
	Within 36 months, TecDara might prevent relevant worsening of symptoms better than DaraVd/DaraPd. It is not known if TecDara also has more favourable effects on the improvement of symptoms or on the quality of life. However, the certainty of the evidence is very low.
PRO 3.4	It is not known if TecDara or CAR-T cell therapy have more favourable effects on symptoms or quality of life in the further course of the disease. This has not been tested in comparative trials. It is possible that symptoms increase and quality of life decreases during and shortly after CAR-T cell treatment.
PRO 4	It is not known if ASCT or other treatments have more favourable effects on symptoms and quality of life in the further course of the disease. This has not been tested in comparative trials. It is possible that symptoms increase and quality of life decreases during and shortly after high-dose chemotherapy and stem cell transplantation.
ADC: antibody drug conjugate, ASCT: autologous stem cell transplantation, Bela: Belantamab mafodotin, CAR-T: Chimeric Antigen Receptor T-cell therapy, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, d: Dexamethasone, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib.	

FAQ 5: What are the risks or side effects?

Adverse events (AE) have been assessed in all trials. We report

- qualitative data on the most important AE
- quantitative data on serious AE

Although treatment discontinuation due to AE might be a relevant outcome, there are several reasons which preclude comparisons of the treatment options:

- When combination therapies are used, treatment discontinuation is operationalised differently in the trials: as referring to the medicines separately, to at least one or more medicines or to all medicines.
- For treatment options with continuous therapy, the proportions for treatment discontinuation will be higher with longer follow-up. However, the length of follow-up is different in the trials.
- With CAR-T cell therapy, the therapy usually consists of bridging therapy, followed by chemotherapy for lymphodepletion and CAR-T cell infusion. Discontinuation of therapy due to AE is possible during bridging therapy and/or chemotherapy. However, this might not necessarily lead to discontinuation of CAR-T cell therapy altogether. As CAR-T cell therapy only involves a single application of CAR-T cells and usually does not include

maintenance therapy, there is no treatment discontinuation possible afterwards.

- With ASCT, discontinuation is possible either during induction therapy (discontinuation of one or more medicine or discontinuation of the whole treatment) or after induction therapy if patients decide not to undergo ASCT. As ASCT usually involves maintenance therapy after the infusion of the stem cells, discontinuation is possible even after ASCT.

Due to these differences, comparing the figures from different trials or even within trials, when different treatment modalities are tested, does not allow for meaningful conclusions. Therefore, we do not include data on treatment discontinuation due to AE in this evidence report.

Most important AE

Most important AE include a selection of very common AE as well as AE of special interest.

Qualitative data (Table 17) have been extracted primarily from AEs with a frequency of at least 10 % as listed in the summary of product characteristics as well as AE listed in treatment guides for patients provided by Myeloma UK [69,70] and the International Myeloma Foundation [71]. Instead of listing every single AE, these have been summarised where possible. Single AE overlapping with other descriptions (e.g. cough or dyspnoea might be a result of infection) are not reported separately either. Where possible, AE are summarised by drug class. AE, which apply only to certain drugs within a drug class, are listed separately. AE of special interest are described separately.

It should be noted that the information in this evidence report is not exhaustive and that the exact frequency of AE might differ when medicines are used in certain combinations. It is also possible that drugs within a drug class differ in the frequency of the listed AE.

Patients should regularly be monitored for the respective AE including blood tests where necessary. In some situations, dose reduction or treatment interruptions might be indicated due to AE.

Table 17: Overview of most important AE and AE of special interest

Treatment	**Most important AE**	**AE of special interest***
All treatment options	low blood counts with increased risk of infection, bleeding and anaemia, fatigue, gastrointestinal symptoms (e.g. diarrhoea)	Infection
CD38 antibodies (Dara, Isa)	IRR; peripheral neuropathy, peripheral oedema	IRR
PI	All PI: peripheral neuropathy, peripheral oedema, skin rash, blood pressure changes	K: IRR

Treatment	Most important AE	AE of special interest*
	K (additionally): IRR, heart problems (e.g. atrial fibrillation, heart failure, myocardial infarction), blood clots, acute kidney failure	
IM	All IM: peripheral oedema, peripheral neuropathy, blood clots, skin rash, SPM Pomalidomide (additionally): heart problems (e.g. atrial fibrillation, heart failure, myocardial infarction), mood changes	SPM
Elotuzumab	IRR, SPM	IRR, SPM
SelVd	peripheral neuropathy, hyponatraemia, cataracts, blurry vision	
Belantamab-Mafodotin	peripheral neuropathy, IRR, ocular toxicity	Ocular toxicity, IRR
Bispecific antibodies	All bispecific antibodies: CRS, Neurotoxicity (ICANS and non-ICANS) Talquetamab (additionally): skin and nail disorders, severely dry skin, oral toxicity (dry mouth, dysgeusia, dysphagia), sometimes requiring nutritional support	CRS, ICANS
CAR-T	Lymphodepletion with cyclophosphamide/fludarabine (additionally): sore mouth and throat, hair thinning or loss, Cilta-cel (additionally): Neurotoxicity (ICANS and non-ICANS), IRR, CRS, SPM	IRR, CRS, ICANS, SPM
ASCT	Induction therapy: depending on the medicines used (see CD38 antibodies, PI, IMiD) G-CSF: Joint or bone pain, injection site reaction, headache, fever High-dose melphalan: gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea), SPM sore mouth and throat, hair thinning or loss	SPM

Treatment	Most important AE	AE of special interest*
	Maintenance therapy: depending on the medicines used (see CD38 antibodies, PI, IMiD)	
Dexamethasone	Mood changes, skin changes (stretch marks, thinning), insomnia, muscle weakness, fluid retention (e.g. peripheral oedema), gastric irritation or ulcers, increased appetite, increased blood sugar	n.a.

ADC: antibody drug conjugate, ASCT: autologous stem-cell transplantation, CAR-T: Chimeric Antigen Receptor T-cell therapy, CRS: cytokine-release syndrome, ICANS: immune effector cell-associated neurotoxicity syndrome, G-CSF: Granulocyte-Colony Stimulating Factor, IMiD: immunomodulatory drug, IRR: infusion/injection-related reaction, n.a. not applicable, PI: proteasome inhibitor, SPM: secondary primary malignancies
* besides infections

Adverse effects of special interest

Infection: An increased risk of infection is a common adverse effect of all treatments for RRMM. Besides advice for hygienic and behavioural measures, patients may be given prophylactic medicines such as antivirals or antibiotics.

Infusion/injection-related reaction (IRR) is an umbrella term for a group of symptoms due to different pathomechanisms which may happen during or shortly after the infusion or injection. Symptoms can include feeling short of breath, cough, chills, nausea and (in severe cases) increased blood pressure. They can be mild but also include life-threatening events (e.g. anaphylaxis). To prevent IRR, prophylactic medicines (e.g. paracetamol, antihistamines) are given before the infusion/injection. For the prevention of delayed IRR, medication might also be required for a few days afterwards.

Cytokine-release syndrome (CRS): CRS occurs when the immune system is highly activated which leads to the excessive release of cytokines. Cytokines are messenger substances which regulate immune response and inflammation. The excessive release of cytokines may lead to a severe, systemic inflammatory response which might damage tissue and organs. Symptoms of CRS can range from mild to life-threatening and include fever, chills, difficulty breathing, dizziness, nausea, headache, tachycardia, low blood pressure up to multi-organ failure. CRS can occur up to several days or more than two weeks after the application and may persist up to a week. To prevent CRS, premedication is given. Patients are monitored closely to recognise and treat CRS early.

Immune effector cell-associated neurotoxicity syndrome (ICANS) and non-ICANS neurotoxicity: ICANS often correlates with CRS but can also occur independently or after the resolution of CRS. Symptoms can be severe, life-threatening or fatal and may include confusion, disorientation, loss of

consciousness, seizures, difficulties to speak, write or read. Patients are monitored closely to recognise and treat ICANS early. Non-ICANS neurotoxicity can be delayed and may include symptoms such as tremors, slower movements, changes in personality, depression, motoric and sensory peripheral neuropathy (e.g. tingling or painful sensations, weakness of extremities) and/or facial numbness.

Ocular toxicity: Ophthalmological adverse events with Belantamab mafodotin affects mainly the cornea. Patients may experience visual disturbances, dry eye and/or photophobia. However, corneal damage might be sometimes only recognisable in ophthalmological exams. Therefore, patients are advised to undergo regular eye checks during treatment and to report any visual disturbances to their doctor. Visual disturbances might interfere with the ability to drive or to operate machinery.

It is recommended to use lubricating eye drops during the treatment and not to use contact lenses. In the case of ocular toxicity, a dose reduction or treatment interruption may be required until the adverse events are resolved or at least significantly reduced. In clinical trials, severe ocular toxicity (Grade ≥ 3) affected 34 to 43 % of patients.

Secondary primary malignancies (SPM): Some myeloma treatments have been associated with an increased risk of secondary primary malignancies (SPM). There are indications for ASCT (probably due to the genotoxic properties of melphalan) for elotuzumab, Cilta-cel and the immunomodulators lenalidomide and pomalidomide as listed in the summary of product characteristics.

SPM might include non-invasive/cutaneous tumours, but also solid tumours and haematological malignancies (Table 18). As a rough estimate, within 3 to 6 years any SPM (including non-invasive SPM) might affect up to 17 % of people receiving one of these treatments, invasive SPM about 3 to 7 % and haematological SPM about 1 to 4 %.

It should be noted, however, that these figures usually rely on few events. Additionally, cross-trial comparisons might be precluded by the fact that the occurrence of SPM might be influenced by several confounding factors such as age or previous therapy. Additionally, there are differences between the trials in the reporting (e.g. any SPM or invasive SPM) as well as the length of follow-up. Therefore, it might be more appropriate only to mention the possibility of SPM rather than to communicate quantitative data.

Table 18: Secondary primary malignancies

Comparison	Follow-up	SPM		
		Any	Invasive	Haematological
EloRd vs Rd [34]	Minimum 48 months	17 % vs 11 %	Not reported	Not reported
EloPd vs Pd [36]	Minimum 45 months	6.7 % vs 3.6 %	Not reported	Not reported
Cilta-cel vs VPd or DaraPd [50] [a]	Median 33.6 months	13.0 % vs 11.5 %	2.9 % vs 3.8 %	3.4 % vs 0.5 %
ASCT vs no ASCT	Median 48 months [10] [b]	8.9% vs 7.4 %	6.6 % vs 4.9 %	1.4 % vs 0.3 %
	Median 76 months [11] [c]	10.7 % vs 10.4 %	6.8 % vs 5.3 %	3.6 % vs 2.5 %
ASCT (with quadruplet or triplet) [12] [d]	Median 48 months	10.5 % vs 7.2 %	Not reported	2.8 % vs 2.6 %

ASCT: autologous stem-cell transplantation, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, Elo: Elotuzumab, P: Pomalidomide, R: Lenalidomide, SPM: secondary primary malignancies, V: Bortezomib.
[a] Table S12
[b] Table S4
[c] Table S5
[d] Table S5

Ability to drive

As listed in the summary of product characteristics, some of the treatment options may have major impact on the ability to drive (Table 19), at least temporarily. Patients should discuss with their doctors on a case-by-case basis the consequences for their everyday life.

Table 19: Impact on the ability to drive

	Minor or moderate	Major
ADC-based triplets	x	
Other triplets	x	
CAR-T		x
Bispecific antibodies		x
ASCT		x

ADC: antibody drug conjugate, ASCT: autologous stem-cell transplantation, CAR-T: Chimeric Antigen Receptor T-cell therapy

Serious AE

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. In all trials, the proportions for serious AE refer to patients experiencing at least one serious adverse event during or shortly after treatment. This was usually until 30 days after the treatment; for treatment with Cilta-cel, however, up to 112 days after the CAR-T cell infusion.

The data have been extracted from the ASCO guideline. These data refer to the period during treatment as reported in the journal publications. Where available, we supplemented the information in the guideline with longer follow-up data for the comparative trials when this facilitates cross-trial comparisons.

Data for other triplets from the trials comparing to doublets (indirect evidence) have not been extracted for the safety outcomes as the differences in length of follow-up preclude the indirect comparisons anyway. Therefore, only direct evidence for other triplets is reported here.

Data for bispecific antibodies in the 4th line of treatment were not available in the ASCO guideline and were therefore extracted primarily from the journal publications. For elranatamab, the results for SAE were not available from the journal publication and were extracted from the US study registry instead.

Data on SAE are shown in Table 20 (direct evidence) and Table 21(indirect evidence).

Table 20: Direct evidence for serious adverse events

Treatment (trial)	Proportion with intervention	Proportion with comparator	Follow-up (median, months)	GRADE	Source
Cilta-cel vs DaraPd or VPd (CARTITUDE-4) [a]	44 per 100	39 per 100	16	Moderate	EP 4.1
	47 per 100	47 per 100	34		[50]
BelaVd vs DaraVd (DREAMM-7)	50 per 100	37 per 100	28	Moderate	EP 4.17
	53 per 100	38 per 100	39		[15]
BelaPd vs VPd (DREAMM-8)	63 per 100	45 per 100	21	Moderate	EP 4.18
TecDara vs DaraPd or DaraVd (MajesTEC-3)	71 per 100	62 per 100	35	Moderate	EP 4.19, [53]

If not otherwise indicated, all results have been extracted from the evidence profiles (EP) in the data supplement of the ASCO guideline [3]. Bela: Belantamab mafodotin, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, d: Dexamethasone, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib.
[a] The difference between the groups is not statistically significant.

Table 21: Indirect evidence for serious adverse events (single arms)

Treatment	Proportion with intervention	Follow-up (median, months)	Source
Bispecific antibodies			
Elranatamab	68 to 69 per 100	15	[a]
Linvoseltamab	75 per 100	12	[b]
Talquetamab	51 to 55 per 100	12	[63] [c]
Teclistamab	65 per 100	14	[58] [d]
ASCT			
Quadruplet induction	57 per 100	48	[12]
Triplet induction	50 per 100		

ASCT: autologous stem-cell transplantation, TCRT: T-cell redirecting therapy (CAR-T or bispecific antibodies)
[a] https://clinicaltrials.gov/study/NCT04649359?tab=results#adverse-events
[b] Serious adverse reactions occurred in 75% of patients who received linvoseltamab. https://www.ema.europa.eu/en/documents/product-information/lynozyfic-epar-product-information_en.pdf
[c] 55% of patients in the 0·4 mg/kg once a week group, 53% of patients in the 0·8 mg/kg every 2 weeks group, and 51% patients in the previous TCRT group had at least one serious adverse event
[d] Tab. S8, any serious adverse event: 64.8%

Interpretation of the data

The data for SAE have been interpreted and are presented here as described for overall mortality (FAQ1) and the risk of death or disease progression (FAQ2) except for the omission of indirect comparisons for other triplets (see above).

ASCT

- Due to the lack of evidence, it is not possible to estimate the direction of the effect in comparison to the other treatment options.
- The proportion of patients with SAE is 50 per 100 and 57 per 100 with triplet and quadruplet induction, respectively, with a follow-up of 48 months.
- As the range is quite similar for both induction options and this is only a very rough estimate, it can be reported as "about half of the patients" in the decision aid.

Bispecific antibodies

Monotherapy, 4th line/3 prior therapies

- Only single-arm trials are available for this treatment option. Additionally, the populations in the trials differ fundamentally from those in the trials with the other therapy options as patients are heavily pretreated and have a substantially higher number of prior lines of therapy. Therefore, they might

be more vulnerable populations than in the other trials which precludes comparison with the other treatments. Therefore, it is not possible to estimate the direction of the effect in comparison to the other treatment options.

- Due to the lack of comparative data, a range for all bispecific antibodies in the 4th line of therapy should be communicated.
- The proportion of patients with SAE is 51 to 75 per 100 with a follow-up of 12 to 15 months.

TecDara

- Compared to CAR-T (Cilta-cel): There is only indirect evidence.
    - At 34 months, the risk of SAE is 47 per 100 with Cilta-cel.
    - At 35 months, the risk of SAE is 71 per 100 with TecDara.
    - Direction of the treatment effect: Based on the difference between the treatment effects, the risk might be higher with TecDara than with Cilta-cel. However, the certainty of the evidence is very low.
    - The figures can be communicated as given above. It should, however, be pointed out that they were compiled from different trials.
- Compared to ADC-based triplets: There is only indirect evidence.
    - The risk of SAE is 63 per 100 with BelaPd at 21 months, 53 per 100 with BelaVd at 39 months and 71 per 100 with TecDara within 35 months.
    - Direction of the treatment effect: Due to the heterogeneity between the ADC-based triplets and the differences in the length of follow-up, it cannot be reliably estimated if the risk of SAE is lower with TecDara or an ADC-based triplet. It is also not clear if this might be different for BelaPd and BelaVd, respectively.
    - The risk of SAE at 21 to 39 months with any of the treatment options is 53 to 71 per 100.
- Compared to other triplets:
    - There is direct evidence in comparison to the other triplets DaraVd or DaraPd at 35 months.
    - Direction of the effect: TecDara probably increases the frequency of SAE compared to DaraVd or DaraPd (GRADE: moderate).

- The proportion of patients with SAE is 71 per 100 with TecDara and 62 per 100 with DaraVd or DaraPd with a median follow-up of 35 months. The difference is statistically significant.
- For the comparison to any other triplet, there is no direct evidence. Therefore, it is unknown if proportions are similar with other triplets.

CAR-T

- Compared to ADC-based triplets: There is only indirect evidence.
  - The proportion of SAE is
    with Cilta-cel 44 per 100 at 16 months and 47 per 100 at 34 months, with BelaVd 50 per 100 at 28 months and 53 per 100 at 39 months, with BelaPd 63 per 100 at 21 months.
  - Direction of the treatment effect: Due to the heterogeneity between the ADC-based triplets and differences in the lengths of follow-up, it cannot be reliably estimated if SAE are more frequent with CAR-T or an ADC-based triplet. It is also not clear if this might be different for BelaPd and BelaVd, respectively.
  - The proportion of SAE with any of the treatment options is 44 to 63 per 100 within 16 to 39 months.
- Compared to other triplets:
  - There is direct evidence for the comparison to the other triplets DaraPd or VPd. At 34 months, the frequency of SAE was similar with Cilta-cel and DaraPd or VPd: 47 per 100. However, the confidence interval includes important harm.
    It should be also noted that the proportion of SAE was similar although the length of treatment is considerably longer with the triplet than with the single-treatment option Cilta-cel. This means: With the triplets, SAE accumulate over time, whereas SAE with Cilta-cel mainly occur within the first weeks after the treatment. This is reflected in the higher rate of SAE with Cilta-cel at a follow-up of 16 months (44 per 100 vs 39 per 100). There are, however, no Kaplan-Meier curves available to explore this phenomenon further.
  - Direction of the effect: Cilta-cel probably has little effect on the frequency of SAE during treatment (GRADE: moderate).
  - For the comparison to any other triplet, there is no direct evidence. Therefore, it is unknown if proportions are similar with other triplets.

ADC-based triplets

The data for the two ADC-based triplets BelaVd and BelaPd appear heterogenous. It should be noted, however, that the trial populations differ in terms of prior therapies and/or refractory status and that longer follow-up is available for BelaPd than for BelaVd.

BelaPd compared to other triplets

- There is direct evidence in comparison to the other triplet VPd. At 21 months, the risk of SAE is 63 per 100 with BelaPd and 45 per 100 with VPd. The difference is statistically significant.
- Direction of the treatment effect: Compared to VPd, BelaPd probably increases the frequency of SAE during treatment (GRADE: moderate).
- For the comparison to any other triplet, there is no direct evidence. Therefore, it is unknown if proportions are similar with other triplets.

BelaVd compared to other triplets

- There is direct evidence in comparison to the other triplet DaraVd. At 39 months, the risk of SAE is 53 per 100 with BelaVd and 38 per 100 with DaraVd. The difference is statistically significant.
- Direction of the treatment effect: Compared to DaraVd, BelaVd probably increases the frequency of SAE during treatment (GRADE: moderate).
- For the comparison to any other triplet, there is no direct evidence. Therefore, it is unknown if proportions are similar with other triplets.

Conclusion for the decision aid

For each treatment comparison, a text module should be developed according to the module matrix (Table 22).

Table 22: Module matrix for serious adverse events

	ADC-based triplets	**Other triplets**	**CAR-T**	**Bispecific antibodies**	**ASCT**
ADC-based triplets					
Other triplets	SAE1.1 [a] SAE1.2 [b]				
CAR-T	SAE2.1	SAE2.2			
Bispecific antibodies	SAE3.1 [c]				
	SAE3.2 [d]	SAE3.3 [d]	SAE3.4 [d]		
ASCT	SAE4				

ADC: antibody drug conjugate, ASCT: autologous stem-cell transplantation, Bela: Belantamab, CAR-T: Chimeric Antigen Receptor T-cell therapy, Dara: Daratumumab, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib

[a] for BelaPd, [b] for BelaVd, [c] for monotherapy 4th line, [d] for TecDara

Separate text modules should be prepared for the comparison of other triplets vs the ADC-based triplets BelaVd and BelaPd, respectively, to account for the direct comparisons available from the DREAMM-7 and DREAMM-8 trials.

As no data are available for ASCT as second-line treatment, the same text module can be used for all comparisons. The text modules should reflect the interpretation of the data (Table 23).

Table 23: Interpretation of the data for SAE

Module	Interpretation
SAE1.1	Serious adverse events are probably more frequent with BelaPd than with the other triplet VPd. It is, however not known if this applies to all other triplets as there are no comparative trials for all triplet options. *What we know from clinical trials* Experiencing at least one serious adverse event within 21 months, concerns approximately • 63 per 100 people with BelaPd • 45 per 100 people with VPd
SAE1.2	Serious adverse events are probably more frequent with BelaVd than with the other triplet DaraVd. It is, however not known if this applies to all other triplets as there are no comparative trials for all triplet options. *What we know from clinical trials* Experiencing at least one serious adverse event within 39 months, concerns approximately • 53 per 100 people with BelaVd • 38 per 100 people with VPd
SAE2.1	It is not known if serious adverse events are more frequent with an ADC-based triplet (BelaPd or BelaVd) or CAR-T cell therapy. There are no trials which compared both treatments directly. *What we know from clinical trials* Approximately, within 16 to 39 months, 44 to 63 per 100 people experience at least one serious adverse event.
SAE2.2	The risk of serious adverse events is overall probably similar with Cilta-cel and the other triplets DaraPd or VPd or slightly higher. This might be especially true for the first weeks after the CAR-T cell treatment. It is, however not known if this applies to all other triplets as there are no comparative trials for all triplet options. *What we know from clinical trials* Experiencing at least one serious adverse event within 34 months, concerns approximately 47 per 100 people with either treatment.

Module	Interpretation
SAE3.1	It is not known if serious adverse events are more frequent with bispecific antibodies or the other treatment options. There are no trials which compared both treatments directly. *What we know from clinical trials* Within 12 to 15 months, approximately 51 to 75 per 100 people experience at least one serious adverse event. These figures apply to patients after three or more previous lines of therapy and with triple-class refractory disease. In the trials with bispecific antibodies, patients had on average more relapses and more lines of therapy than patients in the trials with the other treatments. Therefore, the figures cannot be compared.
SAE3.2	It is not known if serious adverse events are more frequent with TecDara than with an ADC-based triplet (BelaVd or BelaPd). There are no trials which compared both treatments directly. *What we know from clinical trials* Approximately, within 21 to 39 months 53 to 71 per 100 people experience at least one serious adverse event with either treatment option.
SAE3.3	Serious adverse events are probably more frequent with TecDara than with the other triplets DaraVd or DaraPd. It is, however not known if this applies to all other triplets as there are no comparative trials for all triplet options. *What we know from clinical trials* Experiencing at least one serious adverse event within 35 months, concerns approximately • 71 per 100 people with TecDara • 62 per 100 people with DaraPd or DaraVd.
SAE3.4	Serious adverse events might be more frequent with TecDara than with Cilta-cel. However, there are no comparative trials. Therefore, the certainty of the evidence is very low. *What we know from clinical trials* Experiencing at least one serious adverse event within about 3 years, concerns approximately • 47 per 100 people with Cilta-cel • 71 per 100 people with TecDara These figures cannot be directly compared as they were derived from different trials.

Module	Interpretation
SAE4	It is not known if serious adverse events are more frequent with ASCT or with any of the other treatment options. There are no trials which compared treatments directly. *What we know from clinical trials* To our best guess, about half of the patients, who receive ASCT, experience at least one serious adverse event over the course of about 4 years. This estimate, however, is derived from a trial in which patients received ASCT as a therapy for newly diagnosed myeloma, not for relapsed myeloma. It is not clear if the risk of SAE might be higher in relapsed myeloma than in newly diagnosed myeloma.
ADC: antibody drug conjugate, ASCT: autologous stem cell transplantation, Bela: Belantamab mafodotin, CAR-T: Chimeric Antigen Receptor T-cell therapy, Cilta-cel: Ciltacabtagene autoleucel, Dara: Daratumumab, d: Dexamethasone, P: Pomalidomide, Tec: Teclistamab, V: Bortezomib.	

DISCUSSION

SUMMARY OF MAIN FINDINGS

In terms of overall mortality and the risk of death or disease progression, TecDara, Cilta-cel and ADC-based triplets seem more effective than the triplet they were tested against. The only exception is BelaPd for which it is not clear if there is an advantage in overall mortality.

On the other hand, serious adverse events seem to be more common with TecDara and ADC-based triplets. There is some ambiguity in the data if this also applies to Cilta-cel.

The other comparisons rely on indirect evidence and are thus rather uncertain. For monotherapy with bispecific antibodies and ASCT as second line of therapy, no conclusions can be drawn in terms of comparative effectiveness and safety.

The data on symptoms and quality of life are rather complex and often underreported for most comparisons.

A summary of the main comparisons regarding overall mortality, PFS and serious adverse events can be found in Table 24.

Table 24: Summary of results for the main comparisons

	ADC-based triplets	Other triplets	TecDara
CAR-T			
Overall mortality	⇔ ○○○○	CAR-T better survival ●●●○	⇔ ○○○○
PFS	⇔ ○○○○	CAR-T better PFS ●●●○	TecDara better PFS ○○○○
SAE	⇔ ○○○○	CAR-T slightly higher or comparable SAE ●●●○	TecDara higher SAE ○○○○
TecDara			
Overall mortality	⇔ ○○○○	TecDara better survival ●●○○	
PFS	TecDara better PFS ○○○○	TecDara better PFS ●●●●	
SAE	⇔ ○○○○	TecDara higher SAE ●●●○	

CAR-T: Chimeric Antigen Receptor T-cell therapy, PFS: progression-free survival, SAE: serious adverse events, TecDara: Teclistamab-Daratumumab
⇔ direction of effect not estimable, ○○○○ No direct evidence
GRADE for direct comparisons: ●●●● high, ●●●○ moderate, ●●○○ low

Strength, limitations and uncertainties

A strength of this evidence report is the foundation on clinical expertise and patients' needs in terms of PICO and the FAQs and the discussion of the most important treatment options which are recommended and/or preferred in current guidelines. A further strength is the broad evidence base consisting of an evidence-based guideline and journal publications as well as data from regulatory authorities, medical societies and patient information. These data have been assessed thoroughly according to international standards for evidence-based medicine.

However, there are also some important limitations and uncertainties:

- Due to the multitude of available treatments, we focussed on comparing distinct treatment options. Therefore, we did not include information on comparisons of different treatments within one option.
- In some trials, data for overall mortality and PFS were not mature. Conclusions might change with longer follow-up.
- The focus on the rates of serious adverse events overall might not capture differences in special serious adverse events.
- The differences in the modes of application (single or continuous therapy) precluded meaningful conclusions for the outcome discontinuation due to adverse events.

- For the majority of comparisons, only indirect evidence was available which was triangulated for conclusions. We acknowledge that there is considerable uncertainty with this approach, especially as trial populations for the interventions are quite heterogeneous, e.g. in terms of prior therapy. This also raised the question if better approaches, e.g. NMA, would be feasible at all. Therefore, we relied on a best available evidence approach instead.
- It should be noted that in many trials (with the exception of those testing monotherapy with bispecific antibodies) participants had mostly or exclusively up to 3 prior therapies. It is uncertain if the results can be applied to later lines of therapy.
- In the absence of direct comparisons and/or of statistical tests for differences in proportions, we used a threshold of 10% to assume a relevant difference. Although this threshold is based broadly on the ESMO Magnitude of Clinical Benefit Scale for Haematological Malignancy, we are aware that many criteria for the use of this scale are not met in our case. Therefore, it is possible that trials with direct comparisons might lead to different conclusions than this evidence report. However, such trials are not available.
- For ASCT in the 2nd line of therapy, there is no evidence at all except trials testing deferred ASCT in the 1st line of therapy. Therefore, it was not possible to draw conclusions on the efficacy of this intervention in comparison to other treatment options.
- For monotherapy with bispecific antibodies, only single-arm trials are available. The trial populations were heavily pre-treated which precludes comparisons with other interventions tested in earlier lines of therapy.

Comparison with the results of early benefit assessments

In this section, we only discuss results of assessments for the available direct comparisons, as assessments for most triplet options rely on comparisons to doublets which are not relevant for this evidence report.

As of 15.07.2026, final decisions by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) are available only for Cilta-cel and monotherapy with bispecific antibodies.

- There are no comparative trials for the monotherapy with bispecific antibodies. Therefore, no added benefit was acknowledged for elranatamab [72], linvoseltamab [73] and teclistamab [74]. The decision for teclistamab is temporary until January 2027 due to the expected results from the MajesTEC-9 trial. Talquetamab has a marketing authorisation as

orphan drug which leads per se to an acknowledged added benefit. The magnitude, however, was assessed as non-quantifiable [75].

- For Cilta-cel, a hint of a major added benefit was acknowledged for patients with a maximum of 3 prior therapies, but not beyond (patients in later lines of therapy were not included in the trials). This was based mainly on the differences in overall mortality, whereas the data on morbidity were not deemed suitable for the benefit assessment. For overall serious side effects, the assessment found no disadvantage of Cilta-cel. The G-BA assessment points out that there are differences in special serious adverse events, e.g. neurotoxicity, although this is not reflected in the overall rate of serious adverse events [76].

For ADC-based triplets, only IQWiG assessments are available for the time being: For both BelaVd and BelaPd, the data have been assessed as not suitable for the early benefit assessment. The main reason is the availability of only one comparator whereas the appropriate comparator therapy includes several options which have to be chosen individually [77,78].

For TecDara, no assessment (final decision or IQWiG report) is available yet.

With the exception of ADC-based triplets, the assessments are quite similar to those in this evidence report. 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).

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APPENDIX

LITERATURE SEARCHES

Information on medicines

Handsearching websites of relevant organisations 15.06.2026

EMA https://www.ema.europa.eu/

International Myeloma Working Group
https://www.myeloma.org/imwg-publications

Guidelines

Handsearching websites of relevant organisations 09.06.2026

Inclusion criteria: Published 2025-2026

Table 25: Retrieval of the search for guidelines

Organisation	**Hit**
Leitlinienprogramm Onkologie [a]	0 (only guideline from 2022)
ESMO [b]	0 (only guideline from 2021)
EHA/EMN [c]	https://www.nature.com/articles/s41571-025-01041-x (Version 27.05.2025)
ASCO [d]	https://ascopubs.org/guidelines/treatment-multiple-myeloma-asco-living-guideline (Version 2026.1.1)

[a] https://www.leitlinienprogramm-onkologie.de/leitlinien/
[b] https://www.esmo.org/guidelines/esmo-clinical-practice-guidelines-haematological-malignancies
[c] https://ehaweb.org/clinical-practice/guidelines-by-areas-of-disease
[d] https://ascopubs.org/topics/asco-guidelines/hematologic-malignancies

RCTs

PubMed 16.06.2026

#1: "myeloma"[Title/Abstract] AND ("relaps*"[Title/Abstract] OR "refract*"[Title/Abstract])

#2: "random*"[Title/Abstract] OR "randomized controlled trial"[Publication Type]

#3: 2026/02/01:3000/12/31[Date - Publication]

#4: #1 AND #2 AND #3 = 37 hits

Search strategy saved for automated updates.

Update search 01.07.2026

Hits = 10

SELECTION OF THE EVIDENCE

Guidelines

Table 26: Selection of guidelines

Guideline	Suitable for PICO?	Suitable for data extraction?	Decision
EHA/EMN 2025	Y	N (no systematic searches)	Included to inform PICO and background information on medicines
ASCO 2026.1.1	Y	Y	Included to inform PICO and for data extraction

RCTs

Abstract screening

Search 16.06.2026

n = 37 (see separate Rayyan file)

Excluded: n = 34

Included for full-text screening: 3

Search 01.07.2026

N = 10 (see separate Rayyan file)

Excluded: n = 10

No inclusion for full-text screening

Full-text screening

Mina 2026 https://pubmed.ncbi.nlm.nih.gov/42294841/
MonumenTAL-3: TalDaraP vs. TalDara vs DaraPd (second line)
not yet authorised, included to "studies awaiting classification" for next update

Dimopoulos 2026 https://pubmed.ncbi.nlm.nih.gov/42289183/
SUCCESSOR-2: Mezig-Kd vs Kd (second line)
not yet authorised, included to "studies awaiting classification" for next update

Touzeau 2026 https://pubmed.ncbi.nlm.nih.gov/42212933/
MajesTEC-9: Tec vs. VPd or Kd (second line)
not yet authorised, included to "studies awaiting classification" for next update

RISK OF BIAS ASSESSMENTS

ASCO Guideline

Treatment of Multiple Myeloma: ASCO Living Guideline Version 2026.1.1

Table 27: Assessment of the guideline

Domain	Aspects	Notes
Systematic search of the literature	x Information available on the databases searched x Information available on search terms and/or search strategy x Information available on the date of the search	PubMed (published trials) and clinicaltrials.gov (on-going trials); search strategy Data supplement 2; date of the search: February 27, 2026
Inclusion and exclusion of trials/ publications	x Inclusion and exclusion criteria defined x Information available on the selection process x Information available on excluded trials/publications	Criteria p. 8, selection process p.8, excluded Data supplement 1B Table 6 Not explicitly selection by two independent reviewers, but controlled by guideline panel = sufficient.
Assessment of the evidence	x Risk of bias assessed with appropriate instrument x Certainty of the evidence rated with GRADE x Information available on assessment process	Cochrane Risk of Bias tool. Not explicitly assessment by two independent reviewers, but controlled by guideline panel = sufficient
Presentation of the evidence	x Sufficient description of the trials available x Evidence tables and/or evidence profiles available	Data supplement 1a/1b
Summary	x Methodical rigour sufficient x Suitable for data extraction x Update of the body of evidence necessary x Additional information from trial publications necessary	Comments: Check for newer trials; in evidence tables no information on symptoms or quality of life

GRADE assessment for symptoms and quality of life

Table 28: GRADE assessment

	CARTITUDE-4	**DREAMM-7**	**DREAMM-8**	**MajesTEC-3**
Risk of bias [a]	↓↓ [b, d]	↓↓ [c]	↓↓ [c]	↓↓ [c, d]
Imprecision	n.a.	n.a.	n.a.	n.a.
Inconsistency	↓	↓	↓	↓
Indirectness	n.a.	n.a.	n.a.	n.a.
Publication bias	n.a.	n.a.	n.a.	n.a.
Summary	↓↓↓ **very low**	↓↓↓ **very low**	↓↓↓ **very low**	↓↓↓ **very low**

All ratings start with high as the data have been collected in randomised controlled trials.
[a] All trials are open-label (lack of blinding).
[b] Patient-reported outcomes were assessed in the standard-of-care group once every 3–4 weeks during the first 3 months of the study but only twice—day 1 of bridging therapy and day 1 of lymphodepletion—in the Cilta-cel group during the same time period. This increased the potential to detect early worsening events in the standard-of-care group at the beginning of the trial and the ability to capture worsened patient-reported outcomes in the Cilta-cel group owing to bridging therapy and lymphodepletion
[c] The trials do not report all assessed domains (selective reporting).
[d] It is not clear if the clinically meaningful difference has been established correctly (CARTITUDE-4). The assumed clinically meaningful difference is not reported explicitly (MajesTEC-3).