Managing adverse events associated with BCMA-targeting agents in multiple myeloma: The role of the multidisciplinary team

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The role of the ophthalmologist: Managing adverse events in the treatment of multiple myeloma

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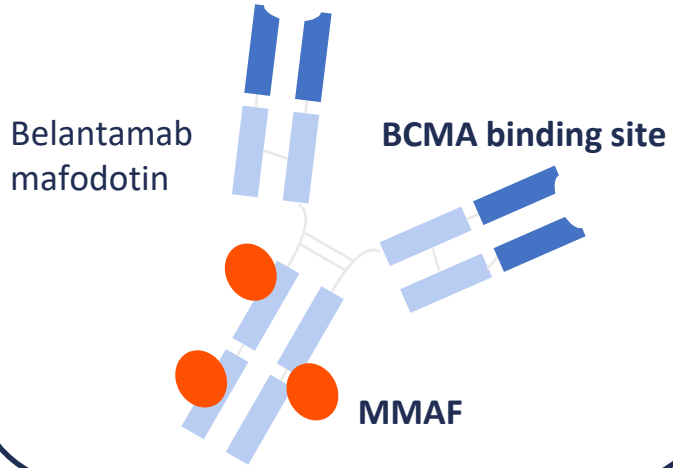
What ocular toxicities have been observed with belantamab mafodotin?

Antibody–drug conjugates in RRMM

Monoclonal antibodies attached to biologically active drugs by chemical linkers[1]



Ocular toxicities[2–4]

- Frequent with ADCs, particularly those containing MMAF
- Can be diverse, but are commonly related to the ocular surface, such as keratitis and dry eye
- Corneal epithelial microcysts/microcystic-like changes have been documented with various MMAF-containing compounds
- Pathogenesis is not fully understood, and corneal findings may be secondary to an off-target or on-target mechanism
- The majority of ocular AEs with ADCs have been reported as mild and reversible

AE, adverse event; ADC, antibody–drug conjugate; BCMA, B-cell maturation antigen; MMAF, microtubule-disrupting agent monomethyl auristatin-F; RRMM, relapsed/refractory multiple myeloma.

1. Martino M, Paviglianiti A. *Expert Opin Biol Ther*. 2021;21:1025–34; 2. Eaton JS, et al. *J Ocul Pharmacol Ther.* 2015;31:589–604; 3. Masters JC, et al. *Invest New Drugs*. 2018;36:121–35; 4. Farooq AV, et al. *Ophthalmol Ther*. 2020;9:889–911.

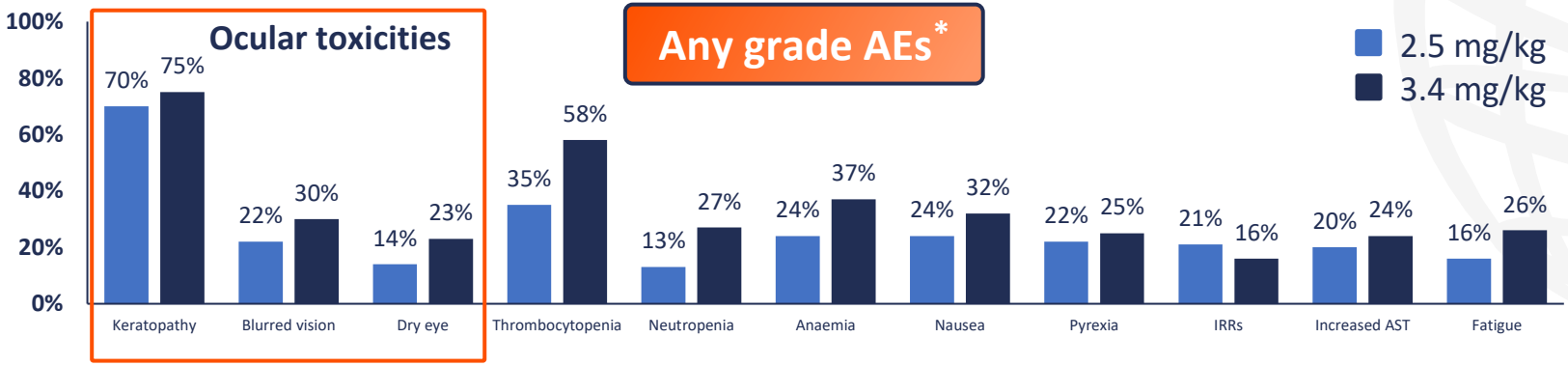
Ocular toxicity with belantamab mafodotin in the Phase II DREAMM-2 study

RRMM and progression after ≥3 prior lines of therapy, including an immunomodulatory drug, PI and anti-CD38 mAb

2.5 mg/kg IV Q3W n=97

3.4 mg/kg IV Q3W n=99

The proportion of randomly assigned patients in the ITT population who achieved an ORR, as assessed by an IRC



*≥20% in either 2.5 mg/kg or 3.4 mg/kg IV Q3W cohorts.

AE, adverse event; AST, aspartate aminotransferase; CD38, cluster of differentiation 38; IRC, independent review committee; IRR, infusion-related reaction; ITT, intention-to-treat; IV, intravenous; mAB, monoclonal antibody; ORR, overall response; PI, proteasome inhibitor; Q3W, every three weeks; RRMM, relapsed/refractory multiple myeloma.

Lonial S, et al. *Lancet Oncol.* 2020;21:207–21. Clinicaltrials.gov identifier: NCT03525678.

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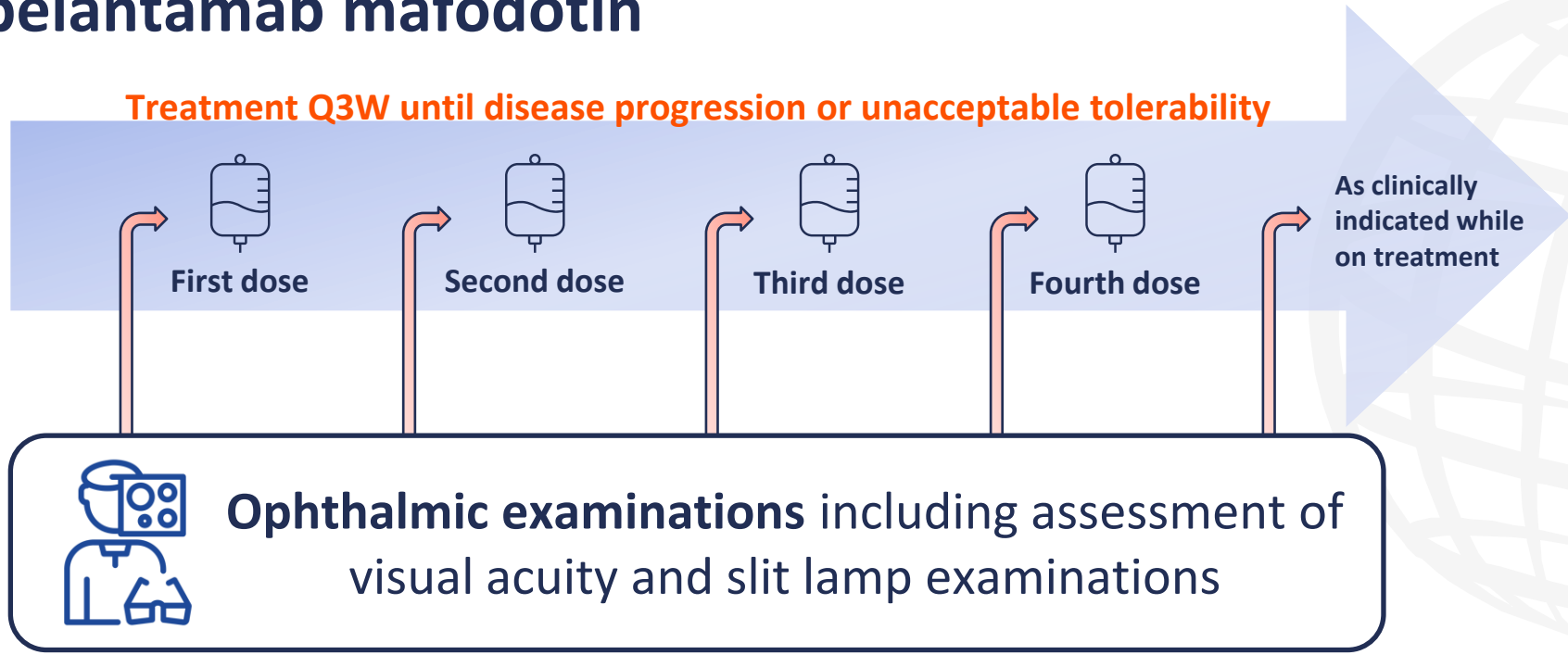
How should a patient receiving belantamab mafodotin be monitored for possible ocular adverse events?

Monitoring for ocular adverse events associated with belantamab mafodotin



EMA, European Medicines Agency; Q3W, every three weeks.

EMA Summary of Product Characteristics. 2020. Available at: www.ema.europa.eu/en/documents/product-information/blenrep-epar-product-information_en.pdf (accessed 19 July 2021).

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How is the severity of ocular events graded?

Grading the severity of corneal events

Severity	Corneal examination findings description	Presentation of MECs (based on density and location)	Change in BCVA due to treatment-related corneal findings
Grade 1 Mild	Mild superficial keratopathy (documented worsening from baseline), with or without symptoms	**Mild** Density: non-confluent Location: predominantly (≥80%) peripheral	Decline from baseline of 1 line on SVA
Grade 2 Moderate	Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity	**Moderate** Density: semi-confluent Location: predominantly (≥80%) paracentral	Decline from baseline by 2 or 3 lines (and SVA not worse than 20/200)
Grade 3 Severe	Severe superficial keratopathy with or without diffuse microcyst-like deposits involving the central cornea, sub-epithelial haze (central), or a new central stromal opacity	**Severe** Density: confluent Location: predominantly (≥80%) central	Decline from baseline of more than 3 lines (and SVA not worse than 20/200)
Grade 4 Severe	Corneal epithelial defect, such as corneal ulcers. These should be managed promptly and as clinically indicated by an eye care professional	Not applicable, these events are not graded based on MECs	SVA worse than 20/200

BCVA, best-corrected visual acuity; KVA, keratopathy and visual acuity; MEC, microcystic-like epithelial change; SVA, Snellen visual acuity.
Lonial S, et al. *Blood Cancer J.* 2021;11:103.

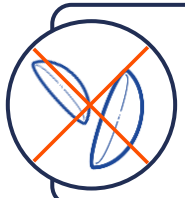
How can ocular events be managed in patients with multiple myeloma treated with belantamab mafodotin?

Managing adverse events associated with belantamab mafodotin[1–3]

Severity	Recommended dose modifications
Grade 1 Mild	• Continue treatment at current dose
Grade 2 Moderate	• Withhold treatment until improvement in either exam findings or BCVA to grade 1/mild • Resume at a reduced dose of 1.9 mg/kg
Grade 3 Severe	• Withhold treatment until improvement in either exam findings or BCVA to grade 1/mild • Resume at a reduced dose of 1.9 mg/kg
Grade 4 Severe	• Withhold treatment until improvement in examination findings and BCVA to grade 1/mild • Consider treatment discontinuation based on a benefit–risk assessment • For worsening symptoms that are unresponsive to appropriate management, consider discontinuation • If continuing treatment, resume at a reduced dose of 1.9 mg/kg

Advise patients to use preservative-free lubricant eye drops at least 4 times a day in both eyes

Prophylactic steroid eye drops are no longer recommended



Avoiding use of contact lenses unless clinically warranted

BCVA, best-corrected visual acuity.

1. Lonial S, et al. *Blood Cancer J.* 2021;11:103; 2. Popat R, et al. *Haematologica.* 2020;105:e261; 3. Farooq AV, et al. *Ophthalmol Ther.* 2020 Dec;9:889–911.

How can eye care professionals work with the wider patient care team to provide the best care possible?

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Multidisciplinary approach to RRMM treatment

Patient receiving belantamab mafodotin

Before starting treatment

Nurses, NPs and PAs

- Refer patient to eye care professional
- Help to educate the patient about not wearing contact lenses, how to report ocular symptoms and operating heavy machinery

Haematologist/oncologist

- Educate themselves on the wider RRMM care team
- Educate the patient on the potential risk of corneal events, and monitoring and management strategies according to local label

Eye care professional

- Perform baseline eye examination
- Obtain eye-related clinical history from patient and advise haematologist of relevant ocular history

On treatment

Nurses, NPs and PAs

- Routinely question patient on impact of any ocular symptoms on daily activities
- Discuss whether additional support for daily activities is available in the event of any BCVA changes

Haematologist/oncologist

- Review eye examination reports to determine supportive measures based on severity of ocular event and local label recommendations
- Share information with patient care team that may impact treatment schedule

Eye care professional

- Provide haematologist/oncologist with information on corneal events
- Reiterate education given prior to treatment

BCVA, best-corrected visual acuity; NP, nurse practitioner; PA, physician assistant; RRMM, relapsed/refractory multiple myeloma.

Lonial S, et al. *Blood Cancer J*. 2021;11:103.

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Managing adverse events associated with CAR T-cell therapy in the treatment of multiple myeloma

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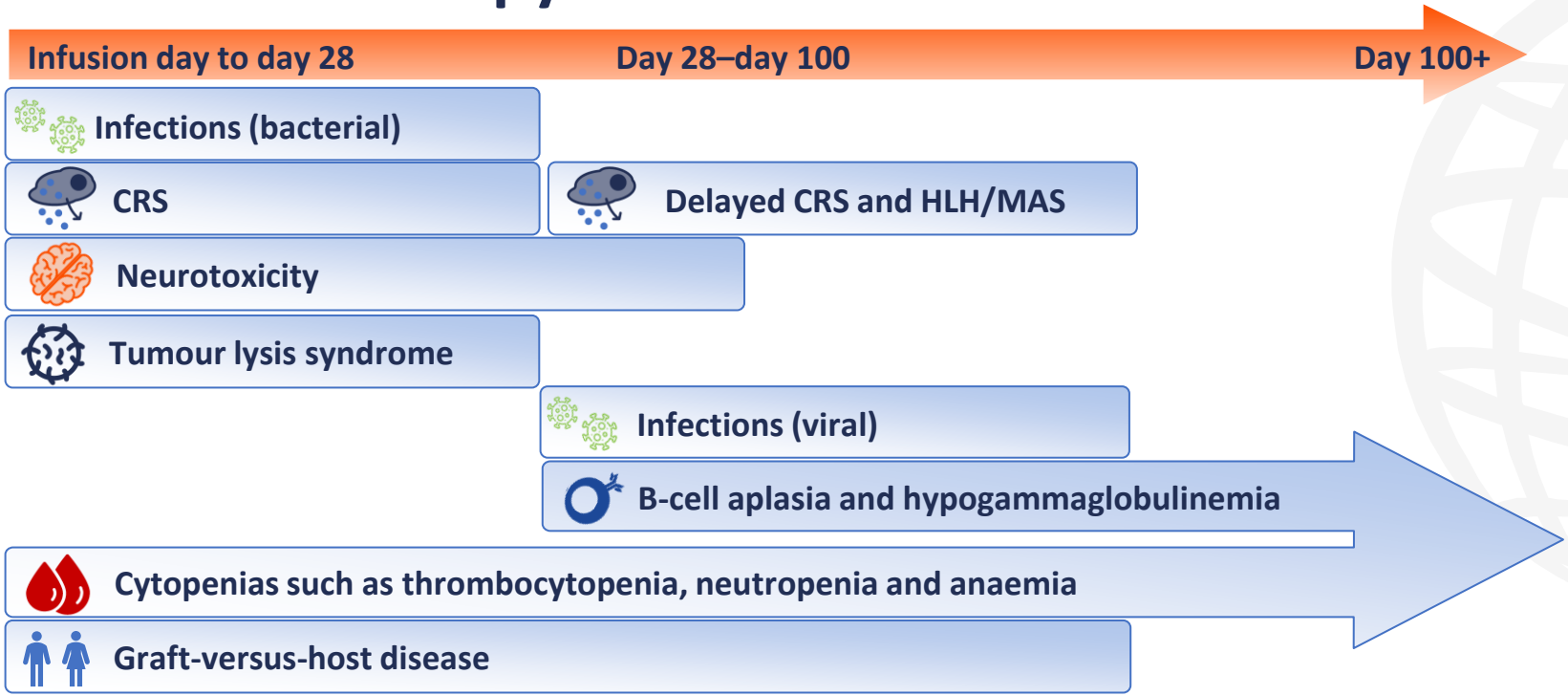
What are the possible adverse events of BCMA-targeting CAR T-cell therapies?

Timing of adverse events associated with CAR T-cell therapy[1,2]



CAR, chimeric antigen receptor; CRS, cytokine release syndrome; HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome.

1. Yakoub-Agha I. *Haematologica*. 2020;105:297–316; 2. Einsele H, et al. EP1003. Presented at: European Hematology Association 2021 Virtual Congress, 9–17 June 2021; 3. Liu P, et al. *Front Oncol*. 2020;10:1975.

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How can adverse events be monitored in patients with multiple myeloma treated with CAR T-cell therapy and where is MDT involvement important?

Monitoring CAR T-cell therapy adverse events

Adverse event	Management strategies
CRS	• Monitor temperature, hypotension and hypoxia • Laboratory monitoring of C-reactive protein and ferritin levels (optional)
Neurotoxicity	• Serial cognitive testing, such as handwriting tests • EEG, MRI and LP as clinically indicated
Haematological events	• Daily haematology and chemistry laboratory tests
Infections	• During the cytopenias phase (early phase): monitor temperature and blood culture • After discharge: monitor PCR for CMV, EBV and other viruses as clinically indicated

CAR, chimeric antigen receptor; CMV, cytomegalovirus; CRS, cytokine release syndrome; EBV, Epstein–Barr virus; EEG, electroencephalography; LP, lumbar puncture; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

Yakoub-Agha I, et al. *Haematologica.* 2020;105:297–316.

How can adverse events be managed should they arise?

Managing CAR T-cell therapy adverse events[1,2]

Adverse event	Management strategies
CRS	• Supportive care, e.g. antipyretics, oxygen and intravenous fluids • Circulatory and respiratory support for hypotension and hypoxia, respectively • Tocilizumab and corticosteroids for persistent or severe CRS
Neurotoxicity	• Corticosteroids • Antiseizure prophylaxis in patients with history of seizures or CNS disease • Symptomatic measures, e.g. head raised at 30° angle, suspend oral nutrition, replace oral drugs by IV • Clonazepam and levetiracetam if seizures occur • Consider acetazolamide for papillary oedema • Consider hyperosmolar therapy if cerebral oedema
Haematological events	• G-CSF to shorten duration of neutropenia (avoid if patient has CRS/ICANS) • Immunoglobulin replacement in patients with hypogammaglobulinemia and recurrent infections with encapsulated bacteria
Infections	• Antibiotic, antiviral, systemic antifungal and anti-pneumocystis prophylaxis • For patients with a history of hepatitis B infection, prophylaxis with tenofovir is recommended
GvHD	• Potential benefit of systemic immunosuppression should be balanced against effect on CAR T-cell function

CAR, chimeric antigen receptor; CNS, central nervous system; CRS, cytokine release syndrome; G-CSF: granulocyte colony stimulating factor; GvHD, graft-versus-host disease; ICANS, immune effector cell-associated neurotoxicity syndrome; IV, intravenous.

1. Yakoub-Agha I, et al. *Haematologica.* 2020;105:297–316; 2. Berdeja JG, et al. *Lancet*. 2021;398:314–24.

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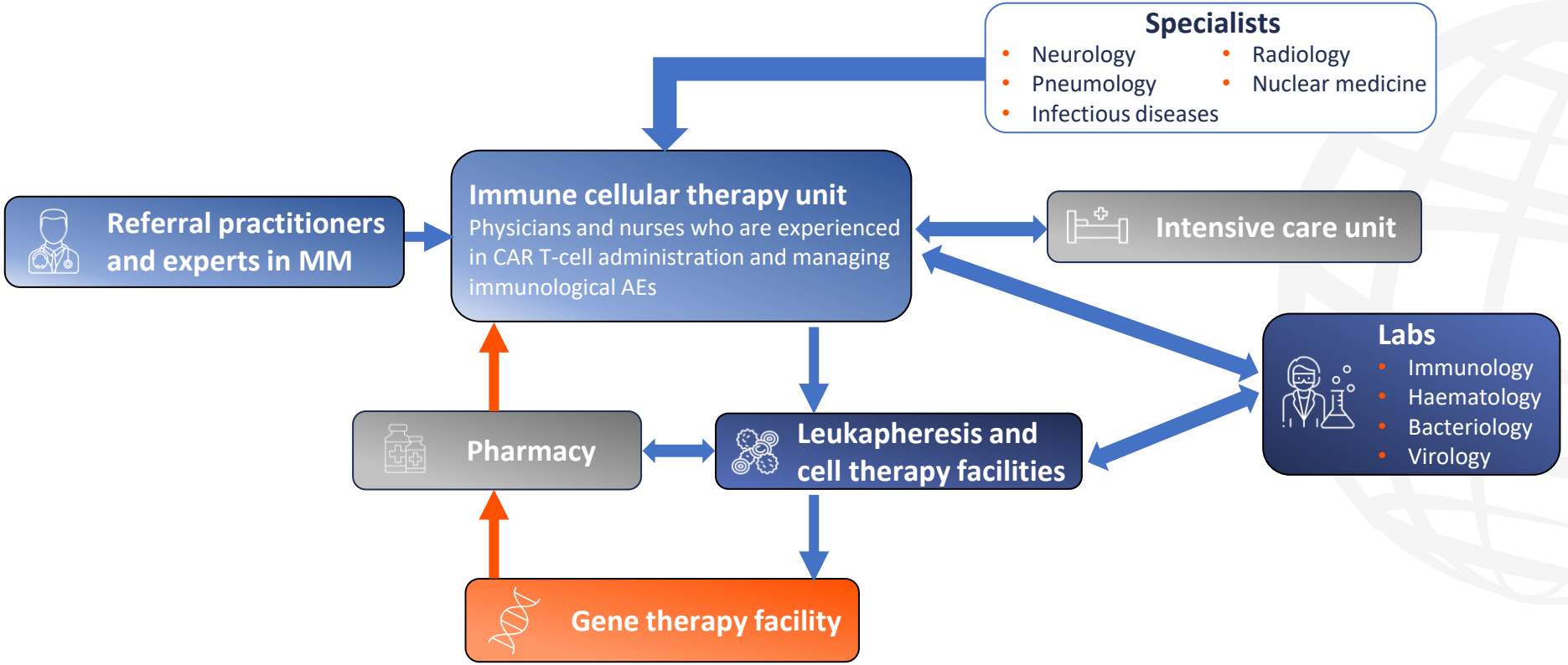
How can haematologists work with the wider patient care team to provide the best care possible?

Multidisciplinary approach to AE management[1,2]



AE, adverse event; CAR, chimeric antigen receptor; MM, multiple myeloma.

1. Yakoub-Agha I. *Current Res Transl Med.* 2018;66:57–8; 2. Chomienne C, et al. *HemaSphere.* 2019;00:00. http://dx.doi.org/10.1097/HS9.0000000000000280.

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The role of MDT management for patients receiving BCMA-targeting agents in the treatment of multiple myeloma

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In the context of BCMA-targeting agents, which aspects of patient care may benefit from an MDT approach?

MDT role in the patient journey[1–3]

Treatment selection	During treatment	Following treatment
• Determine patient suitability for CAR T-cell therapy based on medical history and physical condition	• Provide appropriate patient education • Monitor for possible AEs • Provide rapid responses to mitigate any AEs	• Provide effective patient education • Monitor for any long-term TEAEs

AE, adverse event; CAR, chimeric antigen receptor; MDT, multidisciplinary team; TEAE, treatment-emergent adverse event.

1. Lonial S, et al. *Blood Cancer J*. 2021;11:103; 2. Yakoub-Agha I, et al. *Haematologica*. 2020;105:297–316; 3. Yakoub-Agha I. *Curr Res Transl Med*. 2018;66:57–8.

Which HCPs may need to be involved in the MDT for a patient treated with a BCMA-targeting agent, and why?

Members of the MDT[1–4]

With belantamab mafodotin

Eye care professionals are required to monitor for possible ocular toxicities

With all BCMA-targeting agents

Haematologists/oncologists are central to the treatment of RRMM

Nurses have a critical role in patient education, and monitoring and managing AEs

With CAR T-cell therapy

Neurologists must be readily available in the event of neurological toxicity

ICU admission might be necessary for CRS or ICANS

AE, adverse event; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit; MDT, multidisciplinary team; RRMM, relapsed/refractory multiple myeloma.

1. Lonial S, et al. *Blood Cancer J*. 2021;11:103; 2. Yakoub-Agha I, et al. *Haematologica*. 2020;105:297–316; 3. Yakoub-Agha I. *Curr Res Transl Med*. 2018;66:57–8; 4. Chomienne C, et al. *HemaSphere*. 2019;00:00. http://dx.doi.org/10.1097/HS9.0000000000000280.

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How can the MDT support a patient being treated with belantamab mafodotin?

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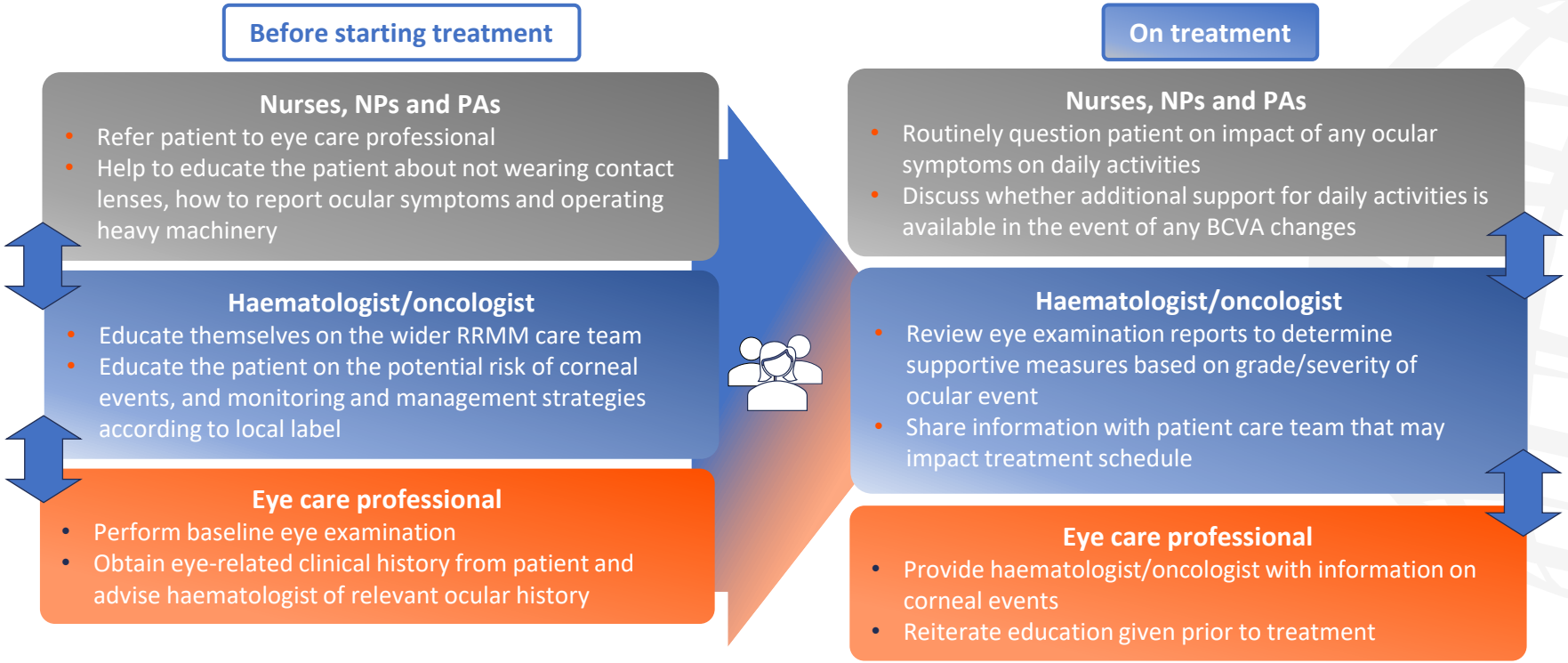
MDT approach to treatment with belantamab mafodotin



BCVA, best-corrected visual acuity; MDT, multidisciplinary team; NP, nurse practitioner; PA, physician assistant; RRMM, relapsed/refractory multiple myeloma.

Lonial S, et al. *Blood Cancer J*. 2021;11:103.

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How can an MDT support a patient being treated with BCMA-targeted CAR T-cell therapy?

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MDT approach to treatment with CAR T-cell therapy[1–4]

Community HCPs/nurses

Long-term AE monitoring

Neurologists

Management of neurological AEs

Haematologists/oncologists

CAR T-cell administration and management of AEs

Intensive care specialists

Management of certain AEs, e.g. CRS and ICANS

Radiologists

Monitoring for signs of AEs

Hospital nurses

Rapid treatment administration for AEs

AE, adverse event; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; HCP, healthcare professional; MDT, multidisciplinary team.

1. Yakoub-Agha I, et al. *Haematologica*. 2020;105:297–316; 2. Yakoub-Agha I. *Curr Res Transl Med*. 2018;66:57–8; 3. Chomienne C, et al. *HemaSphere.* 2019;00:00. http://dx.doi.org/10.1097/HS9.0000000000000280; 4. Yoon JG, et al. *AJR Am J Roentgenol.* 2021 Jun 30. doi: 10.2214/AJR.21.26091 (Online ahead of print).