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SCIENCE MEDICINES HEALTH

The role of single arm trials in the authorisation of new medicines

Joint PSI/EFSPI HTA SIG Webinar: Indirect treatment comparisons

18 March 2024

Presented by Andrew Thomson and Marcia Rueckbeil
Data Analytics and Methods Task Force – European Medicines Agency

Summary of talks

- The EU reflection paper on single-arm trials - Marcia
- The regulatory assessment of single-arm trials - Andrew
  - How do EU regulators make decisions?
  - Decision making for different EU committees
  - Examples of single arm trials

Reflection paper on single-arm trials

Draft under revision following public consultation

Disclaimer

The views expressed in this presentation are my personal views 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.

Reflection paper on single-arm trials

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Reflection paper on **work plans** from EMA's

- Committee for Medicinal Products for Human Use **(CHMP)**
- Committee for Advanced Therapies **(CAT)**
- Methodology Working Party **(MWP)**
- Oncology Working Party **(ONCWP)**

Public consultation in 2023

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1 17 April 2023
2 EMA/CHMP/564424/2021
3 Committee for Medicinal Products for Human Use (CHMP)

4 Reflection paper on establishing efficacy based on single-
5 arm trials submitted as pivotal evidence in a marketing
6 authorisation
7 Considerations on evidence from single-arm trials

8 Draft

Draft agreed by Drafting Group on single-arm trials	27 January 2023
Adopted by CHMP for release for consultation	17 April 2023
Start of public consultation	21 April 2023
End of consultation (deadline for comments)	30 September 2023

Motivation for a reflection paper on single-arm trials

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- Relevant proportion of marketing authorisation dossiers with **pivotal data** from single-arm trials (SATs)
- Across **different therapeutic areas**, including for rare diseases
- Recurring **challenges for regulatory assessment** across dossiers
- No dedicated regulatory guidance

- ➢ Clarify under which **exceptional** circumstances SATs can generate fit-for-purpose pivotal evidence for regulatory decision making
- ➢ Relevance of public consultation

Reflection paper on single-arm trials: Scope

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In scope

- Methodological considerations across all therapeutic areas
- SATs which are submitted as pivotal evidence for **benefit-risk decision making**
- Efficacy
- Issues specific to SATs: design, conduct and assessment

Not in scope

- Therapeutic area specific guidance
- Guidance on **external controls**
- Considerations on 'feasibility' of RCTs
- Safety

Reflection paper on single-arm trials: Draft structure

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Section 3: Define and clarify challenging key concepts in SATs

Section 4: Translate concepts into practice, by key considerations

Draft for public consultation

Table of contents

Estimands and treatment effect of interest

- Focus of RP on main estimand(s) to establish efficacy
- Treatment effect in ICH E9: effect attributed to a treatment, usually comparison of treatments
- Estimands equally important than in RCTs, but **more challenging to apply**, e.g.
  - Only investigational treatment observed
  - Intercurrent events: Timing of initiating treatment

Isolation of treatment effect and treatment effect estimates

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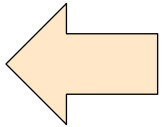
Strong requirements

Isolation of treatment effect

Observed individual outcome on EP cannot occur without active treatment in any patient

- Knowledge of clinical context, qualitative reasoning, no doubt on causality
- Only exceptionally possible, usually residual uncertainty



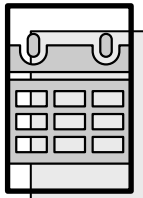
Treatment effect estimate

- Contrast to 'no effect' (e.g. 0%) as assumed counterfactual
- Estimate impacted by patient selection

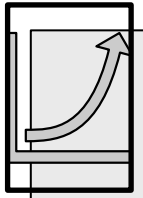
- Individual outcomes must not be subject to bias, variability, measurements error, flaws in study conduct
- In general, cannot be verified

Choice of endpoints

Isolation of treatment effect for interpretation; challenge if not clinically most relevant



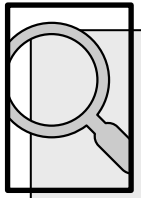
Time to event generally difficult



Continuous also difficult due to variability, measurement error, regression to the mean

Acceptability of endpoint(s) is **therapeutic area specific discussion**.

Choice of endpoints



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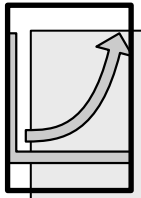


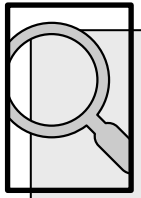
Continuous also difficult due to variability, measurement error, regression to the mean

Events **occur in absence or presence of treatment**, e.g. time-to-death.

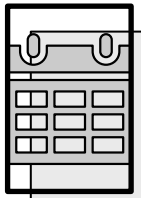
Course of disease and prognostic factors impact TTE.

Starting point of risk: 'time 0' unknown, ≠ start of trial/ treatment.

Choice of endpoints



Isolation of treatment effect for interpretation; challenge if not clinically most relevant



Time to event generally difficult

Continuous also difficult due to variability, measurement error, regression to the mean

Regression towards the mean occurs whenever we **select an extreme group based on one variable** and then measure […] the same variable at a different point in time) for that group. (Bland and Altman, 1994)

Target and trial population

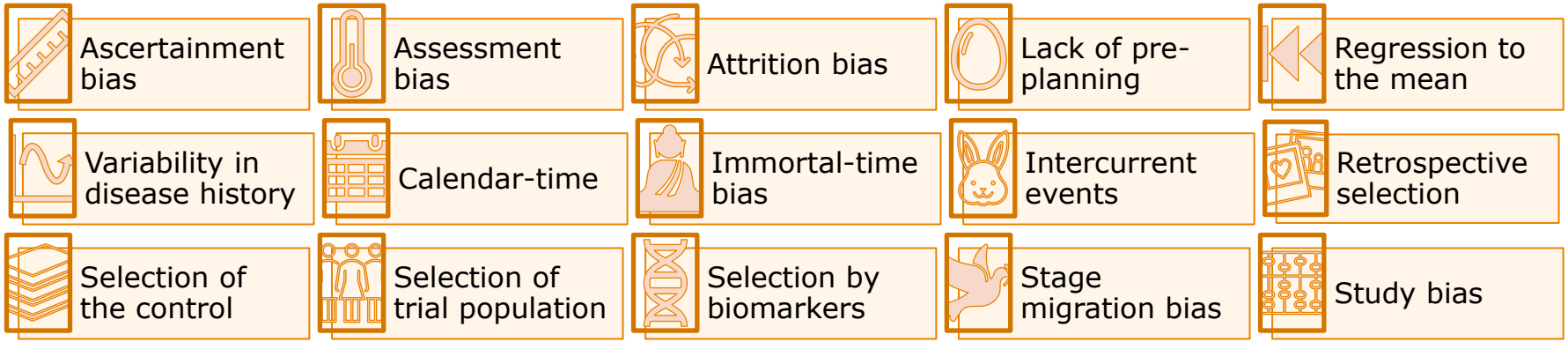
- Trial population determines plausibility of assumptions about **hypothetical control** (**counterfactual**)
- **Prognostic variables** may compromise generalisability from trial to target population
- Not possible to **disentangle prognostic from predictive effects** based on results from single-arm trials

Even more important to have detailed account of screening & selection.

Statistical principles

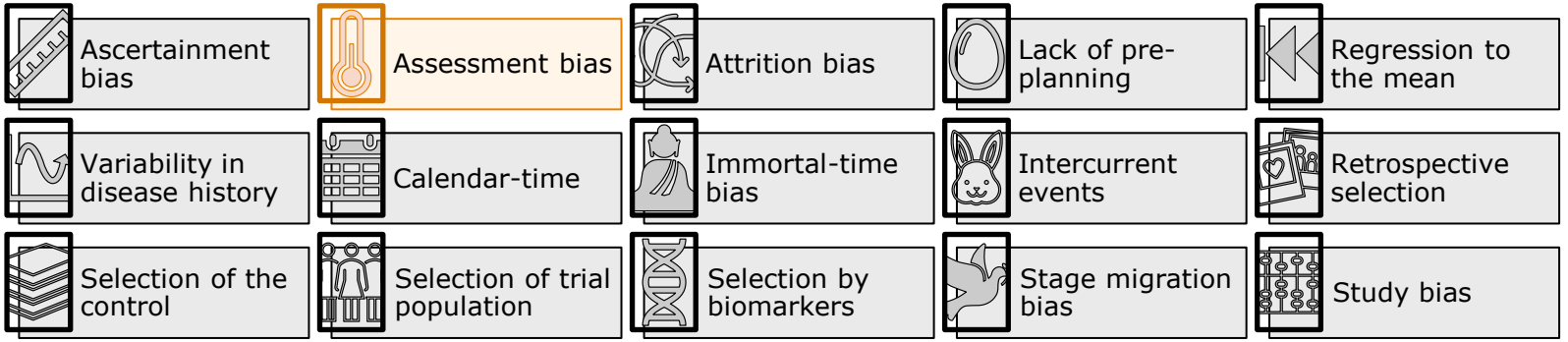
- Standards as for **confirmatory** setting
- **Pre-specification** even more critical
  - adherence to study protocol and statistical model (unplanned changes critical)
  - trial success criterion…
  - …often a threshold, consider its meaning & uncertainty
- **Analysis** considerations
  - Timing of treatment initiation: informed consent, but…
  - retrospective exclusion of patients violating entry criteria
  - Quantifying uncertainty of estimates via confidence intervals

Sources of bias and potential mitigation



Strategies necessary to reduce risk for bias, but **not sufficient to fully remove bias**

Sources of bias and potential mitigation



Definition

Knowledge of the therapy can influence the outcome assessment

Mitigation

Endpoints should be objective and, if possible, assessments should be made independently and preferably **unaware** of timing in relation to treatment.

The regulatory assessment of single-arm trials

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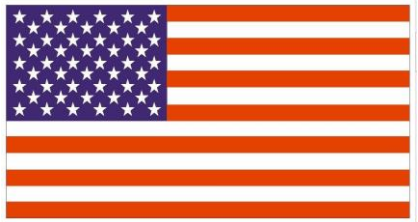


21 CFR § 314.126 - Adequate and well-controlled studies.

The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.

historical control designs are usually reserved for special circumstances.

In the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy

The Agency shall provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products

To this end, the Agency, acting particularly through its committees, shall undertake the following tasks: advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy

Decision Making

CHMP*

Positive benefit risk balance
Absolute decision making
No limit on licences
Is not "one in, one out"

COMP

> or <

Demonstrate significant benefit
(Often) Relative decision making
Is a limit on exclusivity

20 * Also applies to CAT, who assess advanced therapies for and on behalf of CHMP

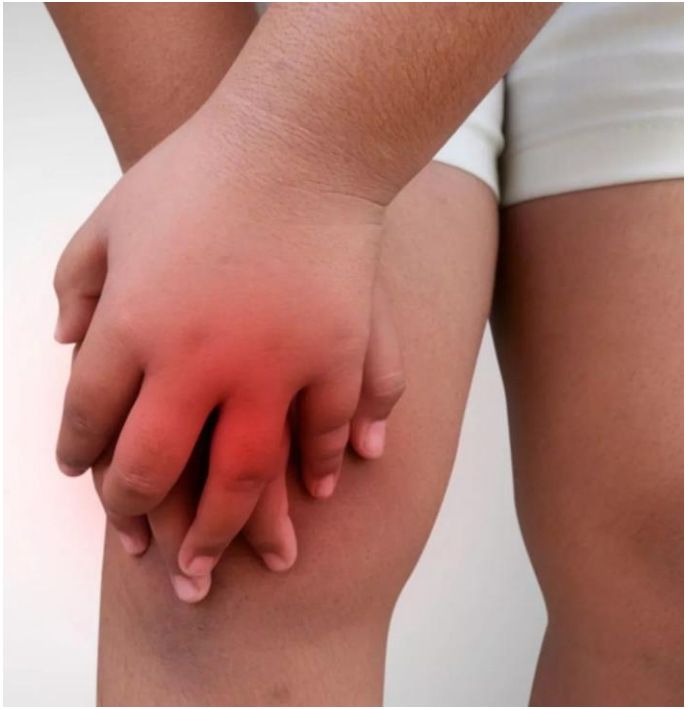
RCTs remain the cornerstone of decision making

- Remain the regulatory gold standard
- Not always possible
  - Perceived ethical reasons
  - Unwillingness of patients to be randomised to control
- Not always necessary
  - Clinical Development is not limited to de novo Phase 3 clinical trials
  - Other reasons (See Marcia’s presentation)

Randomisation is not always necessary

Guidance (both extrapolation and JIA guidance)

"For example in juvenile idiopathic arthritis medicines where a clear PK-PD relationship and therapeutic window has been established in adult arthritis models, an extrapolation plan could be based primarily on PK and dose finding studies, supported with single-arm clinical data."



Very Different Use Case to SAT paper

Randomisation is not always possible

For a new contraceptive method (e.g. new steroid/s, lowered steroid dose, new administration form), non-comparative studies are accepted but a sufficient number of cycles should be studied to obtain the desired precision of the estimate of contraceptive efficacy. The key studies, carried out in a sufficiently representative population, should normally be at least large enough to give the overall Pearl Index (number of pregnancies per 100 woman years) with a two-sided 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed 1 (pregnancies per 100 woman years).

No "true" rate of what would have happened had OCs not been used

Indirect comparisons to support claim for orphan designation at the time of marketing authorization

- Upcoming publication

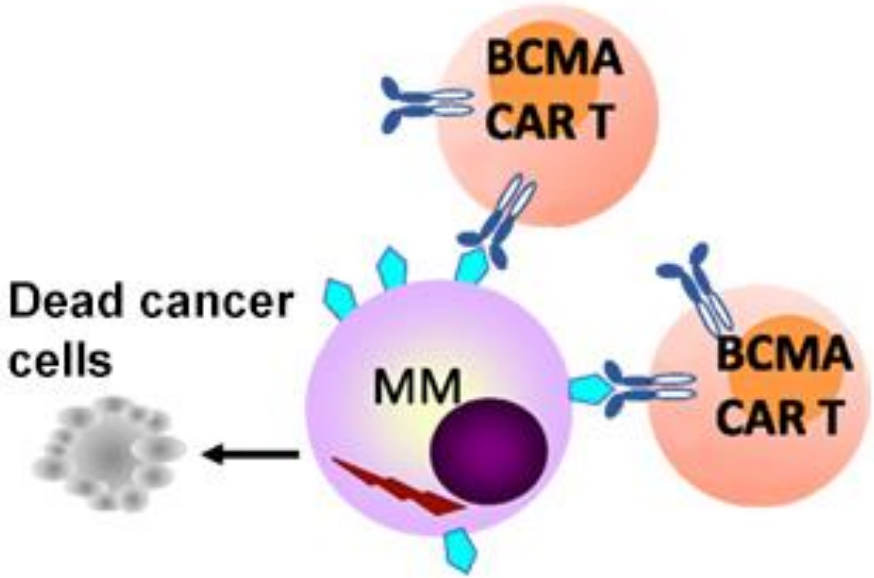
Quantitative, Indirect comparisons

Side-by-side comparisons	Simple side-by-side comparison	113	Presentation of summary statistics for a variable (e.g. objective response rate for 'response') by treatment arms. The treatment arms are from separate studies, no statistical methods for cross-trial comparisons are applied (e.g. difference between objective response rates from different studies).
	Pooled side-by-side comparison	16	Same as the simple side-by-side comparison, but the effect size from one or more of the comparators is derived from pooling results from several studies
Inferential comparison with aggregate external data	Matching-adjusted indirect comparison	22	Comparing individual patient data from the investigational product, with aggregate data from one comparator from another study by means of re-weighting the individual patient data to match the baseline characteristics of the aggregate comparator data [7].
	Simulated Treatment Comparison	8	A regression-based approach estimating the effect of an investigational product based on individual patient data and adjusted for baseline characteristics compared with aggregate data for the comparator. The approach can have the additional element of simulation where samples are drawn from the joint covariate distribution of the aggregate data [13].
	Bucher Method	7	Compares two or more products which have the same comparator (e.g. placebo) via indirect adjustment [14].
	Meta-analysis	1	Estimates the effects of two products using aggregate data from at least two independent studies. The combined (pooled) effect estimate is based on the weighted average of the independent studies [15].
	Network Meta-Analysis	2	Compares more than two products with data from independent studies by combining direct and indirect evidence, here based on aggregate data [16].

- Summary of quantitative indirect comparison methods used
- Within MAICs:
  - 6 times anchored (1 x oncology)
  - 16 times unanchored (11 x oncology)

Assessing single arm trials – a COMP perspective

- *The sponsor argued that cilta-cel is of significant benefit over existing methods of treatment for the target patient population based on the improved and deepened ORR and prolonged PFS observed in the pivotal study CARTITUDE-1.*
- SAT supported the CHMP decision – both for cilta-cel (Carvikyi) as well as ide-cel (Abecma)



25 From https://www.ema.europa.eu/system/files/documents/orphan-maintenance-report/carvykti_-_orphan_maintenance_assessment_report_en.pdf

What was actually done?

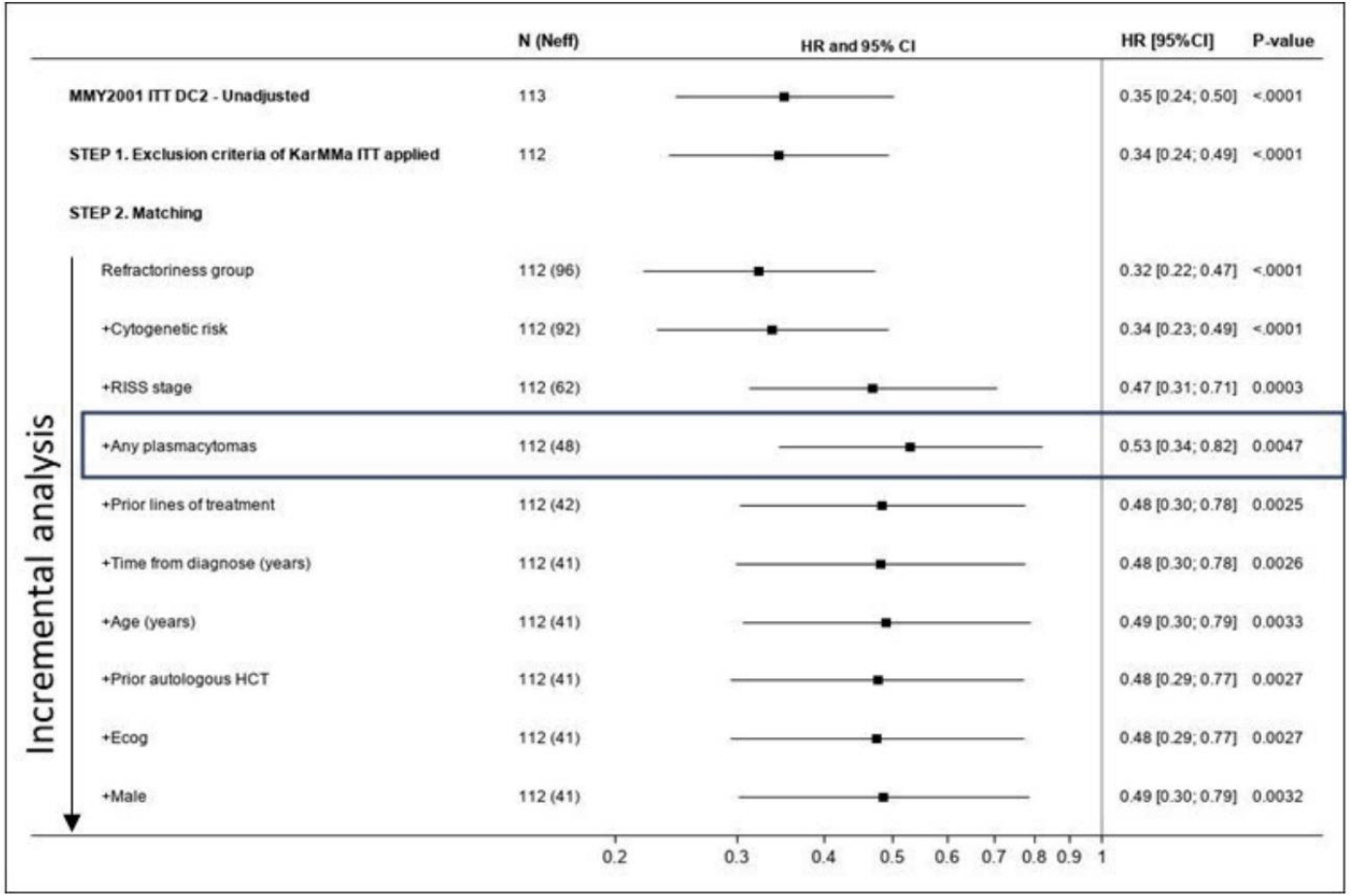
- *"Indirect comparison of the outcomes between patients treated with cilta-cel (Carvykti) in CARTITUDE-1 (N=97) versus patients treated with ide-cel (Abecma) in KarMMa (N=128)."*
- *"Imbalances between patient populations from the two pivotal studies on prognostic patient/disease characteristics were adjusted for using the approach of unanchored MAIC."*
- *"The prognostic factors to be considered in the analyses were a priori identified and ranked by importance, based on input from independent clinical experts."*

Baseline differences

		Cilta-cel (CARTITUDE-1)	Ide-cel (KarMMa)
N patients		97	128
Refractory Status	<tri-refractory	12%	16%
	Tri-quad-refractory	45%	58%
	Penta-refractory	42%	26%
Cytogenetic Risk	High	25%	35%
	Standard	75%	65%
R-ISS stage	I	34%	11%
	II	59%	72%
	III	7%	17%
Plasma-cytomas	Yes	20%	39%
	No	80%	61%

"The sponsor concluded that the study populations are very similar, with only minor differences between the patient populations in the two clinical studies. Specifically, the infused and enrolled populations in KarMMa included slightly more patients with high cytogenetic risk, Revised ISS (R-ISS) stage II/III, and plasmacytomas than CARTITUDE-1, and CARTITUDE-1 included slightly more penta-refractory patients than KarMMA"

Results



Conclusions

- *"It should be noted that the observed imbalances for these risk factors were adjusted for in the unanchored MAIC approach conducted for both the infused and enrolled populations. However, this has led to a reduction of the effective sample size in the MAIC approach as compared to the actual sample size."*
- *"The efficacy data from CARTITUDE-1 combined with the presented outcomes of the unanchored MAIC approach provide adequate evidence to support the claim for significant benefit of cilta-cel based on better efficacy"*
- This is one of the clearer cut examples we have seen. The acceptability of the unanchored MAIC may depend on the robustness of the results seen and the magnitude of the benefit
- Further guidance is foreseen in COMP and MWP work plans

CHMP / CAT assessment

"Cilta-cel showed clinically significant response rates in a heavily pre-treated RRMM population. Since the pivotal study had a single-arm design, the applicant provided a comparison with real world data that can be considered as supportive evidence. Besides the ORR data, sCR is also showing convincing results."

"However, due to the missing randomised control group, uncertainties about the actual treatment effect exists."

"While data on PFS and OS are presented in the efficacy assessment, single arm trials in oncology are not suitable to ascertain a treatment effect on OS or PFS due to the lack of a comparator. Data on these endpoints are therefore not included in the PI."

"Limitations of these type comparisons are noted and data is considered to be supportive"

30 From https://www.ema.europa.eu/en/documents/assessment-report/carvykti-epar-public-assessment-report_en.pdf

Conclusions

- How regulators assess single arm trials will depend on the question being asked
  - Relative efficacy is important to some decisions
- Guidance has been issued for how the benefit risk will be assessed
  - Revised version of Reflection Paper expected to be published later in 2024
- Guidance on how to assess this from a COMP perspective will be forthcoming