EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

RWD-derived external controls case study

Abecma (EMEA/H/C/004662/0000)

Joint HMA/EMA Big Data Steering Group workshop on RWE methods

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- Introduction to Abecma
- Regulatory context
- Main results
- Details on methodology and external controls

Disclaimer

The views expressed in this presentation are the personal views of the presenters and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

The results shown in this presentation are based on the EPAR (EMA/409800/2021) and SmPC.

Clinical & Regulatory context

Abecma (idecabtagene vicleucel, ide-cel)

- MAH: Bristol Myers Squibb EEIG
- CAR-T cell product, first CAR-T cell approved for **treatment of RRMM (relapse refractory multiple myeloma)** in 4th line)
- **Conditional** Marketing Authorisation received on 18 August 2021
- Beneficiary of PRIority MEdicines **(PRIME)** scheme
- Orphan medicinal product

Clinical & Regulatory context

Abecma (idecabtagene vicleucel)

Indication at time of approval:

Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Approval of initial indication was based on:

- pivotal study **MM-001** (**KarMMa-1**). The study was a phase 2, open-label, single-arm, multicentre study that evaluated the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior antimyeloma therapies including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and who were refractory to the last treatment regimen.
- supportive studies **CRB-401** dose-escalation study and **NDS-MM-003**: A global, non-interventional, retrospective, multi-center study to generate real-world evidence of subjects with relapsed and refractory multiple myeloma with prior exposure to an anti-CD38 antibody

Efficacy

Efficacy was assessed on the basis of overall response rate (ORR)(primary endpoint), complete response (CR) rate (key secondary endpoint) and duration of response (DOR)(secondary endpoint), as determined by an independent review committee. Other key efficacy endpoint included minimal residual disease (MRD) using next-generation sequencing (NGS).

	Enrolled[a] (N = 140)	Treated population Target dose of Abecma (CAR-positive T cells)			
		150 x 10^{6}[b] (N = 4)	300 x 10^{6} (N = 70)	450 x 10^{6} (N = 54)	Total 150 to 450 x 10^{6} (N = 128)
Overall response rate (sCR+CR+VGPR+PR), n (%)	**94 (67.1)**	**2 (50.0)**	**48 (68.6)**	**44 (81.5)**	**94 (73.4)**
95% CI[c]	59.4, 74.9	6.8, 93.2	56.4, 79.1	68.6, 90.7	65.8, 81.1
CR or better, n (%)	**42 (30.0)**	**1 (25.0)**	**20 (28.6)**	**21 (38.9)**	**42 (32.8)**
95% CI[c]	22.4, 37.6	0.6, 80.6	18.4, 40.6	25.9, 53.1	24.7, 40.9
VGPR or better, n (%)	**68 (48.6)**	**2 (50.0)**	**31 (44.3)**	**35 (64.8)**	**68 (53.1)**
95% CI[c]	40.3, 56.9	6.8, 93.2	32.4, 56.7	50.6, 77.3	44.5, 61.8
MRD-negative status[d] and ≥ CR					
Based on treated patients	**–**	**4**	**70**	**54**	**128**
n (%)	–	1 (25.0)	17 (24.3)	15 (27.8)	33 (25.8)
95% CI	–	0.6, 80.6	14.8, 36.0	16.5, 41.6	18.5, 34.3
Time to response, n	**94**	**2**	**48**	**44**	**94**
Median (months)	1.0	1.0	1.0	1.0	1.0
Min, max	0.5, 8.8	1.0, 1.0	0.5, 8.8	0.9, 2.0	0.5, 8.8
Duration of response (PR or better)[e], n	**94**	**2**	**48**	**44**	**94**
Median (months)	10.6	13.0	8.5	11.3	10.6
95% CI	8.0, 11.4	2.8, 23.3	5.4, 10.9	10.3, NE	8.0, 11.4

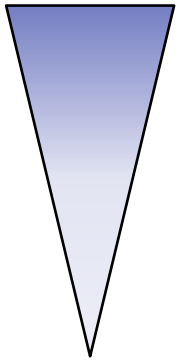
Study design, external controls & methodology

Real-word data sources (Study NDS-MM-003)

Sources - Clinical sites, registries, research databases collated in a single data model

EMA Interactions: PRIME and Scientific Advice

RRMM cohorts



Broad (N = 1949)	≥ 18 years, received at least 3 prior regimens, including an immunomodulatory agent, a PI, and an anti-CD38 antibody, matching timelines
Eligible (N = 190)	similar characteristics to MM-001, e.g. refractory to last regime, one documented treatment after T0, measurable disease assessment, exclusion criteria
Matched (N = 76–80)	Eligible cohort with matched baseline characteristics to MM-001 subjects, N depending on imputed data set

Methodology

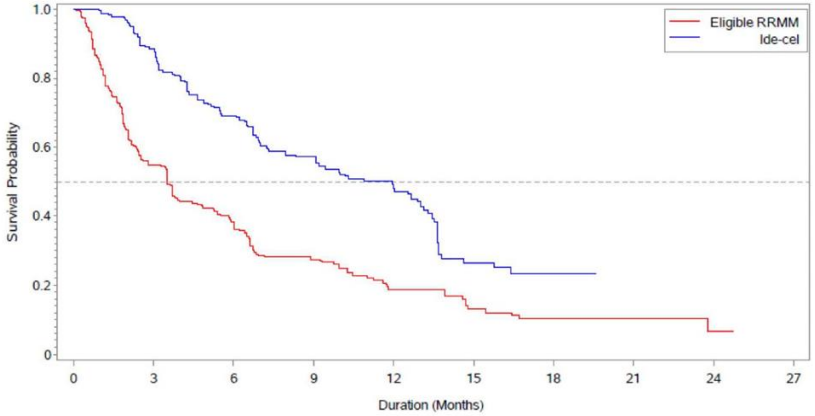
- Primary endpoint: ORR - percentage of subjects who achieved a partial response (PR) or better
- Propensity score (PS) methodology was used to ensure that RW subjects in the *Eligible RRMM cohort* were comparable to the ide-cel cohort
  - Eligible RRMM cohort: older, somewhat less heavily pre-treated, lower degree of refractoriness
- Trimmed stabilised inverse probability of treatment weights (IPTW)
  - Covariates: age, sex, bone lesions, time from initial diagnosis, number of prior regimens, cytogenetic high risk/low risk, refractory to immunomodulatory agents, refractory to PI, refractory to anti-CD38 antibody, and baseline lab tests (platelet, hemoglobin, albumin, and calcium)
  - Allowing for ≤ 30% missing values for highly prognostic covariates in Eligible RRMM cohort
  - Very important predictors by scientific steering committee (ie, age, albumin, number of prior regimens) forced into the model irrespective of lack of association with group membership

Results (MM-001 vs. NDS-MM-003)

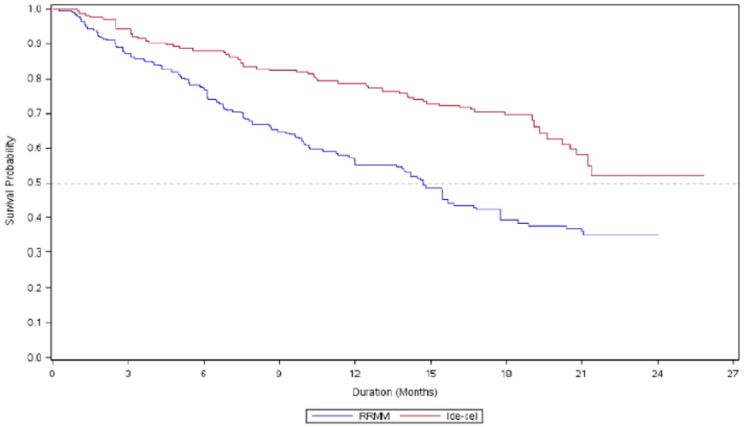
Comparison between **Balanced RRMM** (trimmed stabilised IPTW) to MM-001 cohort

Clinically relevant and statistically significant benefit for ide-cel

PFS – HR: 0.43 (95% CI: 0.30, 0.62, p < 0.0001)



OS – HR: 0.46 (95% CI 0.29, 0.73, p = 0.001)



RWD-derived external controls case study - Abecma

Limitations (highlighted by the CHMP)

- Long time-period allowed for collection of baseline data (up to 60 days from index date)
- Overlapping recruitment periods for external cohort and MM-001 at same study centres
- Robustness difficult to verify
- Highly selected study population
- Large proportion of missing data (up to 30%) for some included co-variates
- Several co-variates excluded from the PS model due to >30% missing data

General considerations

- External control fit only for contextualisation of study results of pivotal study MM-001
- Potential unknown confounders and other differences cannot fully be addressed (by propensity scoring methods)
- Challenges with time-to-event endpoints in non-randomised comparison setting
- Draft guide on SmPC 5.1: Usage of p-values discouraged, no external control data
- Randomised and non-randomised evidence

Any questions?

Further information

[Insert relevant information sources or contact details as applicable.]

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Development programme at the time of submission

- one **Phase 1** dose-finding study (CRB-401),
- three ongoing, uncontrolled **Phase 2** studies (MM-001 [KarMMa], MM-001 - Japan and MM-002),
- One ongoing **Phase 3** randomized, controlled trial (RCT) (MM-003 [KarMMa-3]), and
- two long-term **safety follow up** studies (GC-LTFU-001 and LTF-305).

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EMA interactions

PRIME recommendations

- Use of external control to facilitate quantifying the magnitude of the benefit
- Seeking Scientific Advice for external control

Scientific Advice

- Protocol assistance
- Global, non-interventional, retrospective study (NDS-MM-003)

Early engagement with EMA through PRIME and Scientific Advice was highlighted as key learning (slides, EMA, RWE Workshop, June 2023)