# ACT EU - Clinical Trial Methodology

# Randomisation and the role of external data

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**The views expressed are personal views and not necessarily the views of EMA or CBG-MEB**

Radboudumc

# Outline

- A brief introduction to ACT-EU & Methodology priorities
- Randomisation: An example outside of oncology
- Single arm trials & external data in regulatory evaluation
- Key take aways & expected next steps

# Accelerating Clinical Trials in the EU (ACT EU)

## Challenges

Need for more impactful multi-state trials to drive decision-making

Need for an overarching strategy to bring stakeholders together

Multiple actors requiring clear roles and responsibilities

Need to leverage the EU's strong healthcare and research infrastructure

A multi-stakeholder approach for progress in clinical trials

## ACT EU vision

EU as an attractive region for clinical research

**Larger and more impactful CTs**, with seamless coordination among regulators and stakeholders

Smart CTs through **regulatory, technological and process innovation**

Empowering, engaging and supporting **stakeholders**

# Clinical trial methodologies

- Aligned clinical trial guidance development across the EU network & drug life cycle.
- Bring together key decision makers during the clinical trial life cycle (including MWP, CTCG, HTA).

- Help stakeholders navigate the EU clinical trial guidance landscape.

- Dedicated workshops on topics of interest: **External controls**, Platform trials & Bayesian statistics first priorities.

**Delivered in 2024**

| | |
|---|---|
| **Q2-Q4 2024** | Coordination of guidance between MWP, CTCG and HTA coordination group established |
| **Q2-Q4 2024** | Ongoing activities on best practice on guidance development |

# An example outside of oncology.

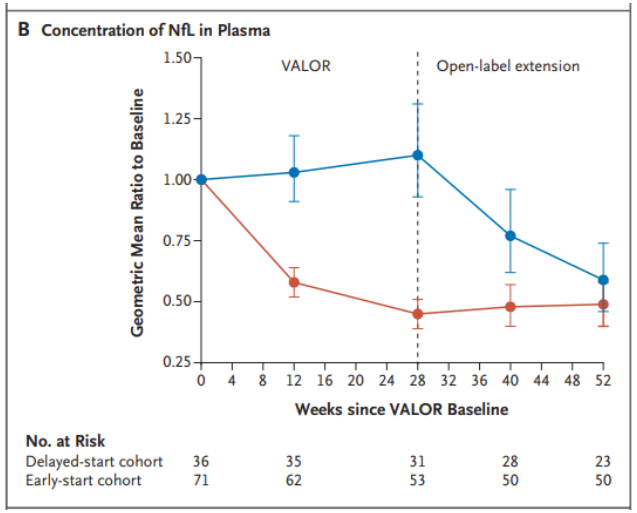
Approval under exceptional circumstances (Qalsody)

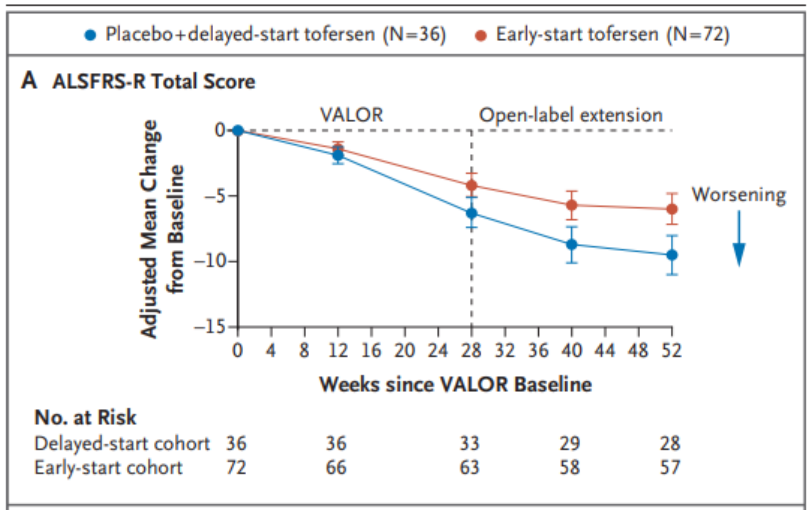
| End Point | Placebo (N=21) | Tofersen (N=39) |
|---|---|---|
| **Primary end point** | | |
| ALSFRS-R total score† | | |
| Adjusted mean change from VALOR baseline | −8.14 | −6.98 |
| Adjusted mean difference: tofersen minus placebo (95% CI) | | 1.2 (−3.2 to 5.5) |
| P value according to joint rank test and multiple imputation | | 0.97 |

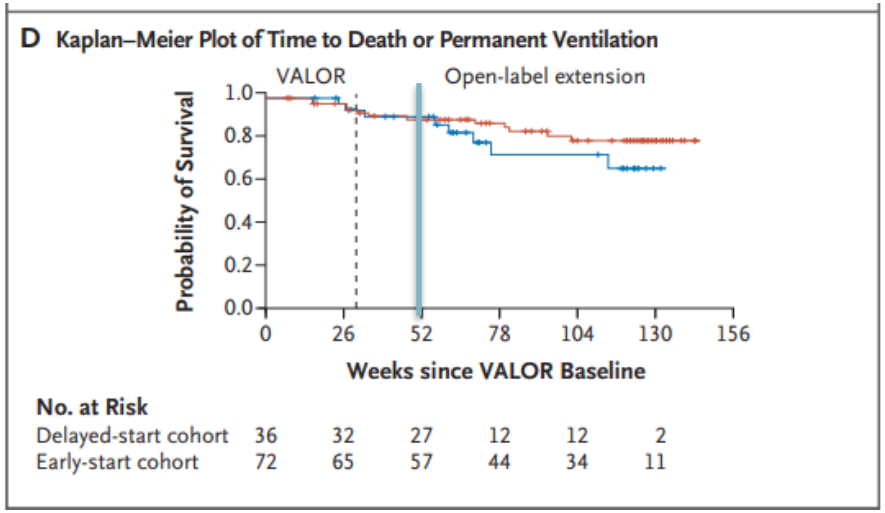
ORIGINAL ARTICLE

## Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T.M. Miller, M.E. Cudkowicz, A. Genge, P.J. Shaw, G. Sobue, R.C. Bucelli, A. Chiò, P. Van Damme, A.C. Ludolph, J.D. Glass, J.A. Andrews, S. Babu, M. Benatar, C.J. McDermott, T. Cochrane, S. Chary, S. Chew, H. Zhu, F. Wu, I. Nestorov, D. Graham, P. Sun, M. McNeill, L. Fanning, T.A. Ferguson, and S. Fradette, for the VALOR and OLE Working Group*

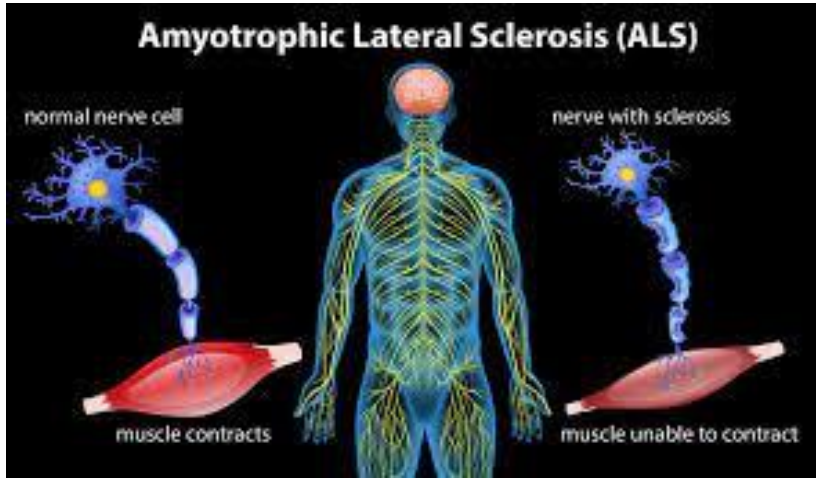


# An example outside of oncology.

- ALS is a rare disease with extremely poor prognosis and substantial suffering.
- No effective treatments exist (beyond riluzole,……) for most patients.
- In contrast to other settings: randomisation is the standard.
- Randomisation essential for interpretation.



# Single arm trials & external data in regulatory evaluation

**Abecma original CMA**

CAR- T cell therapy in patients with relapsed and refractory multiple myeloma.

Adult patients with relapsed and refractory multiple myeloma who have received at least **three** (*two*) prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

# Single arm trials & external data in regulatory evaluation

## Abecma original CMA

9 September 2024
EMA/CHMP/458061/2024
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation application

Considerations on evidence from single-arm trials

Open-label single-arm Phase 2 study.

Primary objective to evaluate efficacy, defined as ORR of ide-cel in subjects with RRMM.

Alternative hypothesis: ORR is > 50%, with a target ORR of 70%.

Total enrolled: 140

Ide-cell treated: 128

# Single arm trials & external data in regulatory evaluation

| | Ide-cel Treated Population<br>Ide-cel (CAR+ T cells) target dose | | | | Enrolled Population (N = 140) |
|---|---|---|---|---|---|
| | $150 \times 10^6$ (N=4) | $300 \times 10^6$ (N=70) | $450 \times 10^6$ (N=54) | 150 to $450 \times 10^6$ (N=128) | |
| ORR - n (%) | 2 ( 50.0) | 48 (68.6) | 44 (81.5) | 94 (73.4) | 94 (67.1) |
| 95% CI[b] | ( 6.8 , 93.2) | 56.4, 79.1 | 68.6, 90.7 | 65.8, 81.1 | 59.4, 74.9 |
| p-value[c] | - | - | - | < 0.0001 | < 0.0001 |

- Treatment effect needs to be isolated in a single arm trial -> ORR
- Treatment impact on PFS, OS and HRQoL cannot be reliably estimated in SAT's
- Surrogacy of ORR for PFS or OS in a strict is not generally available or assumed

# Single arm trials & external data in regulatory evaluation

Real World Data study added to submission package (CMA)

Study NDS-MM-003 was a global, non-interventional, retrospective study 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.

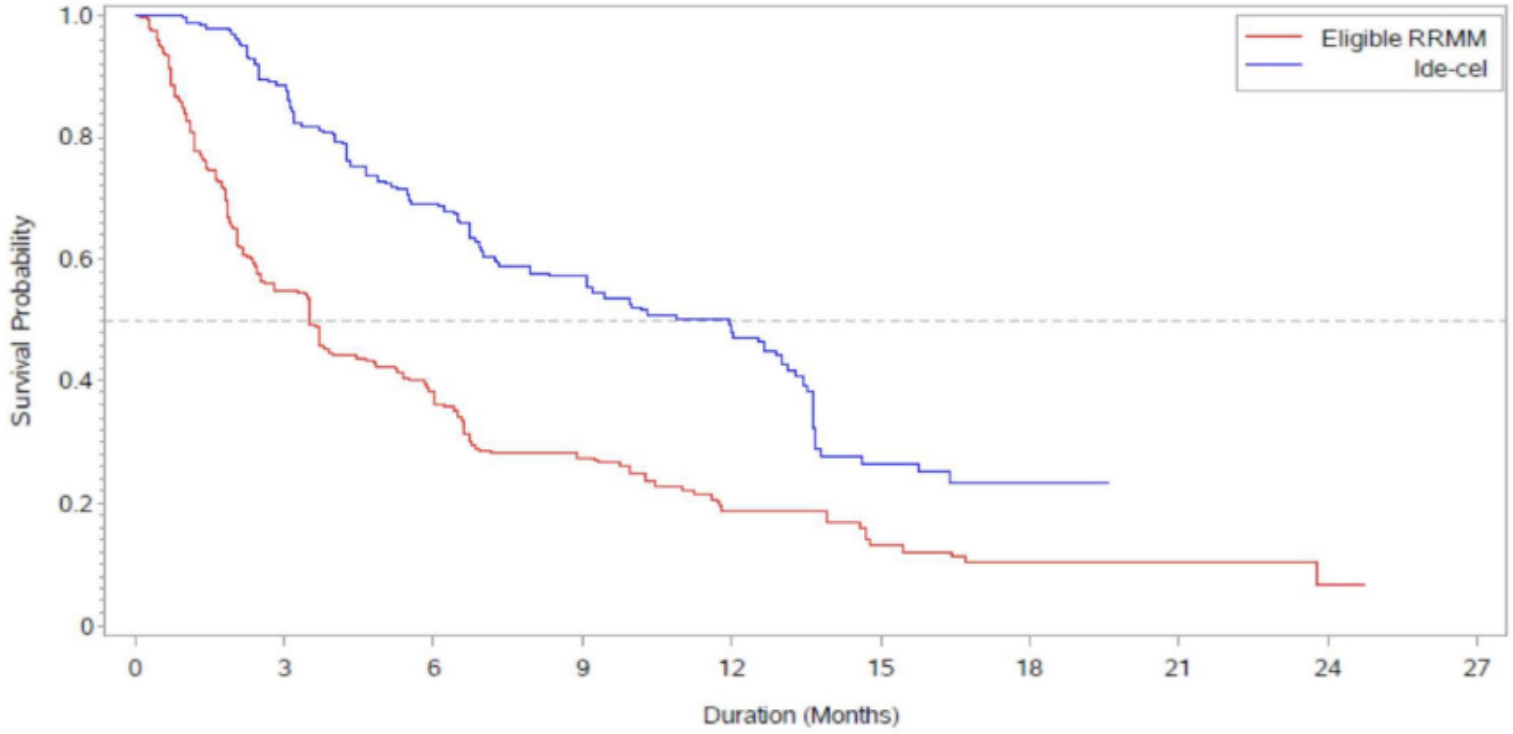
Leading to 190 matched subjects

Primary endpoint ORR (at least PR), Secondary included DoR, PFS and OS

# Single arm trials & external data in regulatory evaluation

| Method<br>Response | Eligible RRMM Cohort[a]<br>(N = 190) | Ide-cel Enrolled Cohort[a]<br>(N = 140) |
|---|---|---|
| | | |
| | 69.4 | |
| | (60.3, 80.0) | |
| | - | |
| | - | |
| | 52.0 | |
| | (42.3, 63.9) | |
| | - | |
| | - | |

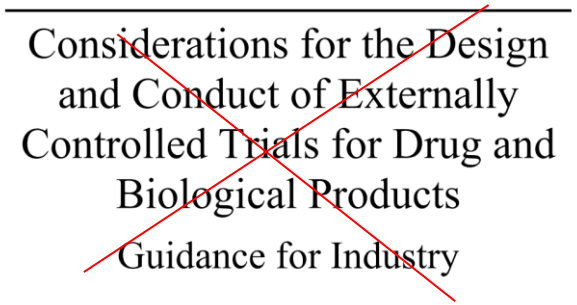
**Figure 27: PFS According to EMA Censoring Rules Adjusted for Trimmed Stabilised IPTW for Subjects in the Eligible RRMM and Ide-cel Enrolled Cohorts**



# Single arm trials & external data in regulatory evaluation

- Most common augmentation of clinical evidence in these settings.
- Not by design and not prospectively planned:

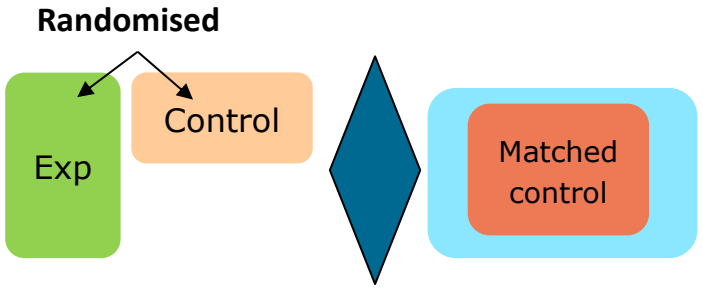
  **Not an external control arm or externally controlled trial**



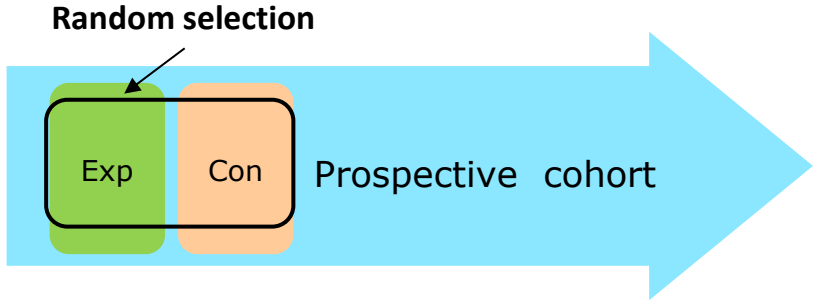

- Even with well-established and well-applied methodology, residual bias difficult to assess.
- Difficult to consider confirmatory (hypothesis testing misplaced).
- CMA decision driven by SAT & external data comparisons not in original label.

# Single arm trials & external data in regulatory evaluation

## Prospective designs with external control arms




Hybrid design




Trials Within Cohorts


Non-randomised control

DOI: 10.1002/pst.2120

MAIN PAPER

WILEY

**The use of external controls: To what extent can it currently be recomm**

Kessels et al. BMC Medical Research Methodology (2023) 23:117 https://doi.org/10.1186/s12874-023-01941-5

BMC Medical Research Methodology

Hans Ulrich Burger[1] | Chri
Armin Koch[4] | Martin Pos

RESEARCH Open Access

**The Trial within Cohorts (TwiCs) study design in oncology: experience and methodological reflections**

Rob Kessels[1], Anne M. May[2*], Miriam Koopman[3] and Kit C. B. Roes[4]

Indirect comparisons:

- Important in the drug life cycle (HTA,..).
- At core of innovative proposals.

Randomised comparison anchor to control bias.

# Single arm trials & external data in regulatory evaluation

**Abecma full MA:** KarMMa-3 trial

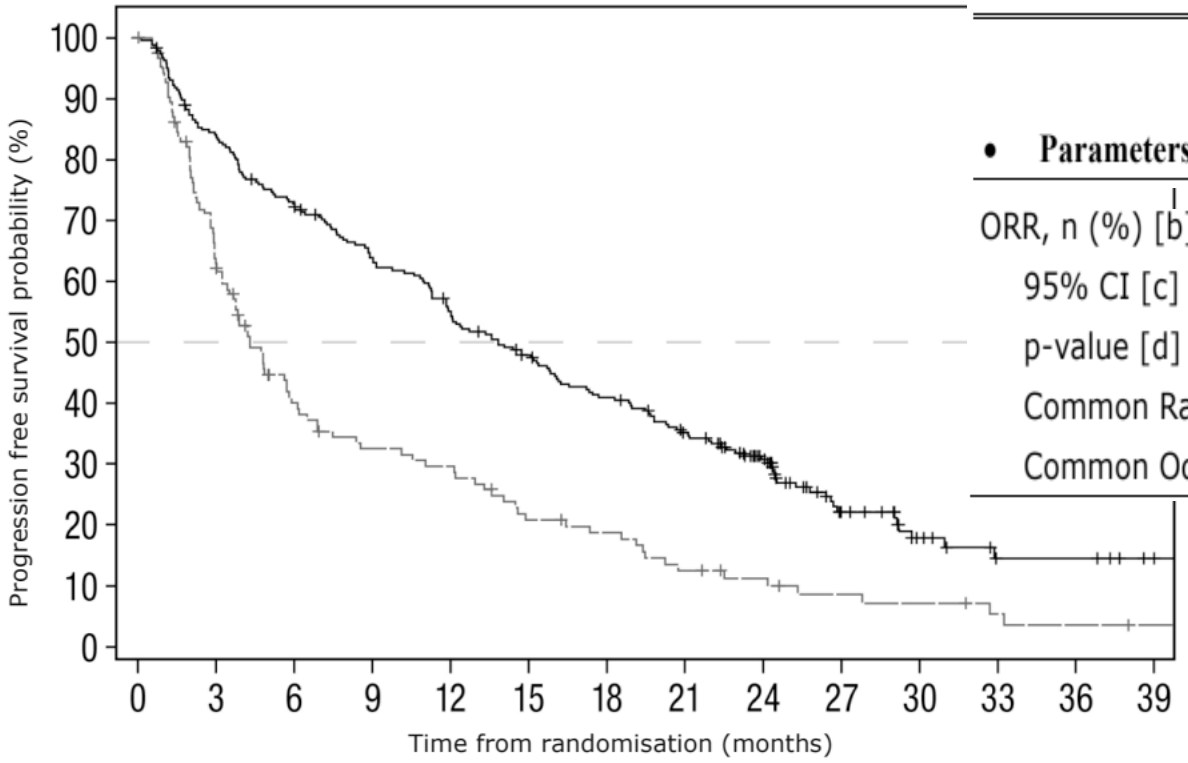
Phase 3 Multicenter, *Randomized*, Open-Label Study of BB2121 Versus Standard Regimens In Subjects With Relapsed And Refractory Multiple Myeloma (RRMM) (2:1 ratio).

| | |
|---|---|
| Primary endpoint: | PFS by IRC assessment. |
| Key secondary: | ORR and OS |
| Numbers of subjects: | 254 and 132 per group randomised (ITT) |

# Single arm trials & external data in regulatory evaluation

## **Abecma full MA:** KarMMa-3 trial

**Figure 10.** **Kaplan-Meier plot of progression-free survival based on IRC assessment in KarMMa-3 study (intent-to-treat population). (DCO 28 April 2023)**

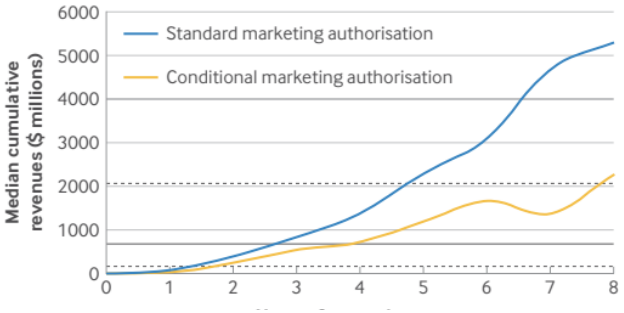



| • Parameters | • Ide-cel (N=254) n (%) | • Standard Regimens (N=132) n (%) |
|---|---|---|
| ORR, n (%) [b] | 181 (71.3) | 55 (41.7) |
| 95% CI [c] | 65.7, 76.8 | 33.3, 50.1 |
| p-value [d] | <.0001 | |
| Common Rate Difference (97.2% CI) [e] | 29.3 (18.1, 40.5) | |
| Common Odds Ratio (97.2% CI) [e] | 3.54 (2.14, 5.85) | |

# Key take aways & next steps

Increase value of external data by prospective design.

- Distinguish true external control arms from use of external data.




thebmj | *BMJ* 2024;384:e077391 | doi: 10.1136/bmj-2023-077391

Randomisation (even with small sample size) early in development may improve time to patients.

- Providing anchor for essential indirect comparisons.

Regulatory & ACT EU to engage with stakeholders on external control and Bayesian statistics.