Idecabtagene vicleucel (Abecma®) for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies

General information

Drug description (1)

Idecabtagene vicleucel (Abecma®, ide-cel, bb2121) is a genetically modified autologous immunotherapy consisting of human T cells transduced with lentiviral vector encoding a chimeric antigen receptor (CAR)
that recognises B-cell maturation antigen.

Indication (2)

Idecabtagene vicleucel (Abecma®) is indicated for the treatment of adult patients with relapsed and refractory MM who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy.

Incidence (3)

In Austria, in 2022, the age-standardised incidence rate[1] for plasmacytoma and myeloma was 7.2/100,000 men and 4.9/100,000 women.
In total, 556 patients were newly diagnosed with plasmacytoma and myeloma, respectively.

Current treatment (4)

- For the treatment of MM (third-line and beyond), Onkopedia recommends the following:
  - The choice of therapy in patients with relapsed or refractory disease after second-line therapy depends on the patient´s aims and, essentially, on the patient´s experiences with prior therapies.
  - Recent data, regarding patients who received at least 2 lines of therapies, can be summarised as follows:
    - Repetition of second-line therapy in patients with long, deep remission and good tolerability.
    - New double- or triple combinations of second-line therapy agents.
    - Additional options:
      - Panobinostat, combined with bortezomib/dexamethasone (as compared to bortezomib/dexamethasone) leads to prolongation of PFS, but not of OS.
      - Pomalidomide combined with low-dosed dexamethasone (as compared with high-dosed dexamethasone) lead to a prolonged PFS and OS and increases the remission rate. The additional combination with cyclophosphamide increases the response rate, but also the haematological toxicity.
      - With daratumumab monotherapy, 30% of heavily pretreated patients achieve at least partial remission and a median PFS of 4 months.
      - Cytostatic agents: Efficient "classical" cytostatic agents are bendamustine, cyclophosphamide, doxorubicin and melphalan, each as monotherapy or as combination therapy. This also includes therapy regimens such as DCEP or DT-PACE that are partially administered by continuous infusion.

Regulatory status

EMA (2)	FDA
Approval status for this indication: On 25 January 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Abecma®. The CHMP adopted an extension to the existing indication to include treatment of adult patients with relapsed and refractory MM who have received at least two prior therapies. <u>The full indications for Abecma® will be as follows:</u> ❖ Abecma® is indicated for the treatment of adult patients with relapsed and refractory MM who have received at least ~~three~~[2] **two** prior therapies, including an immunomodulatory	**Approval status for this indication**: Abecma® is indicated for the treatment of adult patients with relapsed or refractory MM after two or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody (5). In April 2023, the manufacturer announced that the FDA has accepted the companies' supplemental Biologics License Application for Abecma® with the KarMMa-3 study that investigated the treatment of adult patients with relapsed and refractory MM who have received

[1] European Standard Population 2013.
[2] New text in bold, removed in strikethrough.

agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy. **Other indications**: none ✓ **Advanced therapy** ✓ **Orphan status** ✓ **Medicine under additional monitoring** ✓ **PRIME: priority medicine**[3]	an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody (6). UPDATE: Request approved by the FDA on 4 April 2024 (7). **Other indications**: none

Manufacturer

The manufacturer of Abecma® is Bristol Myers Squibb Pharma.

Costs

Currently, there is no cost information available.

Posology (1)

- Abecma® must be administered in a qualified treatment centre. Abecma® therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for the administration and management of patients treated with Abecma®.
- A minimum of one dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion of Abecma®. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.
- Abecma® is intended for autologous use only. Manufacture and release of Abecma® usually takes about 4-5 weeks.
- Treatment consists of a single dose for infusion containing a dispersion of CAR-positive viable T cells in one or more infusion bags. The target dose is 420 x 10^6 CAR-positive viable T cells within a range of 260 to 500 x 10^6 CAR-positive viable T cells.
- **Pre-treatment (lymphodepleting chemotherapy)**
  - Lymphodepleting chemotherapy consisting of cyclophosphamide 300 mg/m^2 IV and fludarabine 30 mg/m^2 IV should be administered for 3 days.
  - Abecma® is to be administered 2 days after completion of lymphodepleting chemotherapy, up to a maximum of 9 days. The availability of Abecma® must be confirmed prior to starting the lymphodepleting chemotherapy. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving Abecma®.
- **Pre-medication**
  - To minimise the risk of infusion reactions, the patient should be pre-medicated with paracetamol (500 to 1,000 mg orally) and diphenhydramine (12.5 mg IV or 25 to 50 mg orally) or another H1-antihistamine, approximately 30 to 60 minutes before infusion of Abecma®.
  - Prophylactic use of systemic corticosteroids should be avoided as the use may interfere with the activity of Abecma®. Therapeutic doses of corticosteroids should be avoided 72 hours prior to the start of lymphodepleting chemotherapy and following Abecma® infusion except for the management of CRS, neurologic toxicities and other life-threatening emergencies.
- Clinical assessment prior to infusion
  - Abecma® treatment should be delayed in some patient groups at risk.
- Monitoring after infusion
  - Patients should be monitored for the first 10 days following infusion at the qualified treatment centre for signs and symptoms of CRS, neurologic events and other toxicities.
  - After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

[3] PRIME is a scheme launched by EMA to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.

- Patients should be instructed to remain within proximity (within 2 hours of travel) of the qualified treatment centre for at least 4 weeks following infusion.

Warnings and precautions (1)

❖ **Traceability**
- The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years after expiry date of the product.

❖ **Reasons to delay treatment**
- Due to the risks associated with Abecma® treatment, infusion should be delayed up to 7 days if a patient has any of the following conditions:
  - Unresolved serious AEs (especially pulmonary events, cardiac events or hypotension) including those after preceding chemotherapies.
  - Active infections or inflammatory disorders (including pneumonitis, myocarditis or hepatitis).
  - Active graft-versus-host disease (GVHD).

❖ **Autologous use**
- Abecma® is intended solely for autologous use and should under no circumstances be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the Abecma® infusion bag, cassette and the release for infusion certificate. Abecma® must not be administered if the information on the patient-specific label does not match the intended patient.

❖ **Concomitant disease**
- Patients with active central nervous system (CNS) disorder or inadequate renal, hepatic, pulmonary or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

❖ **CNS pathology**
- There is no experience of use of Abecma® in patients with CNS involvement of myeloma or other pre-existing, clinically relevant CNS pathologies.

❖ **Prior allogeneic stem cell transplantation**
- It is not recommended that patients receive Abecma® within 4 months after an allogeneic stem cell transplant (SCT) because of the potential risk of Abecma® worsening GVHD. Leukapheresis for Abecma® manufacturing should be performed at least 12 weeks after allogeneic SCT.

❖ **Prior treatment with an anti-BCMA therapy**
- There is limited experience with Abecma® in patients exposed to prior BCMA-directed therapy. There is limited experience of retreating patients with a second dose of Abecma®. Responses after Abecma® retreatment were infrequent and less durable when compared to initial treatment. Additionally, fatal outcomes were observed in retreated patients.

❖ **CRS**
- CRS, including fatal or life-threatening reactions occurred following Abecma® infusion. Nearly all patients experienced some degree of CRS. The median time to onset of CRS was 1 day (range: 1 to 12).
- Monitoring and management of CRS
  - CRS should be identified based on clinical presentation. Patients should be evaluated and treated for other causes of fever, hypoxia and hypotension. CRS has been reported to be associated with findings of haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) and the physiology of the syndromes may overlap. MAS is a potentially life-threatening condition, and patients should be closely monitored for evidence of MAS. Treatment of MAS should be administered per institutional guidelines.
  - One dose of tocilizumab per patient must be on-site and available for administration prior to Abecma® infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.
  - Patients should be monitored for the first 10 days following Abecma® infusion at the qualified treatment centre for signs and symptoms of CRS. After the first 10 days following infusion, the patient should be monitored at the physician's discretion. Patients should be counselled to remain within proximity (within 2 hours of travel) of the qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS occur at any time.
  - At the first sign of CRS, treatment with supportive care, tocilizumab or tocilizumab and corticosteroids should be instituted, as indicated in product information. Abecma® can continue to expand and persist following administration of tocilizumab and corticosteroids.

- Patients who experience CRS should be closely monitored for cardiac and organ functioning until resolution of symptoms. For severe or life-threatening CRS, intensive care unit level monitoring and supportive therapy should be considered.
- If concurrent neurologic toxicity is suspected during CRS, manage the neurologic toxicity according to the recommendations in product information and use the more aggressive intervention of the two reactions specified in product information.
- Earlier escalation (i.e. higher corticosteroid dose, alternative anticytokine agents, anti-T cell therapies) is recommended in patients with refractory CRS within 72 hours post Abecma® infusion characterised by persistent fever, end-organ toxicity (e.g. hypoxia, hypotension) and/or HLH/MAS not improving in grade within 12 hours of first line interventions.

❖ **Neurologic adverse reactions**

- Neurologic toxicities, such as aphasia and encephalopathy, which may be severe or life-threatening, occurred following treatment with Abecma®. The median time to onset of the first event of neurotoxicity was 2 days (range: 1 to 10 days). Grade 3 parkinsonism has also been reported, with delayed onset. Neurologic toxicity may occur concurrently with CRS, after CRS resolution or in the absence of CRS.
- Monitoring and management of neurologic toxicities
  - Patients should be monitored for the first 10 days following Abecma® infusion at the qualified treatment centre for signs and symptoms of neurologic toxicities. After the first 10 days following infusion, the patient should be monitored at the physician's discretion. Patients should be counselled to remain within proximity (within 2 hours of travel) of the qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs and symptoms of neurologic toxicities occur at any time.
  - If neurologic toxicity is suspected, manage according to the recommendations in product information. Other causes of neurologic symptoms should be ruled out. Intensive care supportive therapy should be provided for severe or life-threatening neurologic toxicities.
  - If concurrent CRS is suspected during the neurologic toxicity reaction, it should be managed according to the recommendations in product information and the more aggressive intervention used for the two reactions specified in product information.

❖ **Prolonged cytopenias**

- Patients may exhibit prolonged cytopenias for several weeks following lymphodepleting chemotherapy and Abecma® infusion. Blood counts should be monitored prior to and after Abecma® infusion. Cytopenias should be managed with myeloid growth factor and blood transfusion support according to institutional guidelines.

❖ **Infections and febrile neutropenia**

- Abecma® should not be administered to patients with active infections or inflammatory disorders. Severe infections, including life-threatening or fatal infections, have occurred in patients after receiving Abecma®. Patients should be monitored for signs and symptoms of infection before and after Abecma® infusion and treated appropriately.
- Prophylactic, pre-emptive and/or therapeutic antimicrobials should be administered according to institutional guidelines.
- Febrile neutropenia was observed in patients after Abecma® infusion and may be concurrent with CRS. In the event of febrile neutropenia, infection should be evaluated and managed with broad-spectrum antibiotics, fluids and other supportive care as medically indicated.

❖ **Viral reactivation**

- Cytomegalovirus (CMV) infection resulting in pneumonia and death have occurred following Abecma® administration. Patients should be monitored and treated for CMV infection according to clinical guidelines.
- HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with medicinal products directed against plasma cells.
- Screening for CMV, HBV, active HIV and active HCV must be performed before collection of cells for manufacturing.

❖ **Hypogammaglobulinaemia**

- Plasma cell aplasia and hypogammaglobulinaemia can occur in patients receiving treatment with Abecma®. Immunoglobulin levels should be monitored after treatment with Abecma® and managed per institutional guidelines including infection precautions, antibiotic or antiviral prophylaxis and immunoglobulin replacement.

❖ **Secondary malignancies**

- Patients treated with Abecma® may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy of T cell origin occurs, the company should be contacted to obtain instructions on the collection of patient samples for testing.

❖ **Hypersensitivity reactions**

- Allergic reactions may occur with the infusion of Abecma®. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO), an excipient in Abecma®. Patients not previously exposed to DMSO should be observed closely. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptom should be monitored prior to the start of the infusion, approximately every ten minutes during the infusion and every hour, for 3 hours, after the infusion.

❖ **Interference with serological testing**
- HIV and the lentivirus used to make Abecma® have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received Abecma®.

❖ **Blood, organ, tissue and cell donation**
- Patients treated with Abecma® should not donate blood, organs, tissues and cells for transplantation.

❖ **Long-term follow-up**
- Patients are expected to be enrolled in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Abecma®.

❖ **Excipients**
- This medicinal product contains up to 33 mmol (752 mg) sodium per dose, equivalent to 37.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This medicinal product contains up to 7 mmol (274 mg) potassium per dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

Study characteristics (8, 9, 10, 11)

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
KarMMa-3 NCT03651128	386 (2:1)	single infusion of ide-cel (target dose range, 150×10^6 to 450×10^6 CAR-positive T cells	one of five standard regimens[4]	PFS	18.6 months	**ongoing**[5], randomized, international, open-label, phase 3 trial	-	2seventy bio and Celgene, a Bristol-Myers Squibb company	KarMMa-3 trial (10)

Inclusion criteria[6]	Exclusion criteria[7]	Patient characteristics at baseline (ITT population, n=254 vs. n=132)
❖ ≥ 18 years of age with documented diagnosis of MM and measurable disease, defined as: • M-protein (sPEP ≥ 0.5 g/dL or uPEP ≥ 200 mg/24 hours) and/or • Light chain MM without measurable disease in the serum or urine: Serum immunoglobulin free light chain ≥ 10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free light chain ratio.	❖ Nonsecretory MM. ❖ Any of the following laboratory abnormalities: • ANC < 1,000/µL • Platelet count: < 75,000/µL in subjects in whom < 50% of bone marrow nucleated cells are plasma cells and platelet count < 50,000/µL in subjects in whom ≥ 50% of bone marrow nucleated cells are plasma • Haemoglobin < 8 g/dL (< 4.9 mmol/L) • Serum creatinine clearance < 45 mL/min • Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L) • Serum AST or ALT > 2.5 × ULN • Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome	❖ Median age (range): 63 (30–81) vs. 63 (42–83) years ❖ <65 years: 59% vs. 59% ❖ ≥65 years: 41% vs. 41% ❖ ≥75 years: 5% vs. 7% ❖ Male sex: 61% vs. 60% ❖ Race • Asian: 3% vs. 4% • Black: 7% vs. 14% • White: 68% vs. 59% • Other: 1% vs. 3% • Not available or not reported: 21% vs. 20% ❖ Median time from initial diagnosis to screening (range): 4.1 (0.6–21.8) vs. 4.0 (0.7–17.7) years

[4] Daratumumab, pomalidomide, and dexamethasone; daratumumab, bortezomib, and dexamethasone; ixazomib, lenalidomide, and dexamethasone; carfilzomib and dexamethasone; or elotuzumab, pomalidomide, and dexamethasone.
[5] The KarMMa trial is currently ongoing; the estimated study completion date is 04/2027.
[6] For detailed in- and exclusion criteria, please see trial protocol.
[7] Due to the high number of exclusion criteria, this list is not exhaustive.

- ❖ Patient has received at least 2 prior MM regimens.
- ❖ Patient has received prior treatment with a proteasome inhibitor- and an immunomodulatory compound-containing regimen for at least 2 consecutive cycles.
- ❖ Patient must be refractory to the last treatment regimen.
- ❖ Patient achieved a response (minimal response or better) to at least 1 prior treatment regimen.
- ❖ ECOG PS of 0 or 1.
- ❖ Recovery to Grade 1 or baseline of any non-hematologic toxicities due to prior treatments, excluding alopecia and Grade 2 peripheral neuropathy.
- ❖ Adequate vascular access for leukapheresis
- ❖ Females of childbearing potential must:
  - Have negative pregnancy test(s) as verified by the investigator.
  - Either practice true abstinence from heterosexual contact or agree to use, and be able to comply with, effective measures of contraception without interruption.
  - Agree to abstain from breastfeeding during study participation.
  - Refrain from egg cell donation.
- ❖ Male subjects must:
  - Practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential.
  - Refrain from sperm donation.

- INR or activated partial thromboplastin time > 1.5 × ULN, or history of Grade ≥ 2 haemorrhage within 30 days, or subject requires ongoing treatment with chronic, therapeutic dosing of anticoagulants.
- ❖ Inadequate pulmonary function defined as oxygen saturation < 92% on room air.
- ❖ Prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years (for exceptions, please see trial protocol).
- ❖ Active or history of plasma cell leukaemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis.
- ❖ Known CNS involvement with myeloma.
- ❖ Clinical evidence of pulmonary leukostasis and disseminated intravascular coagulation.
- ❖ Known COPD with a forced expiratory volume in 1 second 50% of predicted normal.
- ❖ History or presence of clinically relevant CNS pathology.
- ❖ Previous history of an allogeneic HSCT treatment with any gene therapy-based therapeutic for cancer, investigational cellular therapy for cancer or BCMA targeted therapy.
- ❖ Subject has received ASCT within 12 weeks prior to randomization.
- ❖ Subject has received any of the following within the last 14 days prior to randomization: Plasmapheresis; major surgery; radiation therapy other than local therapy for myeloma-associated bone lesions; use of any systemic anti-myeloma drug therapy.
- ❖ Echocardiogram or multigated acquisition with LVEF< 45%.
- ❖ Ongoing treatment with chronic immunosuppressants.
- ❖ Patient is positive for HIV (HIV-1), chronic or active hepatitis B or active hepatitis A or C.
- ❖ Patient has uncontrolled systemic fungal, bacterial, viral or other infection or requiring IV antimicrobials.
- ❖ History of class III or IV CHF or severe nonischaemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months prior to randomization.

- ❖ Median time to progression during last previous antimyeloma therapy (range): 7.1 (0.7–67.7) vs. 6.9 (0.4–66.0) months
- ❖ Extramedullary disease: 24% vs. 24%
- ❖ High tumour burden: 28% vs. 26%
- ❖ ECOG PS score:
  - 0: 47% vs. 50%
  - 1: 52% vs. 47%
  - ≥2: <1% vs. 3%
- ❖ R-ISS disease stage:
  - I: 20% vs. 20%
  - II: 59% vs. 62%
  - III: 12% vs. 11%
  - Unknown: 9% vs. 8%
- ❖ Cytogenetic abnormalities
  - High-risk abnormality: 42% vs. 46%
- ❖ Median no. of previous regimens (range): 3 (2–4) vs. 3 (2–4)
- ❖ Previous autologous HSCT: 84% vs. 86%
  - 1 Transplantation: 66% vs. 66%
  - >1 Transplantation: 19% vs. 20%
- ❖ Previous radiation therapy: 35% vs. 35%
- ❖ Refractory status:
  - Immunomodulatory agent: 88% vs. 94%
  - Proteasome inhibitor: 74% vs. 72%
  - Anti-CD38 monoclonal antibody: 95% vs. 94%
- ❖ Double-class–refractory disease: 67% vs. 69%
- ❖ Triple-class–refractory disease: 65% vs. 67%
- ❖ Penta-refractory disease: 6% vs. 4%

Efficacy (I vs. C)	**Safety** (I vs. C, n=250 vs. n=126)
<u>Data-cutoff date 18 April 2022, median follow-up 18.6 months (interim analysis)</u> **Median PFS in the ITT population**: 13.3 months vs. 4.4 months; HR for disease progression or death 0.49 (95% CI, 0.38-0.65); p<0.001	**AES of any grade**: 99% vs. 98% **AEs of grade 3 or 4:** 93% vs. 75%

PFS at 6 months: 73% vs. 40%
12-month PFS: 55% vs. 30%
PR or better: 71% vs. 42%; odds ratio 3.47 (95% CI, 2.24-5.39); p<0.001 by a two-sided Cochran–Mantel–Haenszel test
CR or stringent CR: 39% vs. 5%
Median time to response: 2.9 months vs. 2.1 months
Median duration of response: 14.8 months (95% CI, 12.0-18.6) vs. 9.7 months (95% CI, 5.4-16.3)
MRD-negative status within 3 months before the occurrence of at least a CR: 20% vs. 1%
OS data: immature

Cellular Kinetics

- At the data-cutoff date (1 March 2022), a total of 224 patients could be evaluated for ide-cel pharmacokinetics.
- After infusion, CAR-positive T cells underwent rapid multi-log expansion; maximum expansion occurred at a median of 11 days.
- Exploratory analyses indicated that higher quartiles of ide-cel expansion were associated with longer PFS.
- Considerable interpatient variability in cell expansion (a situation inherent to CAR T-cell biology) was noted, and the lowest quartile of expansion was present across all actual dose levels.

BCMA Expression

- Although evaluable samples from ide-cel–treated patients at disease progression were limited, BCMA-expressing bone marrow tumour cells were observed in all 6 evaluable biopsy samples.
- Soluble BCMA was detectable at disease progression in 82 of 84 evaluable patients.

AEs of grade 5: 14% vs. 6%
Serious AEs: 52% vs. 38%
TRAEs of grade 5: 3% vs. 1%[8]
Second primary cancer: 6% vs. 4%
CRS: 88% of patients in the ide-cel group, mostly grade 1 or 2 (83%)
Investigator-identified neurotoxic events: 15% in the ide-cel group
Encephalopathy: in 1 patient 317 days after the ide-cel infusion[9]
Deaths during the trial: 30% vs. 26%[10]
Discontinuations from the study after the initial treatment: 38% vs. 26% (most commonly due to death: 30% vs.15%)

Patient-reported outcomes (12)

Although the impact of Idecabtagene vicleucel compared to standard triplet regimens on the changes in HRQoL was defined as a secondary objective, data is currently not available.

- The median follow-up was 18.6 months (IQR 14.0-26.4); PRO compliance was higher than 75% throughout.
- Overall least-squares mean changes from baseline favoured ide-cel with Hedges' g effect sizes from 0.3 to 0.7 for most domains.
- Patients in the ide-cel group showed statistically significant and clinically meaningful improvements across the primary PRO domains of interest, except for QLQ-MY20 disease symptoms, side effects of treatment, and EQ-5D-5L index score, which showed improvement across assessment visits but did not exceed the within-group minimally important difference thresholds.
- The ide-cel group had shorter times to clinically meaningful improvement than the standard regimens group in QLQ-C30 domains except in role functioning, diarrhoea, and financial difficulties; in QLQ-MY20 domains except body image; and in EQ-5D-VAS.

ESMO-MCBS version 1.1 (13)

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	<6 months	PFS: +8.9 months	0.49 (0.38-0.65)	HR≤0.65 AND gain ≥1.5 months	3	+14.0% serious AEs	significantly improved	-1[11]/+1[12]/+1[13]	4

[8] The most common of these events was sepsis.
[9] The event was considered by the investigator to be related to worsening pneumonia and to Clostridium difficile colitis, not to treatment with ide-cel.
[10] Death was most commonly due to disease progression (17% vs. 17%). The incidence of death from infectious disease was similar in the two groups (5% vs. 5%).
[11] Downgrade 1 level due to incremental toxicity.
[12] Upgrade 1 level due to ≥10% improvement of PFS at 1 year.
[13] Upgrade 1 level due to significantly improved QoL.

Risk of bias (RCT) (14)					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no high risk	unclear[14] unclear risk	yes[15] high risk	unclear

Ongoing trials (15)		
NCT number/trial name	Description	Estimated study completion date
NCT03651128/KarMMa-3	Please see above.	04/2027
NCT03361748/KarMMa	A Phase 2, multicentre study to determine the efficacy and safety of bb2121 in subjects with relapsed and refractory MM.	11/2024
NCT04855136/KarMMa-7	An exploratory phase 1/2 trial to determine recommended phase 2 dose, safety and preliminary efficacy of bb2121 combinations in subjects with relapsed/refractory MM	12/2026
NCT03601078/KarMMA-2	A phase 2, multi-cohort, open-label, multicentre study to evaluate the efficacy and safety of bb2121 in subjects with relapsed and refractory MM and in subjects with clinical high-risk MM.	12/2030

Available assessments

- In May 2022, NICE published a Health Technology Briefing "Idecabtagene vicleucel for treating relapsed or refractory multiple myeloma after 2 therapies" (16).
- No further assessments were identified via NICE, CADTH, ICER or G-BA.

Other aspects and conclusions

- In January 2024, the **CHMP adopted an extension to the existing indication** for Abecma®, for the treatment of adult patients with relapsed and refractory MM who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy. This indication is **approved by the FDA since April 2024.**
- **KarMMA-3 (NCT03651128)** is an **ongoing**, randomized, open-label, **phase 3 trial**, evaluating idecabtagene vicleucel as compared with standard regimens in patients with triple-class–exposed relapsed and refractory MM who had received two to four lines of therapy previously and who had disease refractory to the last regimen. Patients ≥18 years of age with documented diagnosis of MM and measurable disease, who had received two to four previous therapies including daratumumab, an immunomodulatory agent, and a proteasome inhibitor for at least two consecutive cycles and who had
  documented disease progression within 60 days after the completion (last dose) of the last therapy, and had an ECOG PS of 0 or 1, were included. There was a wide range of exclusion criteria, including nonsecretory MM, laboratory abnormalities or inadequate pulmonary function.
- The **primary endpoint** of KarMMa trial was **PFS**. At a median follow-up of 18.6 months, the median PFS was significantly prolonged: 13.3 months in the ide-cel group vs. 4.4 months in the standard-regimen group (HR for disease progression or death 0.49; 95% CI, 0.38-0.65; p<0.001).
- According to PRO analyses, patients in the ide-cel group showed statistically significant and clinically meaningful improvements across the primary PRO domains of interest, with the exception of QLQ-MY20 disease symptoms, side effects of treatment, and EQ-5D-5L index score, which showed improvement across assessment visits but did not exceed the within-group minimally important difference thresholds. The **ESMO-MCBS** for Haematological Malignancies was applied, resulting in a final adjusted magnitude of clinical benefit of 4.
- Due to the ongoing status of KarMMA-3 (currently only interim data is available), the **risk of bias was considered unclear**. However, the risk is **increased** by the open-label design and the industry-funded background.

[14] The KarMMa trial is ongoing; currently, only interim data is available.
[15] The KarMMa-3 trial was designed by the sponsors in collaboration with academic investigators. Medical writing assistance was funded by the sponsor.

- Beside the ongoing KarMMa trial, no further phase 3 trials were identified. Three phase 1/2 trials, assessing idecabtagene vicleucel in patients with MM are currently listed on ClinicalTrials.gov.
- **Final analysis data** from the KarMMa-3 trial, as well as **further phase 3 data** is **required** to confirm the interim analysis results of KarMMA-3.

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Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, ANC=absolute neutrophil count, ASCT=autologous stem cell transplantation, AST=aspartate aminotransferase, BCMA=B-cell maturation antigen, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CHF=congestive heart failure, CMV=cytomegalovirus, CNS=central nervous system, COPD=chronic obstructive pulmonary disease, CR=complete response, CRS=cytokine release syndrome, DCEP=dexamethasone, cyclophosphamide, etoposide and cisplatin, DMSO= dimethyl sulfoxide, DT-PACE=dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, EQ-5D=EQ 5 dimensions, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GVHD=graft versus host disease, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HLH= haemophagocytic lymphohistiocytosis, HSCT=haematopoietic stem cell transplantation, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, INR=International normalized ratio, Int.=intention, IQR=interquartile range, IV=intravenous, LVEF=left ventricular ejection fraction, MAS=macrophage activation syndrome, MG=median gain, MM=multiple myeloma, MRD=minimal residual disease, n=number of patients, NICE=National Institute for Health Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, POEMS syndrome=polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes, PR=partial response, PRO=patient-reported outcomes, QLQ=quality of Life questionnaire, QLQ-MY20=Multiple Myeloma Module, QoL=quality of life, R-ISS= revised International Staging System, RNA=ribonucleic acid, SAE=serious adverse event, SCT=stem cell transplant, sPEP=serum protein electrophoresis, ST=standard treatment, ULN=upper limit of normal, uPEP= urine protein electrophoresis, VAS=visual analogue scale, WHO=World Health Organization

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