Fimea
Finnish Medicines Agency

Overview of the use of external controls in submissions to the European Medicines Agency

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External comparsons in different regulatory contexts

- **External controls to establish positive B/R**

  - RCT is always the preferred solution, use of external control always requires a clear justification
  - Need to assess both benefit and risk of the treatment

- **External controls in other regulatory contexts** (demonstration of major therapeutic advantage for a conditional approval, extended + 1 year marketing protection, significant clinical benefit for orphan maintenance assessment, accelerated assessment, PRIME designation, PIPs)

  - Often requires comparisons to several treatment options, comparative data often not available, question of interest more limited

External controls to establish positive B/R

- Is the use of an external comparator acceptable? = Why a randomised controlled trial was not performed?

  ” Randomised controlled trials (RCTs) are the standard for providing confirmatory evidence on the efficacy of an investigational treatment.(…) it is the responsibility of the applicant to justify to regulators the reasons for deviating from the expected standard.”

  “Designs that prospectively include a non-randomised external control (arm) in the trial protocol may not be considered SATs, but key considerations in this paper may still apply due to the lack of randomisation.”
  (Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation application)

Contextualisation

- Benefit/risk assessment is ”absolute”, superiority over approved treatment options is not a regulatory requirement
- Results cannot be assessed in isolation from clinical knowledge
- Relevance emphasized in situations when patient population is ”new” (change in SOC, population defined based on a new biomarker etc.), selected based on strict citeria (”population of unicorns”)
- Not asking for statistical comparison

What the external comparison is needed for?

- To demonstrate that outcomes are impossible without treatment, to demonstrate relevance of a treatment effect, or to demonstrate superiority?
- Magnitude of difference: external comparisons have been generally used as a part of the B/R assessment in cases where the difference between experimental treatment and comparator is big enough to leave room for uncertainties
- Need for external comparison should be identified before clinical trial data is available
- Attempts to rescue negative trials based on comparisons to external data are generally not accepted

Example: Zolgensma (onasemnogene abeparvovec) for treatment of SMA

- Outcomes of a pivotal single arm study were compared to the expected outcomes based on the two natural history cohorts derived from the PCNR and NeuroNext studies
- “The outcomes exceed the natural course of SMA type 1 that showed survival rates of about 25% at 13.6 months of age and 8% at 20 months of age. Patients in the **natural history cohorts only show a decline** in CHOP-INTEND score and never reach a score above 40 after 6 months of age. The milestone of independent sitting is **never reached** in the natural history cohorts. This is considered a large and clinically meaningful effect. It **exceeds the natural course of SMA 1 on all these parameters many times**.”

Example of Yescarta MAA

- Yescarta in the initial MAA: Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy
    - this was the first CAR-T product, MAA based on a **small single arm study** ZUMA -1 phase2 and in order to provide external comparisons a **retrospective metaanalysis Scholar-1** was designed; both studies were considered as main studies the external controls metaanalysis study aimed to provide a comparison to better determine **the magnitude of effect of Yescarta.**
    - SCHOLAR-1 was a patient pooled, retrospective analysis, which integrated data from 636 patients from 2 randomized Phase 3 studies (LYSARC-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational databases (MD Anderson Cancer Center and Mayo Clinic/University of Iowa Specialized Program of Research Excellence [SPORE]) of patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL), with refractory defined as progressive disease (PD) or stable disease (SD) < 6 months as best response to last line of chemotherapy (≥ 4 cycles of first-line or 2 cycles of later-line therapy) or relapse ≤ 12 months after autologous stem cell transplantation (ASCT).
    - obtaining the historical control data of Scholar-1, provided solid evidence of the magnitude of efficacy of Yescarta as in the ITT population the ORR was 66% as compared to the external control in SCHOLAR of 26%

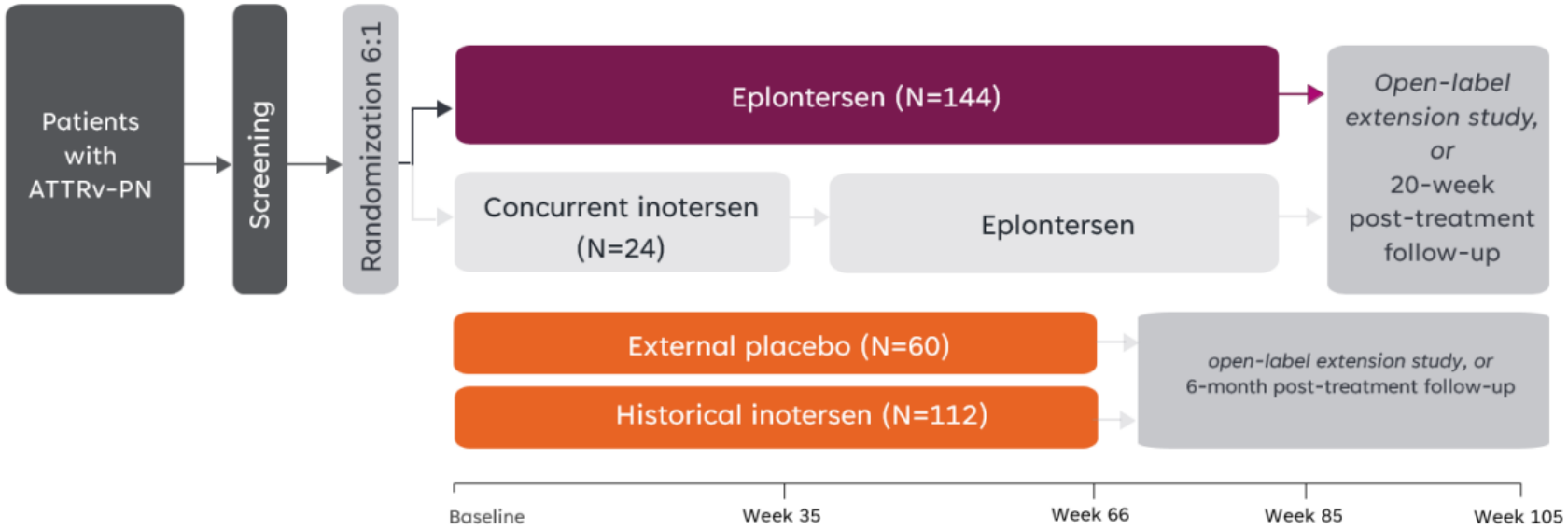
Is the clinically relevant endpoint suitable for comparisons between different data sources?

- Is the data collected as a part of routine care regardless of treatment response?
- Systematic disease assessment, or dependent on availability of multiple pieces of clinical information?
- Timing and frequency of follow-up?
- Does the treatment received have an impact on follow-up or availability of specific clinical data?
- Example GvHD: complex response assessment of 11 organ systems vs. survival data

Is the data source suitable?

Example: Wainzua (eplontersen)

- Wainzua is a medicine used to treat nerve damage caused by hereditary transthyretin (ATTRv) amyloidosis
- Primary comparison eplontersen vs. external placebo arm



ATTR-PN, transthyretin-mediated amyloidosis with polyneuropathy; N = number of patients in treatment group.
Source: Figure 1, ION-682884-CS3 CSR, Module 5.3.5.1.

Example: Abecma (Idecabtagene vicleucel) for treatment of multiple myeloma
PRIME

- PRIME designation: “In case authorised treatments or established methods exist, the expected improvements should be discussed through a critical review **comparing authorised or clinically established treatments and the proposed product**.”
- PRIME kick-off: “The Rapporteur and EMA had concerns around the Applicant’s intention to provide a literature review summary but not **an external control containing patient level data**. This approach not to include an external control may result in difficulties quantifying the magnitude of the benefit.”
  - ”population of unicorns”: Median age 60 (median age for diagnosis of MM ~70y), median number of prior lines 6, many co-morbidities excluded, ECOG 0-1…)
  - No SOC for heavily pre-treated population
- “Due to the number of products approved, the Applicant was advised to consider an external control group for demonstration of significant benefit as lack of control arm poses a challenge with establishment of significant clinical benefit based on a single arm trial. “

Abecma: Accelerated assessment

- “Importance of the observed effects of the product should be discussed, as well as the **expected added value of the product and impact on medical practice in comparison to existing treatments** (if any). Added value over existing methods would normally be based on meaningful **improvement of efficacy and/or safety** and/or in exceptional cases, major improvements to patient care (e.g. allows ambulatory vs. hospital treatment only) **using robust evidence**. Discuss also **how the overall B/R balance compares** with that of current methods.”
- “(…) the promising ORR and CR rate observed, and the possibility for long-term disease control suggested that Ide-cell might indeed represent a major therapeutic advantage over existing therapies.”

Source: Abecma EPAR

Example: Abecma (Idecabtagene vicleucel)
B/R assessment

- Study MM-001 was an open-label, single-arm, multicentre, multinational, Phase 2 study to evaluate the efficacy and safety of ide-cel in subjects with RRMM who had received at least 3 prior regimens including an immunomodulatory agent, a PI, and an anti-CD38 antibody, and who were refractory to their last prior treatment regimen
- The success criterion: “lower limit of the 95% confidence intervals (CIs) for the ORR was greater than 50%. The selection of a null hypothesis of 50% ORR was based on the observed clinical activity of the best available single agent therapy in a heavily pretreated RRMM patient population. Daratumumab demonstrated a response rate ranging from 29% to 36% in RRMM patients who had received at least 3 prior lines of therapy including an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI) or who were double refractory. The null hypothesis of 50% ORR represented an approximately 50% improvement over daratumumab”

Source: Abecma EPAR

Abecma: external comparisons

- Systematic literature review (11 RWS and 13 clinical trials): ”ORR for the CAR-T therapies ranged from 27% to 100%, and for the non-CAR-T therapies ORRs of 21% to 48% were reported.”
- Population Matching-adjusted indirect comparisons (MAICs), using PS weights to adjust for cross-study differences, were undertaken using individual subject-level data from Study MM-001 for ide-cel and aggregated summary data from STORM part 2 (selinexor) and DREAMM-2 (belantamab mafodontin) primary publications (MAIC – STORM-II; MAIC-DREAMM-2).

Source: Abecma EPAR

Abecma: external comparator

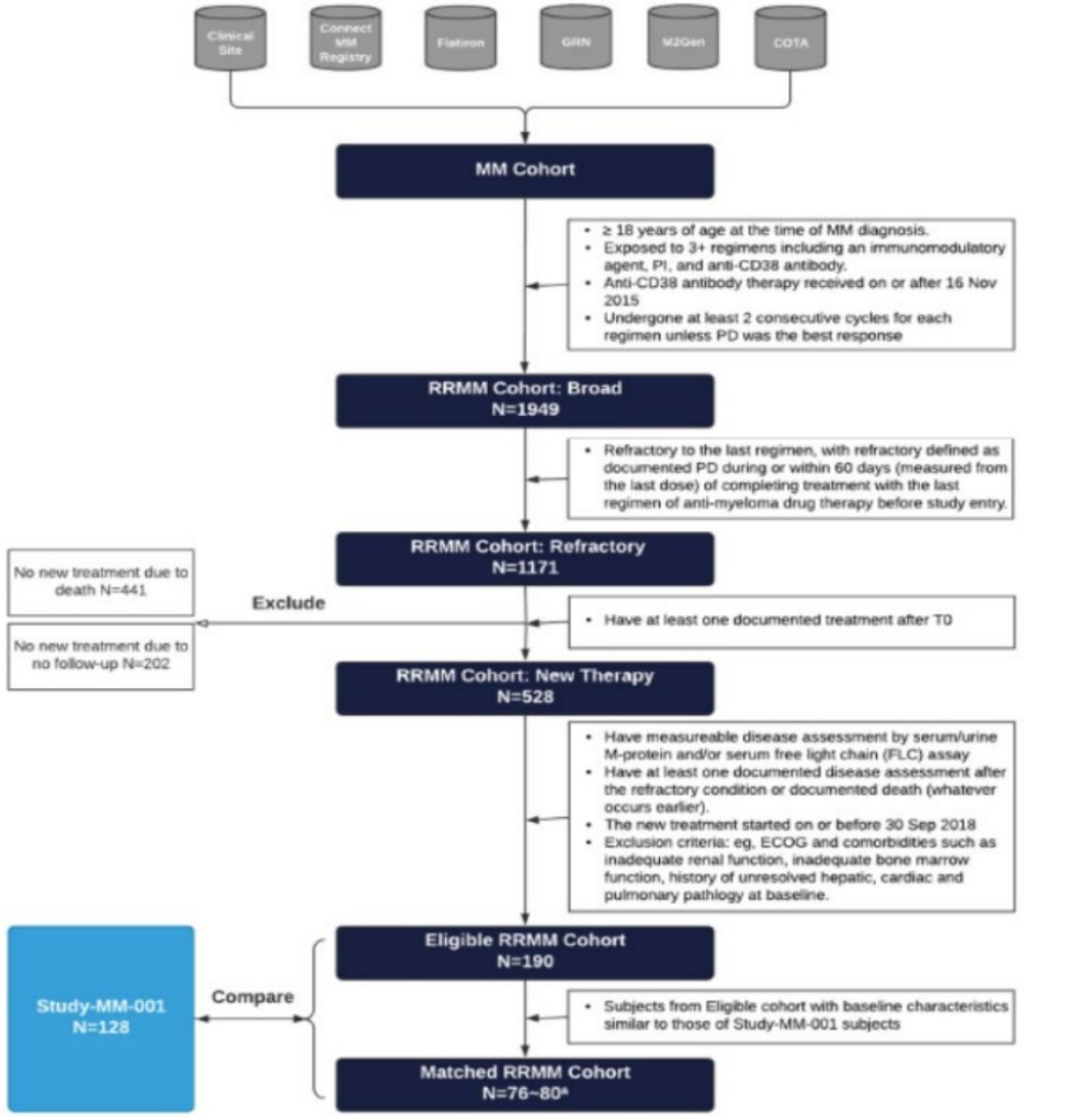
- NDS-MM-003: A global, non-interventional, retrospective, multi-center study to generate real-world evidence of subjects with relapsed and refractory multiple myeloma with prior exposure to an anti-CD38 antibody set up **to generate an external comparison arm for study MM-001**.
- Data from sources including clinical sites, registries, and research databases were collated in a single data model, and further analysed.
- Endpoints ORR, DoR, PFS, OS

Source: Abecma EPAR

Abecma: external control

- Very large data sources
  → 1949 patients fulfilling the requirements for prior therapies
  → 528 received new therapy
  → 190 fulfilled key criteria (at least one disease assessment)
  → matched cohort n=76-80
- There were more than **90 different regimens** in the eligible patient cohort (n=190) and 74.7% were able to receive 3 or more drug combinations as their index therapy.

Figure 26: Construction of the RWD cohort



ECOG = Eastern Cooperative Oncology Group; GRN = Guardian Research Network; max = maximum; min = minimum; MM = multiple myeloma; PD = progressive disease; PI = proteasome inhibitor; RRMM = relapsed and refractory multiple myeloma; T0 = baseline.
[a] Numbers (Min-Max) of matched subjects from 30 imputed datasets.

Source: Abecma EPAR

Abecma: external comparison

- “The adjusted indirect comparisons to the NDS-MM-003 study demonstrated a clinically relevant and statistically significant benefit for ide-cel across all pre-defined efficacy endpoints, with an ORR of 69.4% (95% CI: 60.3, 80.0) for the ide-cel enrolled population vs 32.0% (95% CI: 24.1, 42.5) for the RW eligible cohort. The HR for PFS (0.43 (95% CI: 0.30, 0.62, $p < 0.0001$) was also compelling in favour of ide-cel.”
- “However, despite extensive efforts to match the patient populations, the comparisons are limited by several factors including the rather long time period (up to 60 days from the index date) allowed for the collection of baseline data, the overlapping recruitment periods for the RWS and the MM-001 at the same study centres, the large proportion of missing data (up to 30%) for some included co-variates and several co-variates excluded from the PS model due to >30% missing data.”

Source: Abecma EPAR

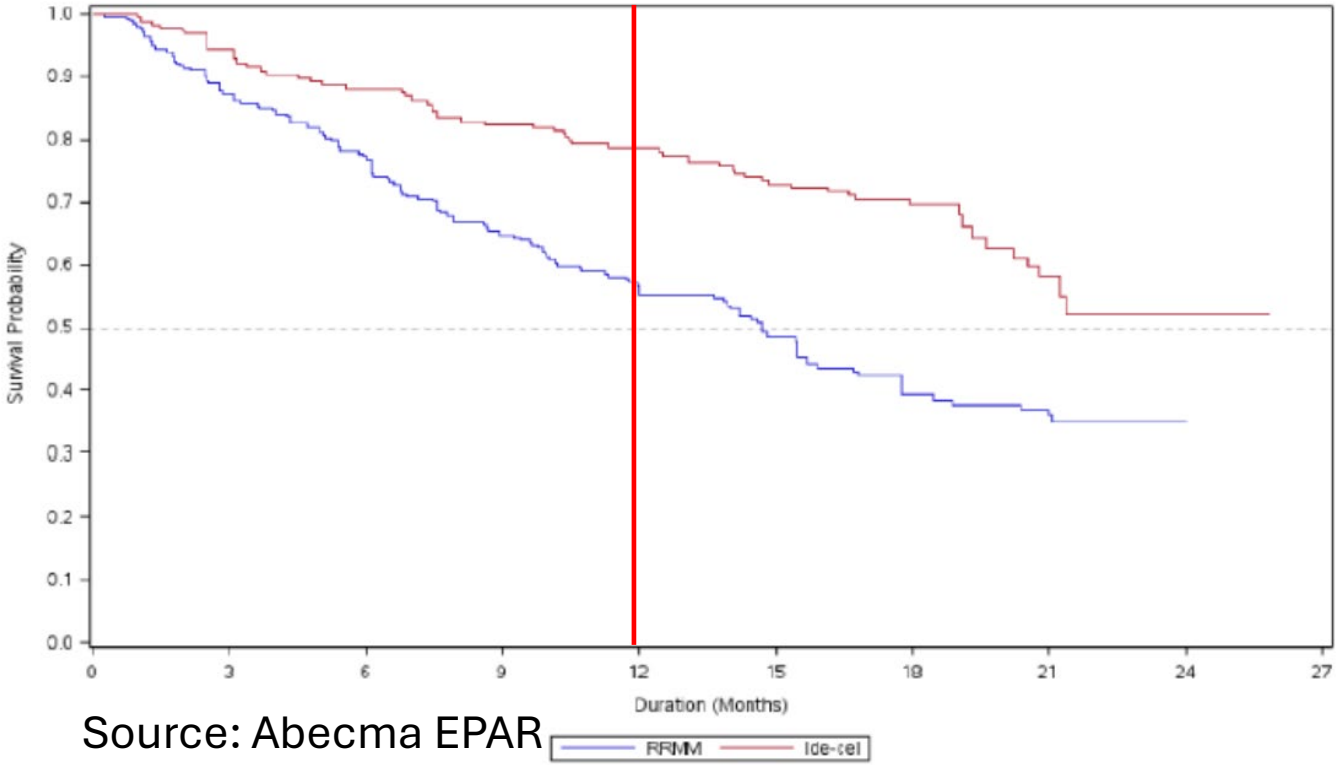
Example: Abecma (Idecabtagene vicleucel)
B/R assessment

- “Furthermore, the robustness of the adjusted indirect treatment comparison based on the RWS is difficult to verify, considering the rather selected study population, and the missing data of several important prognostic factors. Thus, although the ORR/DoR benefit is considered sufficiently compelling in the context of a single arm trial, the true magnitude of the treatment effect, including to what extent the observed responses will be reflected in long term benefit in OS, cannot be reliably ascertained.”
- “Nevertheless, in light of the rather compelling efficacy data, further substantiated by adjusted indirect comparisons to external controls, the provided clinical data package is considered sufficient to allow a benefit/risk assessment. (…) despite the limitations of the indirect treatment comparisons, the results indicate that ide-cel treatment is associated with responses that are well above those reported with current standard of care.”

Source: Abecma EPAR

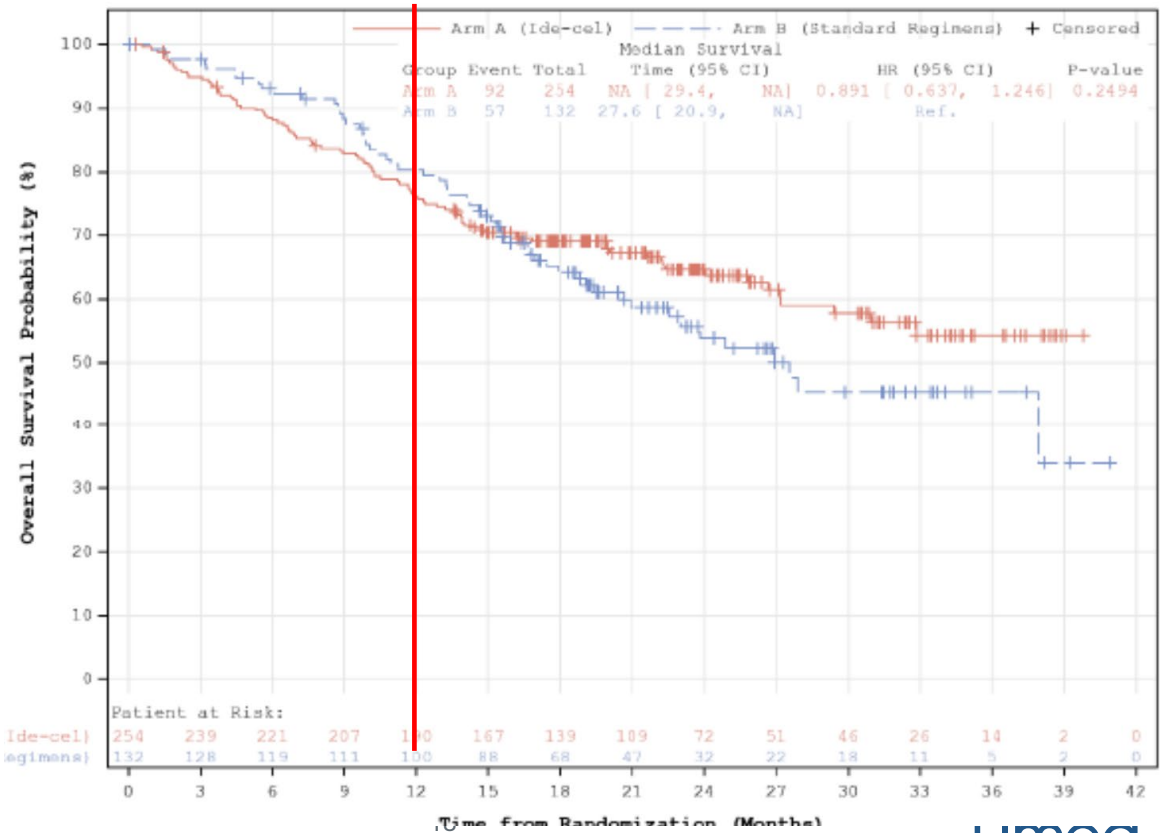
Abecma: External comparison vs. RCT

OS (Abecma vs. external control,
at least 3 prior lines of treatment)



Source: Abecma EPAR

OS (Abecma vs. SOC,
at least 2 prior lines of treatment)



Source: Abecma variation EPAR

Abecma : CMA / MTA

- The advantages should be demonstrated over existing methods used in clinical practice (if any), using robust evidence, **normally from well conducted randomised controlled trials** (evidence-based demonstration of benefit).
- “Recently approved products for RRMM include lenalidomide, pomalidomide, bortezomib, carfilzomib, ixazomib, panobinostat, daratumumab, isatuximab, and elotuzumab. All of these treatments are set from first line to second line or beyond also in different combinations. Belantamab mafodotin and selinexor have been recently granted authorisation for treatment of multiple myeloma in adult patients in forth line and beyond.”
- “Although indirect comparisons of efficacy are challenging in this heterogeneous population, based on high response rate, durability of responses and manageability of the safety profile, ide-cel can be considered to address the unmet medical need to a similar or greater extent than other approved medicinal products.”

Source: Abecma EPAR

Abecma: orphan maintenance assessment

- Although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that [Abecma] will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with relapsed/ refractory multiple myeloma achieve partial and stringent complete responses. This compared favourably with a long list of authorised products to which these patients were not responding anymore. The Committee considered that this constitutes a clinically relevant advantage.
- The comparison between three single-arm studies is, technically, not very informative in terms of quantifying the effects observed. However, taking into consideration similar characteristics of the patient populations enrolled in these studies, and the fact that ide-cel seemed to perform significantly better than both belantamab mafodotin and selinexor in terms of higher overall response rate (ORR) and longer duration of response (DOR), the improved efficacy of this product is accepted.

Source: Abecma orphan maintenance AR

Points to consider when planning external comparisons

- Need for external comparisons should be identified, and external data comparisons planned before clinical trial data is available
- The regulatory question for which the comparison is needed should be well defined
- Data collection, analyses and results should be well reported

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