MHA
Mohsin Haematology Academy

DOTS Masterclass 2026

Lisbon | GSK Symposium

Advances in Relapsed and Refractory Multiple Myeloma

BCMA-directed therapies, treatment sequencing, and the emerging concept of cure

Fact-checked educational symposium notes

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Executive summary

These working notes record the principal teaching points from the DOTS Masterclass GSK symposium held in Lisbon, with full fact-checking against the primary trial publications. The document covers the second-line setting in relapsed and refractory multiple myeloma, BCMA-directed therapeutic modalities, the DREAMM-7 and DREAMM-8 trials, the CARTITUDE-4 and MajesTEC-3 trial results, the regulatory status of belantamab mafodotin across the UK, EU, and US, and the emerging discussion of functional cure in myeloma.

Each major numerical claim is mapped either to a verified primary source or explicitly labelled as symposium-attributed or awaiting source specification. A panel of unresolved or genuinely uncertain points appears immediately before the references so the reader can see what remains debated rather than only what is settled.

Scope and limitations of these notes

These notes are based primarily on information captured by the author during the DOTS Masterclass 2026 symposium, supplemented by targeted verification against selected primary publications, regulatory sources, and reputable academic databases.

They are intended to complement and clarify the material recorded during the masterclass. They should not be read as a comprehensive review of relapsed or refractory multiple myeloma, a systematic literature review, or a formal treatment guideline.

Where a topic, dataset, subgroup analysis, toxicity signal, regulatory detail, or therapeutic option is not included, this may reflect one or more of the following: it was not presented during the symposium; it was not captured in the author's contemporaneous notes; it was outside the intended teaching focus of the session; or it could not be independently verified at the time of review.

Absence from this document should therefore not be interpreted as evidence that the data do not exist, that a therapeutic option is unsupported, or that an issue is clinically unimportant. Conversely, symposium-attributed statements should be interpreted with appropriate caution where the underlying primary source has not been identified.

The purpose of the document is to provide a structured, fact-checked educational record of the material captured at the masterclass, with explicit separation between published evidence, regulatory information, expert interpretation, and unresolved or unverified points.

How to read this document

- Trial efficacy figures are quoted as published. Where two analyses exist (primary and updated), both are listed and the source is named.
- Hazard ratios, 95% confidence intervals, and follow-up durations are included as published.
- References are in Vancouver format with PMID, DOI, and journal volume or page.
- Italic notes throughout flag where evidence is preliminary, where the published data do not support a stronger claim, or where a point is symposium-attributed rather than verified against the primary source.

1. The second-line setting in relapsed and refractory multiple myeloma

1.1 The treatment context

Almost all patients with multiple myeloma eventually relapse. At first relapse, treatment selection is driven by what the patient has already received, the pace and pattern of relapse, cytogenetic risk, organ function, and patient preference. Lenalidomide-refractory disease is now the rule rather than the exception because lenalidomide is used both in induction and in maintenance for newly-diagnosed patients. Multi-class refractory disease, particularly to a lenalidomide-bortezomib backbone, is associated with shorter progression-free survival on every comparator regimen.

1.2 Real-world prescribing patterns

Symposium-presented US real-world data (primary citation not located): approximately 44.4% of patients receive doublet therapy at first relapse, 41% receive triplet therapy, and 2.1% receive a quadruplet regimen. Doublet therapy at first relapse is associated with shorter progression-free survival than triplet therapy. A substantial proportion of patients therefore still receive less than the evidence supports. The percentages above are recorded as presented at the meeting; readers should treat them as symposium-attributed pending identification of the primary source.

1.3 BCMA as a target

B-cell maturation antigen is a member of the TNF receptor superfamily. It is highly expressed on malignant plasma cells, and is also present on normal late-stage B cells and plasmablasts. This biological pattern explains the hypogammaglobulinaemia and infection susceptibility seen with all BCMA-directed approaches, regardless of modality. For patients refractory to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 antibodies, BCMA represents a separate mechanism of action and a meaningful therapeutic option.

1.4 Adjacent emerging classes

Cereblon E3 Ligase Modulatory Drugs (CELMoDs): next-generation cereblon-binding agents, of which iberdomide and mezigdomide are the most clinically advanced, are entering the relapsed and refractory setting. They are mechanistically related to the IMiDs but offer deeper cereblon engagement and activity in lenalidomide-refractory disease. They sit alongside, rather than replace, BCMA-directed therapies in the sequencing discussion and were referenced at the symposium as part of the wider treatment context.

2. BCMA-directed therapeutic modalities

Three modalities are now in clinical use for relapsed and refractory disease.

Modality	Example agent	Mechanism	T-cell dependent	Principal toxicity
ADC	Belantamab mafodotin	BCMA binding, internalisation, MMAF payload causing microtubule disruption and apoptosis	No	Ocular: keratopathy, blurred vision, dry eye
CAR-T	Ciltacabtagene autoleucel (cilta-cel)	Autologous T cells engineered with anti-BCMA chimeric antigen receptor (4-1BB costimulation)	Yes	CRS, ICANS, prolonged cytopenias, infections, parkinsonism reported
BsAb	Teclistamab; elranatamab	BCMA × CD3 bispecific T-cell engagement, off-the-shelf	Yes	CRS, ICANS, infections (CMV, opportunistic)

2.1 Practical contrasts at the bedside

Antibody-drug conjugate (belantamab mafodotin): 30-minute intravenous infusion every 3 weeks, no mandated hospitalisation, no CRS or ICANS reported in DREAMM-7 or DREAMM-8, but ocular adverse events occur in roughly 80% of treated patients with grade 3 or 4 events in approximately 40%. Most ocular events are reversible with dose modification. The ADC modality offers a wider therapeutic window than T-cell-redirecting modalities, with a clearer separation between toxic and therapeutic dose ranges [ref 1, ref 2, ref 3].

CAR-T cell therapy (cilta-cel): Single infusion. Apheresis to infusion typically requires 4 to 6 weeks, with bridging therapy needed for many patients. Cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, prolonged cytopenias, and an increased risk of infection are recognised. Some patients show parkinsonism-like neurotoxicity and second primary malignancies have been reported [ref 4, ref 5, ref 7].

Bispecific antibody (teclistamab plus daratumumab): Subcutaneous administration, off-the-shelf, with step-up dosing requiring inpatient monitoring. Cytokine release syndrome and infection risk are notable. Grade 3 or 4 infections in MajesTEC-3 occurred in roughly half of patients, with infection-related deaths reported [ref 6].

3. DREAMM-7: BVd versus DVd

3.1 Trial design

DREAMM-7 was an international, open-label, randomised, phase 3 trial of belantamab mafodotin plus bortezomib and dexamethasone (BVd) versus daratumumab plus bortezomib and dexamethasone (DVd) in patients with RRMM who had received at least one prior line of therapy. Patients refractory to or intolerant of bortezomib were excluded; this was a bortezomib-refractory exclusion, not a wider PI-refractory exclusion. *494 patients were randomised (243 BVd, 251 DVd) [ref 1, ref 2].*

Baseline characteristics were balanced. Approximately 51% of patients had received only one prior line of therapy. Approximately 52% had prior lenalidomide exposure and approximately 34% had lenalidomide-refractory disease. High-risk cytogenetics (defined as one or more of t(4;14), t(14;16) or del(17p13)) were present in approximately 28% of patients [ref 1, ref 2].

3.2 Efficacy

Endpoint	BVd (n = 243)	DVd (n = 251)
Median PFS (primary analysis, 28.2-month follow-up)	36.6 months (95% CI 28.4 to NR)	13.4 months (95% CI 11.1 to 17.5)
Hazard ratio for progression or death	0.41 (95% CI 0.31 to 0.53)	P < 0.00001
18-month overall survival (primary analysis)	84%	73%
36-month overall survival (updated analysis, 39.4-month follow-up)	74%	60%
Hazard ratio for death (updated analysis)	0.58 (95% CI 0.43 to 0.79)	P = 0.00023
Overall response rate	82.7% (95% CI 77.4 to 87.3)	71.3% (95% CI 65.3 to 76.8)
Complete response or better with MRD-negative status (10^{-5})	25%	10%
PFS2 (updated analysis)	Not reached (95% CI 45.6 to NR)	33.4 months (95% CI 26.7 to 44.9), HR 0.59

Endpoint	BVd (n = 243)	DVd (n = 251)
Any-grade ocular adverse events	79%	29%
Grade 3 or 4 thrombocytopenia	56%	35%

3.3 Safety

Grade 3 or higher adverse events occurred in 95% of BVd patients and 78% of DVd patients in the primary analysis. Serious adverse events were reported in approximately half of BVd patients and 38% of DVd patients. Pneumonia was the most frequent serious infection. There were no cases of cytokine release syndrome or ICANS in the BVd arm [ref 1, ref 2].

Toxicity attribution at the bedside: the ocular adverse events seen with BVd are belantamab-driven, while gastrointestinal toxicity in either arm is largely bortezomib-driven. This separation is useful when investigating new symptoms in a patient on the regimen, since dose-modifying or pausing the right component is the appropriate response.

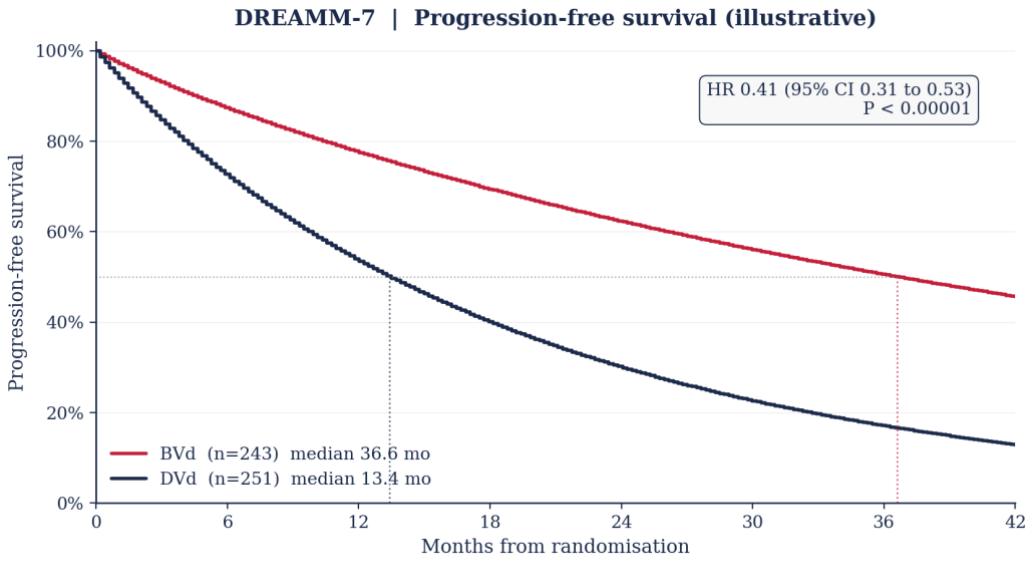
Ocular outcomes (symposium-presented detail): for first events of best corrected visual acuity at 20/50 or worse, approximately 98% of patients showed improvement with dose modification. Rare cases of corneal ulcer were managed by treatment interruption until healing was complete. These figures were presented at the symposium and have not been independently re-verified against the primary publication; they should be treated as symposium-attributed.

Lower rates of opportunistic infection and reduced IVIg use were observed with BVd compared with DVd. Most cases of decreased visual acuity returned to baseline with dose adjustment, and the efficacy benefit of BVd was preserved across patients who required ocular dose modification [ref 1, ref 2].

3.4 PFS2: a useful clinical signal

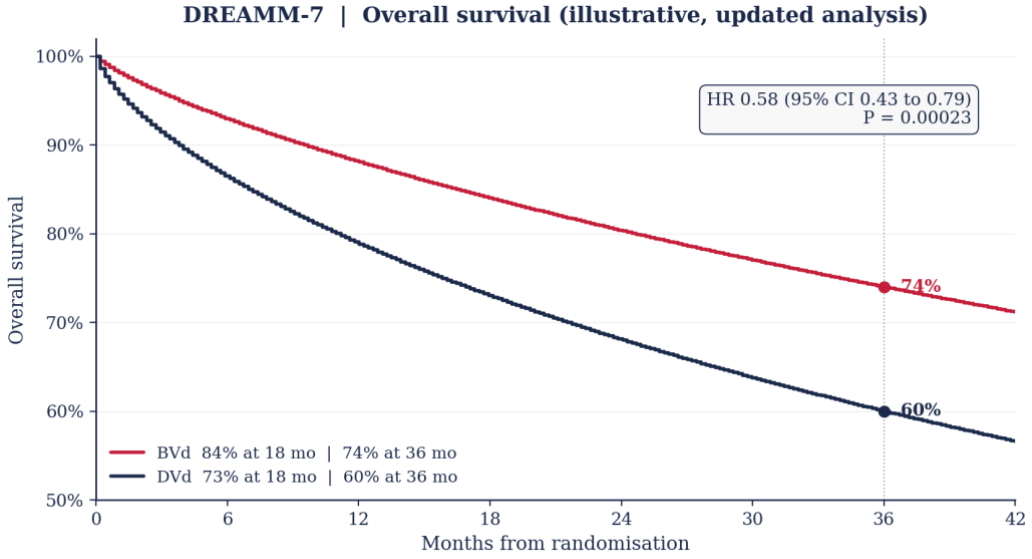
PFS2, the time from randomisation to progression on the next line of therapy or death, was substantially longer with BVd than DVd (median not reached versus 33.4 months, HR 0.59). The benefit of BVd is therefore not lost when the patient moves to subsequent therapy. This is reassuring when balancing first-relapse choice against later options [ref 2].

3.5 Survival curves



Illustrative curve fitted to published landmarks (median PFS). Not a reproduction of the original Kaplan-Meier plot. Source: ref 1.

Figure 1. DREAMM-7 progression-free survival. Illustrative re-creation fitted to published medians. Not a reproduction of the original Kaplan-Meier plot.



Illustrative curve fitted to published OS landmarks at 18 and 36 months. Not a reproduction of the original Kaplan-Meier plot. Source: ref 2.

Figure 2. DREAMM-7 overall survival, updated analysis. Illustrative re-creation fitted to published 18-month and 36-month landmarks.

4. DREAMM-8: BPd versus PVd

4.1 Trial design

DREAMM-8 was an international, open-label, randomised, phase 3 trial of belantamab mafodotin plus pomalidomide and dexamethasone (BPd) versus pomalidomide plus bortezomib and dexamethasone (PVd) in patients with RRMM who had received at least one prior line of therapy that included lenalidomide. Patients refractory to or intolerant of bortezomib were excluded. 302 patients were randomised [ref 3].

All patients had prior lenalidomide exposure and 78% to 81% had lenalidomide-refractory disease. Anti-CD38 refractory disease was present in approximately 23% of patients. High-risk cytogenetics were present in approximately 34% of patients (symposium-presented figure, consistent with the trial-reported profile) [ref 3].

4.2 Efficacy

Endpoint	BPd (n = 155)	PVd (n = 147)
12-month PFS (primary interim, FU 21.8 mo) [ref 3]	71% (95% CI 63 to 78)	51% (95% CI 42 to 60)
Median PFS (primary interim, FU 21.8 mo) [ref 3]	Not reached	12.7 months
Hazard ratio for progression or death (primary) [ref 3]	0.52 (95% CI 0.37 to 0.73); P < 0.001	
Overall response rate (primary) [ref 3]	77% (95% CI 70 to 84)	72% (95% CI 64 to 79)
Complete response or better (primary) [ref 3]	40% (95% CI 32 to 48)	16% (95% CI 11 to 23)
Grade 3 or higher AEs (primary) [ref 3]	94%	76%
Grade 3 or 4 ocular adverse events (primary) [ref 3]	43%	2%
Median PFS (updated post-hoc; source to be specified)	32.6 months	12.5 months

Endpoint	BPd (n = 155)	PVd (n = 147)
PFS2 (updated post-hoc; source to be specified)	47.1 months	21.7 months

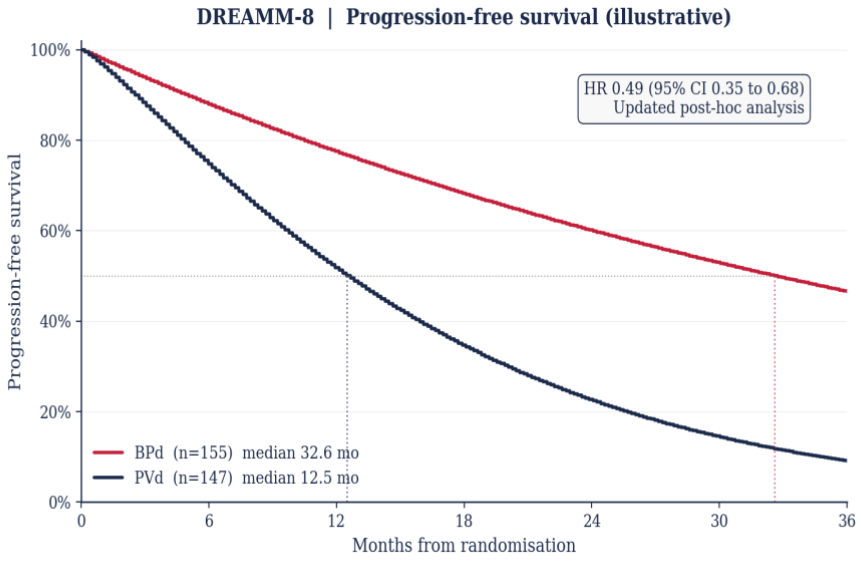
4.3 Safety profile

Any adverse event was reported in over 99% of BPd patients and approximately 96% of PVd patients. The most common grade 3 or 4 adverse events with BPd were ocular events (43%) and infections. There were no cases of cytokine release syndrome or ICANS. Ocular events were managed with dose modification and the efficacy benefit was preserved across patients who required dose adjustments [ref 3].

4.4 Where BPd fits clinically

BPd is well placed for patients who are lenalidomide-refractory but proteasome-inhibitor naive or sensitive, anti-CD38 refractory or unsuitable for an anti-CD38 retreatment, and able to tolerate ocular toxicity. The off-the-shelf profile and outpatient administration are practical assets, particularly when access to CAR-T or bispecific products is limited [ref 3].

4.5 Survival curves



Illustrative curve fitted to published median PFS. Not a reproduction of the original Kaplan-Meier plot. OS data from DREAMM-8 are immature and not plotted. Source: ref 3.

Figure 3. DREAMM-8 illustrative progression-free survival. The figure shows the magnitude and shape of separation between arms, using the updated post-hoc medians (BPd 32.6 mo vs PVd 12.5 mo, source to be specified). It is not a reproduction of the published Kaplan-Meier plot. Primary verified PFS endpoint at 21.8-month follow-up: median PFS not reached vs 12.7 months, HR 0.52 (ref 3).

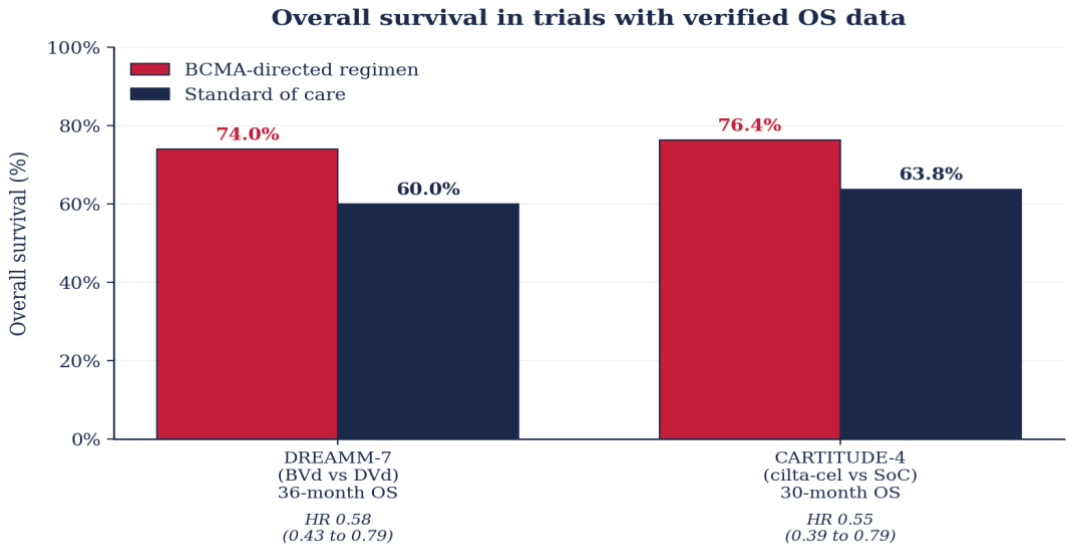
5. Trial efficacy benchmarks and sequencing

5.1 Verified efficacy benchmarks across pivotal trials

Three pivotal BCMA-directed trials in the second-line and later setting are summarised below. DREAMM-7 and CARTITUDE-4 have demonstrated and published overall survival superiority over standard of care. For MajesTEC-3, the published primary analysis demonstrates a marked PFS benefit; the OS data are not in the published abstract and have not been retained as a verified figure here pending review of the full publication.

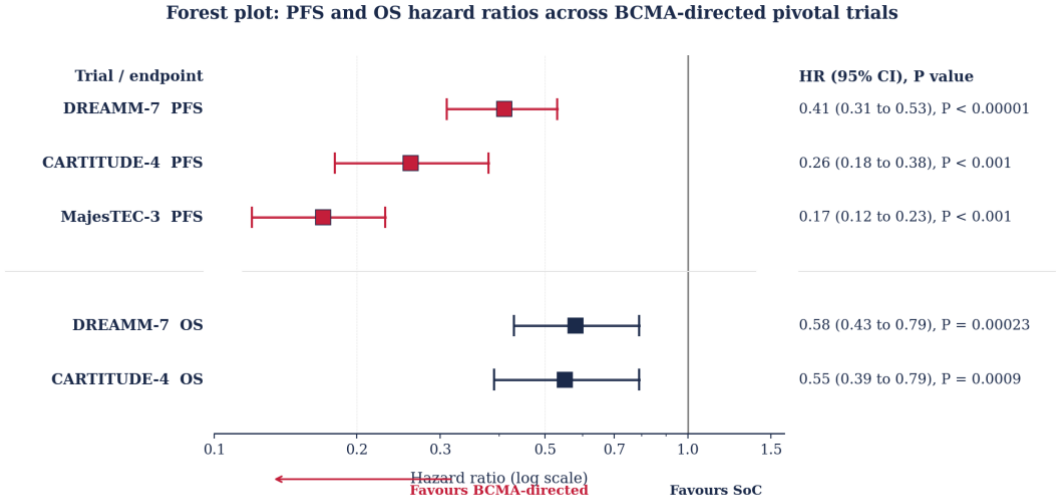
Trial	Regimen	Key efficacy finding	Source
DREAMM-7	BVd vs DVd	36-month OS 74% vs 60%; HR 0.58 (0.43 to 0.79); P = 0.00023	Hungria 2025, Lancet Oncol [ref 2]
CARTITUDE-4	Cilta-cel vs SoC (PVd or DPd)	30-month OS 76.4% vs 63.8%; HR 0.55 (0.39 to 0.79); P = 0.0009	Einsele 2026, Lancet Oncol [ref 5]
MajesTEC-3 (PFS only)	Tec + Dara vs DPd or DVd	36-month PFS 83.4% vs 29.7%; HR 0.17 (0.12 to 0.23); P < 0.001. OS data not retained as a verified figure (see caveat below).	Costa 2026, NEJM [ref 6]

Caveat on MajesTEC-3 overall survival: *the published abstract for MajesTEC-3 reports a marked PFS benefit but does not present an OS figure suitable for use as a verified benchmark. The OS row has therefore not been retained pending review of the full NEJM publication or supplement, at which point it can be restored if confirmed.*



Cross-trial comparison only; populations and SoC comparators differ. MajesTEC-3 OS data not shown because the figure could not be verified from the abstract-level source. Sources: refs 2, 5.

Figure 4. Overall survival in the two trials with verified published OS data: DREAMM-7 at 36 months and CARTITUDE-4 at 30 months. MajesTEC-3 OS data not shown for the reason given above (refs 2, 5).



PFS hazard ratios from primary published analyses. OS hazard ratios from latest published OS analyses. MajesTEC-3 OS not shown because the figure could not be confirmed from the published abstract. Sources: refs 1, 2, 3, 5, 6.

Figure 5. Forest plot of progression-free survival and overall survival hazard ratios. PFS hazard ratios shown for all three trials (DREAMM-7, CARTITUDE-4, MajesTEC-3); OS hazard ratios shown for the two trials with verified published OS (DREAMM-7, CARTITUDE-4). MajesTEC-3 OS not shown (refs 1, 2, 3, 5, 6).

Caveat on cross-trial comparison: *These are not head-to-head comparisons. Patient populations and SoC comparators differ between trials. CARTITUDE-4 enrolled lenalidomide-refractory patients only; MajesTEC-3 enrolled patients largely naive to or non-refractory to anti-CD38 antibodies; DREAMM-7 enrolled bortezomib-non-refractory patients. Cross-trial OS percentages are best read as a guide to where each modality is likely to deliver benefit, not as a head-to-head ranking.*

5.2 Sequencing principles

UK anchor: the current BSH and UK Myeloma Society UK-specific guideline reference for second-line and later management at the time of writing is the BSH/UKMS 2025 relapsed myeloma guideline [ref 15]. The general sequencing principles below align with that guideline and with current NCCN guidance, while leaving room for local commissioning and access decisions.

- **Anti-CD38 retreatment is generally not recommended in patients with documented anti-CD38 refractory disease.** For anti-CD38 naive patients, anti-CD38-based regimens remain a viable option in subsequent lines.
- **Cross-modality activity within BCMA-directed therapies is described but evidence remains limited.** Small case series suggest that bispecific antibodies retain activity after a prior BCMA-directed antibody-drug conjugate, but data are early and the optimal sequencing strategy is not yet defined.
- **Selection between modalities at first relapse usually balances** patient frailty and willingness to tolerate inpatient monitoring (CAR-T, bispecific) against outpatient deliverability and ocular tolerance (belantamab combination), as well as access and time-to-treatment.

5.3 Resistance

Described mechanisms of resistance to BCMA-directed therapy include T-cell dysfunction (relevant to T-cell engaging modalities), antigen escape with reduced cell-surface BCMA expression, and TNFRSF17 mutations affecting the BCMA gene. Soluble BCMA shedding may also reduce drug access to the cell surface. These mechanisms are described in case reports and small series and remain an area of active study; they should be flagged as emerging rather than established.

6. Belantamab mafodotin: regulatory status

The regulatory pathway for belantamab mafodotin has been complicated. After a withdrawal in 2022 to 2024 driven by negative confirmatory data, the agent has now regained approval in selected jurisdictions for use in combination based on the DREAMM-7 and DREAMM-8 trials, with the exact indication differing between regions. The timeline below records the current position as of the date of writing.

- **August 2020:** FDA accelerated approval for monotherapy in heavily pretreated RRMM, based on DREAMM-2.
- **November 2022:** GSK announced the start of the US withdrawal process at the FDA's request, after the confirmatory DREAMM-3 trial failed to meet its primary PFS endpoint versus pomalidomide-dexamethasone.
- **February 2023:** FDA formally revoked the BLA (Federal Register notice published March 2023).
- **2024:** Belantamab withdrawn from EU and UK markets.
- **2025:** FDA accepted a new BLA for the BVd and BPd combinations based on DREAMM-7 and DREAMM-8 data.
- **17 April 2025 (UK):** MHRA approved belantamab mafodotin combinations for relapsed or refractory multiple myeloma: BVd after at least one prior therapy, and BPd after at least one prior therapy including lenalidomide [Regulatory ref R1].
- **July 2025 (EU):** European Commission approved belantamab mafodotin combinations for relapsed or refractory multiple myeloma based on the DREAMM-7 and DREAMM-8 results. Indications include BVd after at least one prior therapy and BPd after at least one prior therapy including lenalidomide [Regulatory ref R2].
- **July 2025 (US ODAC):** FDA Oncologic Drugs Advisory Committee voted 5 to 3 against the benefit-risk profile of BVd, citing concerns about ocular toxicity and overall tolerability. The PDUFA decision date was set for 23 October 2025.
- **23 October 2025 (US):** FDA approved belantamab mafodotin-blmf (Blenrep) in combination with bortezomib and dexamethasone for adults with RRMM who have received at least two prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent. The approval is accompanied by a boxed warning and a REMS programme for ocular toxicity; in the FDA-described DREAMM-7 efficacy population, ocular toxicity was reported in approximately 92% of patients, including grade 3 or 4 events in 77%, with 83% requiring dose modification. These regulatory-described figures are broadly consistent with the published DREAMM-6 Arm B safety profile (93% protocol-defined ocular events, grade 3 or 4 in 77%) [Regulatory ref R3, ref 14].

Current position as of May 2026: Belantamab mafodotin has regained regulatory approval in selected jurisdictions, but indications and access differ by region. In the UK, MHRA approved belantamab mafodotin combinations in April 2025: BVd after at least one prior therapy and BPd after at least one prior therapy including lenalidomide. In the EU, the European Commission approved the same combination indications in July 2025. In the US, FDA approved BVd in October 2025 for adults with RRMM after at least two prior lines including a PI and an IMiD. UK local availability, NICE technology-appraisal status, and Trust formulary or commissioning decisions should still be checked before clinical use; regulatory approval does not by itself guarantee NHS-funded access.

Practical point: *any teaching slide that describes belantamab as 'approved' should be qualified with the year, jurisdiction, and line of therapy specified. The trial efficacy data described above are not in dispute; the indication wording and the question of how, where and when belantamab is available for routine prescribing differs by region.*

7. Clinical case applications

These three case vignettes are illustrative and were used at the symposium to anchor decision-making. They are written here as working examples rather than prescriptive recommendations.

Decision framework: the symposium and current NCCN guidance both organise the choice of second-line therapy around three concurrent factors. **Patient factors** (age, frailty, comorbidities, social and access circumstances, willingness to tolerate hospitalisation), **disease factors** (cytogenetic risk, pace of relapse, extramedullary disease, organ involvement), and **treatment factors** (prior agents, refractory status, time on previous regimen, depth of previous response). The cases below show how these three lenses converge on different choices in different patients.

Case 1. 65-year-old anti-CD38 naive, lenalidomide-refractory, photographer

Profile: ECOG 1, standard-risk cytogenetics, single prior line of lenalidomide-bortezomib-dexamethasone with maintenance, now relapsed. Strong patient preference for minimal hospital visits.

Approach: Reasonable choice between an anti-CD38-based triplet and a BCMA-directed approach. If access permits and the patient is comfortable with ocular monitoring, BVd is well supported by the DREAMM-7 data and offers an outpatient profile compatible with the patient's preferences. An anti-CD38 triplet such as DPd or carfilzomib-based regimens are also rational options. Either decision is defensible.

Case 2. 73-year-old, six years on DRd, now relapsed, with diabetes

Profile: Anti-CD38 and lenalidomide refractory, proteasome-inhibitor naive, ECOG 1, standard-risk cytogenetics, type 2 diabetes on metformin, values quality of life and cooking.

Approach: BVd is well placed in this patient: the proteasome inhibitor is novel for him, the regimen is outpatient-friendly, and dexamethasone dose can be reduced to limit hyperglycaemia. Renal function and prior peripheral neuropathy will guide bortezomib scheduling. Subcutaneous bortezomib is preferred. Carfilzomib-based combinations are an alternative if neuropathy is a concern, although there is no head-to-head comparison with BVd in this population.

Case 3. 67-year-old, prior DVRd plus ASCT plus lenalidomide maintenance, aggressive relapse

Profile: Triple-class exposed (anti-CD38, PI, IMiD), high-risk cytogenetics including del(17p), ISS Stage III, aggressive relapse with extramedullary disease, active professional, family caregiving role.

Approach: Functionally high-risk biology with limited prior options. Cilta-cel offers the strongest published OS benefit in lenalidomide-refractory disease and would be the first choice if the patient can be bridged safely to apheresis and infusion. If access is limited or bridging is not feasible, BPd is a reasonable alternative based on DREAMM-8, especially given the patient is bortezomib-naive with respect to the pomalidomide-bortezomib combination. Teclistamab plus daratumumab would be considered if the patient is not anti-CD38 refractory; the MajesTEC-3 dataset enrolled an anti-CD38 naive or sensitive population and may not extrapolate cleanly here.

Note on transplant timing: in patients who deferred upfront ASCT, current evidence (including DETERMINATION-style data) suggests that delayed transplant in standard-risk disease can give similar overall survival to upfront transplant, although progression-free survival is typically longer with upfront ASCT. In a high-risk patient with aggressive relapse and triple-class exposure, the priority shifts to a deep cytoreduction with a novel mechanism rather than salvage transplant per se.

8. The concept of cure in multiple myeloma

8.1 Functional cure as an emerging goal

Functional cure, defined as durable remission off therapy with sustained MRD negativity and clinical stability, is now an open question rather than a fixed definition. The Engelhardt review in Haematologica (2024) frames this as 'operational' or 'functional' cure rather than biological cure, and notes that the field still lacks a formal consensus definition [ref 8]. The IMWG has not endorsed a single threshold, and clinical trials use a range of MRD sensitivities (10^{-5} to 10^{-6}) and follow-up durations (12 months, 3 years, 5 years) [ref 9, ref 10].

8.2 A working definition for clinical practice

An emerging working definition (not formal IMWG consensus) used in expert forums is sustained MRD negativity at 10^{-6} for more than 5 years, alongside imaging-negative remission and clinical stability off therapy. This is a useful clinical anchor but should not be quoted as a settled definition.

8.3 Empirical evidence for functional cure

The CARTITUDE-1 5-year follow-up (Jagannath, JCO 2025) provides one of the strongest available empirical signals for prolonged treatment-free remission after BCMA-directed CAR-T therapy. With a median follow-up of 61.3 months, median OS was 60.7 months and 32 of 97 treated patients (33%) remained alive and progression-free at 5 years without maintenance treatment after a single cilta-cel infusion. In a single-centre subset of 12 patients, all (100%) were MRD-negative (10^{-5}) and PET-CT negative at year 5 or beyond [ref 7].

Interpretation: *the CARTITUDE-1 5-year follow-up provides an important empirical signal that a subset of heavily pretreated RRMM patients can achieve prolonged treatment-free remission after cilta-cel. Whether this represents functional cure remains a matter for longer follow-up and consensus definition; the data should not be used to support a settled cure claim.*

The 5-year landmark substantially updates the earlier 36-month CARTITUDE-1 follow-up: with the longer dataset, the more useful figure is now the 5-year mark, where one in three treated patients remains progression-free without maintenance after a single cilta-cel infusion.

8.4 Heterogeneity in cure achievability

A 'tale of two cities' framing was used at the symposium to illustrate this heterogeneity: two patients with similar baseline biology can have substantially different long-term outcomes depending on the depth and intensity of first-line therapy. The patient who reaches sustained MRD negativity after a quadruplet induction with anti-CD38 antibody, proteasome inhibitor, IMiD and dexamethasone, followed by transplant and maintenance, sits on a different long-term trajectory from the patient with the same risk profile who received a doublet. The

implication is that access to optimal first-line therapy is itself one of the determinants of whether functional cure is achievable.

Functional cure is not equally accessible across patient subgroups. Standard-risk patients with deep responses to frontline therapy are more likely to achieve sustained MRD negativity than high-risk patients. The MASTER trial showed that, in newly-diagnosed standard-risk patients reaching MRD negativity who entered surveillance off therapy, progression rates were low; however, in high-risk patients with two or more cytogenetic abnormalities, off-treatment progression remained substantial. The achievability of functional cure therefore depends on biology, prior therapy, and access in roughly equal measure.

8.5 What the field still needs

- A formal IMWG consensus definition with a stated MRD threshold and follow-up duration.
- Validation of MRD as a regulatory surrogate in the relapsed setting (the Landgren EVIDENCE meta-analysis supports MRD surrogacy in newly diagnosed disease but not yet definitively in RRMM) [ref 10].
- Long-term safety follow-up across all BCMA modalities to map out late toxicities, second primary malignancies, and immune reconstitution.

9. Unresolved points and caveats

This panel records points where the evidence is preliminary, where the published abstract-level data do not support a stronger claim, or where a symposium-attributed figure has not been independently verified. Including this panel openly avoids the trap of over-interpreting promising trial data as settled clinical reality.

Point	Why it remains uncertain
MajesTEC-3 36-month overall survival	The MajesTEC-3 OS figure is not present in the published abstract and has therefore not been retained as a verified benchmark. The verified primary endpoint is the 36-month PFS (83.4% vs 29.7%; HR 0.17, 95% CI 0.12 to 0.23; P < 0.001). To restore an OS row, the full NEJM publication or supplement should be consulted [ref 6].
CARTITUDE-4 OS at 36 months	Not published. The 30-month figure (76.4%) is the latest reported [ref 5]. Use 30 months until the next analysis is published.
DREAMM-8 updated post-hoc PFS and PFS2 figures (32.6 / 12.5 / 47.1 / 21.7 months)	These figures are presented in this document but the exact updated source (conference report, abstract, supplement, or peer-reviewed update) has not been independently re-verified. The verified core remains the primary NEJM interim analysis at 21.8-month follow-up (median PFS NR vs 12.7 months; HR 0.52) [ref 3]. The post-hoc figures should be source-specified before being quoted in clinical discussion.
Real-world doublet/triplet/quadruplet percentages (44.4 / 41 / 2.1)	Symposium-attributed. The figures were presented at the meeting but the underlying primary citation has not been independently identified. Treat as symposium-attributed pending source verification.
Cross-resistance between BCMA modalities (DREAMM-7 ten-patient signal)	Symposium-attributed: ten DREAMM-7 patients treated subsequently with anti-CD38 or bispecific antibody, with bispecific median duration described as comparable. Not a definitive subgroup analysis. Useful as an early signal that bispecific antibodies retain activity after BCMA-directed ADC, but should not be treated as a published primary finding.
Belantamab regulatory status (US, EU, UK)	As of May 2026, the UK MHRA approved BVd and BPd combinations on 17 April 2025 (ref R1); the European Commission approved the same combinations in July 2025 (ref R2); and the US FDA approved BVd on 23 October 2025 after at least two prior lines including a PI and an IMiD (ref R3). Local NHS commissioning, NICE technology-appraisal status, and Trust formulary decisions should still be confirmed locally before clinical use; regulatory approval does not by itself guarantee NHS-funded access.

Point	Why it remains uncertain
Working definition of cure	MRD-negativity at 10^{-6} sustained beyond 5 years is a useful clinical anchor but is not a formal IMWG-endorsed definition [ref 9]. Phrase carefully when discussing prognosis with patients.
BCVA 20/50 outcome (98% improvement) and corneal ulcer management	Symposium-attributed. The 98% improvement figure for first events at BCVA 20/50 or worse, and the corneal ulcer management approach, were presented at the meeting. They have not been independently re-verified against the primary publication. Use with appropriate framing in patient discussion.

Overall status of this document

This document is intended as a high-level symposium evidence summary suitable for educational circulation. The following points apply:

- DREAMM-7 figures, DREAMM-8 primary interim PFS figures, CARTITUDE-4 citation metadata, CARTITUDE-1 5-year data, and the cautious functional-cure framing are aligned with the primary published sources.
- Belantamab mafodotin regulatory status is presented across all three jurisdictions (UK MHRA April 2025, EU July 2025, US FDA October 2025), with regulatory approval kept separate from NHS commissioning and local availability.
- MajesTEC-3 is presented as a PFS benchmark only; the OS row is intentionally not retained pending review of the full publication.
- DREAMM-8 updated post-hoc figures (32.6 / 12.5 / 47.1 / 21.7 months) are presented but labelled as awaiting exact source specification.
- Symposium-only items (real-world prescribing percentages, ten-patient cross-resistance signal, BCVA 98% improvement figure, corneal ulcer management) are explicitly labelled as symposium-attributed until the primary source, supplement, or abstract is identified.

Re-verification: *the figures and regulatory positions in this document should be re-checked locally before clinical use. Last reviewed against primary sources in May 2026.*

References

All references below have been verified against PubMed and Scite metadata. PMID and DOI are listed where available. References were last verified on 10 May 2026.

1. Hungria V, Robak P, Hus M, Zherebtsova V, Ward C, Ho PJ, et al; DREAMM-7 Investigators. Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024 Aug 1;391(5):393-407. doi: 10.1056/NEJMoa2405090. PMID: 38828933.

2. Hungria V, Robak P, Hus M, Zherebtsova V, Ward C, Ho PJ, et al; DREAMM-7 Investigators. Belantamab mafodotin plus bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (DREAMM-7): updated overall survival analysis from a global, randomised, open-label, phase 3 trial. Lancet Oncol. 2025 Aug;26(8):1067-1080. doi: 10.1016/S1470-2045(25)00330-4.

3. Dimopoulos MA, Beksac M, Pour L, Delimpasi S, Vorobyev V, Quach H, et al; DREAMM-8 Investigators. Belantamab Mafodotin, Pomalidomide, and Dexamethasone in Multiple Myeloma. N Engl J Med. 2024 Aug 1;391(5):408-421. doi: 10.1056/NEJMoa2403407.

4. San-Miguel J, Dhakal B, Yong K, Spencer A, Anguille S, Mateos MV, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. N Engl J Med. 2023 Jul 27;389(4):335-347. doi: 10.1056/NEJMoa2303379.

5. Einsele H, San-Miguel J, Dhakal B, Mateos MV, Spencer A, Anguille S, et al. Cilta-cel in lenalidomide-refractory multiple myeloma (CARTITUDE-4): an updated analysis including overall survival from an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2026 Feb;27(2):254-268. doi: 10.1016/S1470-2045(25)00653-9.

6. Costa LJ, Bahlis NJ, Perrot A, Mateos MV, et al. Teclistamab plus Daratumumab in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2026 Feb 19;394(8):739-752. doi: 10.1056/NEJMoa2514663.

7. Jagannath S, Martin TG, Lin Y, Madduri D, Jackson CC, Banerjee A, et al. Long-Term (≥5-Year) Remission and Survival After Treatment With Ciltacabtagene Autoleucel in CARTITUDE-1 Patients With Relapsed/Refractory Multiple Myeloma. J Clin Oncol. 2025 Sep 1;43(25):2766-2771. doi: 10.1200/JCO-25-00760.

8. Engelhardt M, Wäsch R, Reinhardt H, et al. Functional cure and long-term survival in multiple myeloma: how to challenge the previously impossible. Haematologica. 2024. Available: https://haematologica.org/article/view/11443

9. Kumar SK, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346. (consensus reference for MRD framework).

10. Landgren O, et al. EVIDENCE meta-analysis: evaluating minimal residual disease as an intermediate clinical endpoint for multiple myeloma. Blood. 2024.

11. Cavo M, Terpos E, Bargay J, Einsele H, Cavet J, Greil R, et al. Management of Relapsed-Refractory Multiple Myeloma in the Era of Advanced Therapies: Evidence-Based Recommendations for Routine Clinical Practice. Available via PMC: https://pmc.ncbi.nlm.nih.gov/articles/PMC10093129/ (supports the patient-factor / disease-factor / treatment-factor framework used in the case section).

12. CDA-AMC review: Belantamab mafodotin (Blenrep), bortezomib, dexamethasone. NCBI Bookshelf. Available: https://www.ncbi.nlm.nih.gov/books/NBK619896/ (independent technology assessment supporting the DREAMM-7 efficacy and ocular safety summary).

13. CDA-AMC review: Belantamab mafodotin, pomalidomide, dexamethasone. NCBI Bookshelf. Available: https://www.ncbi.nlm.nih.gov/books/NBK619897/ (independent technology assessment supporting the DREAMM-8 primary efficacy and safety summary).

14. Popat R, Augustson B, Cannell P, et al. Efficacy and Safety of Belantamab Mafodotin with Bortezomib Plus Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma: the DREAMM-6 Arm B Trial. Clin Cancer Res. 2026. doi: 10.1158/1078-0432.CCR-25-3216. (supports the FDA-described ocular toxicity figures: 93% protocol-defined ocular events, 77% grade 3 or 4.)

15. Jenner M, Boyd K, Choudhuri S, Parrish C, Garg M, Stern S; British Society of Haematology and UK Myeloma Society. Management of relapsed multiple myeloma: A British Society of Haematology and UK Myeloma Society guideline. Br J Haematol. 2025 Oct 10. doi: 10.1111/bjh.70149. PMID: 41069303. Final pagination reported as Br J Haematol. 2025;207(6):2322-2354. (the current BSH and UK Myeloma Society UK-specific guideline reference for relapsed myeloma management at the time of writing.)

Regulatory sources (non-academic)

R1. GSK. Blenrep (belantamab mafodotin) combinations approved by UK MHRA in relapsed or refractory multiple myeloma. 17 April 2025. Available: https://www.gsk.com/en-gb/media/press-releases/blenrep-belantamab-mafodotin-combinations-approved-by-uk-mhra-in-relapsedrefractory-multiple-myeloma/

R2. GSK. Blenrep (belantamab mafodotin) combinations approved in EU for treatment of relapsed or refractory multiple myeloma. 24 July 2025. Available: https://www.gsk.com/en-gb/media/press-releases/blenrep-belantamab-mafodotin-combinations-approved-in-eu-for-treatment-of-relapsedrefractory-multiple-myeloma/

R3. US FDA. FDA approves belantamab mafodotin-blmf for relapsed or refractory multiple myeloma. 23 October 2025. Available: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belantamab-mafodotin-blmf-relapsed-or-refractory-multiple-myeloma (includes the boxed warning and REMS information for ocular toxicity referenced in section 6.)

R4. US FDA. Federal Register Notice: GlaxoSmithKline Intellectual Property Development Ltd. England; Announcement of the Revocation of the Biologics License for BLENREP. 30 March 2023. Effective revocation date: 6 February 2023.

R5. GSK. Press release: GSK provides an update on Blenrep (belantamab mafodotin-blmf) US marketing authorization. 22 November 2022.

R6. FDA Oncologic Drugs Advisory Committee (ODAC) meeting outcome, July 2025: 5-3 vote on the benefit-risk profile of belantamab mafodotin in combination with bortezomib and dexamethasone. PDUFA date: 23 October 2025. Briefing documents available from FDA.

Searches were performed on 10 May 2026 using PubMed (NLM), Scite (smart citations and metadata), and Consensus (peer-reviewed corpus). Where journal volume and page were available, both have been included; where the article number is in lieu of pagination, the DOI is the canonical link.