Statistical considerations for CAR-T cell development

Updates from an European regulator

Benjamin Hofner
Head of Data Science & Methods

Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit.

The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

Paul-Ehrlich-Institut

Acknowledgements & Disclaimer

I am grateful for input from

- Attila Sebe,
- Matthias Renner,
- Martina Schüßler-Lenz, and
- Jan Müller-Berghaus.

However, the views are my own and **do not** necessarily represent the views of

- any of my colleagues,
- the Paul-Ehrlich-Institut (PEI),
- the European Medicines Agency (EMA), or
- any other European regulatory agency (NCA).

CURRENTLY LICENSED CAR-T CELL PRODUCTS

Licensed CAR-T cell products in EU

Commercial name (Target)	Active substance	(Simplified) Indications	Rapps	Approval	Pivotal Trials
Kymriah (CD19)	Tisagenlecleucel	B-ALL, DLBCL, FL	NOMA, MHRA	MA	3 SATs (+1)
Yescarta (CD19)	Axicabtagene ciloleucel	PMBCL, DLBCL, HGBL, FL	PEI, FAMHP	MA	2 SATs 1 RCT
Tecartus (CD19)	Brexucabtagene autoleucel	Mantle Cell Lymphoma, B-ALL	PEI, NOMA	cMA	2 SATs
Abecma (BCMA)	Idecabtagene vicleucel	Multiple Myeloma	NOMA, FIMEA	cMA	1 SAT
Breyanzi (CD19)	Lisocabtagene maraleucel	FL3B, PMBCL, DLBCL, HGBL	AIFA, FAMHP	MA	2 SATs, 1 RCT
Carvykti (BCMA)	Ciltacabtagene autoleucel	Multiple Myeloma	PEI, AEMPS	cMA	1 SAT

(currently) hematologic tumours

approved indications mainly based on SATs

Sources: Giorgioni et al 2023 (doi: 10.3390/ijms241411803), EPAR: Kymriah, EPAR: Yescarta, EPAR: Tecartus, EPAR: Abecma, EPAR: Breyanzi, EPAR: Carvykti

RECURRING ISSUES

IN CLINICAL DEVELOPMENT

Dose finding / dose selection

- Dose finding was **not conducted** for all trials / indications
  - If dose finding was implemented, this was usually based on a very limited range of doses
- Actual doses often **deviate** from the chosen target dose
  - Otherwise the patient could not be treated at all (what is there is there)
- CAR-T cells are "**living drugs**"—They can proliferate and expand in vivo and hence the dose is not as relevant as for other products
  - Dose-response / dose-exposure hard to derive

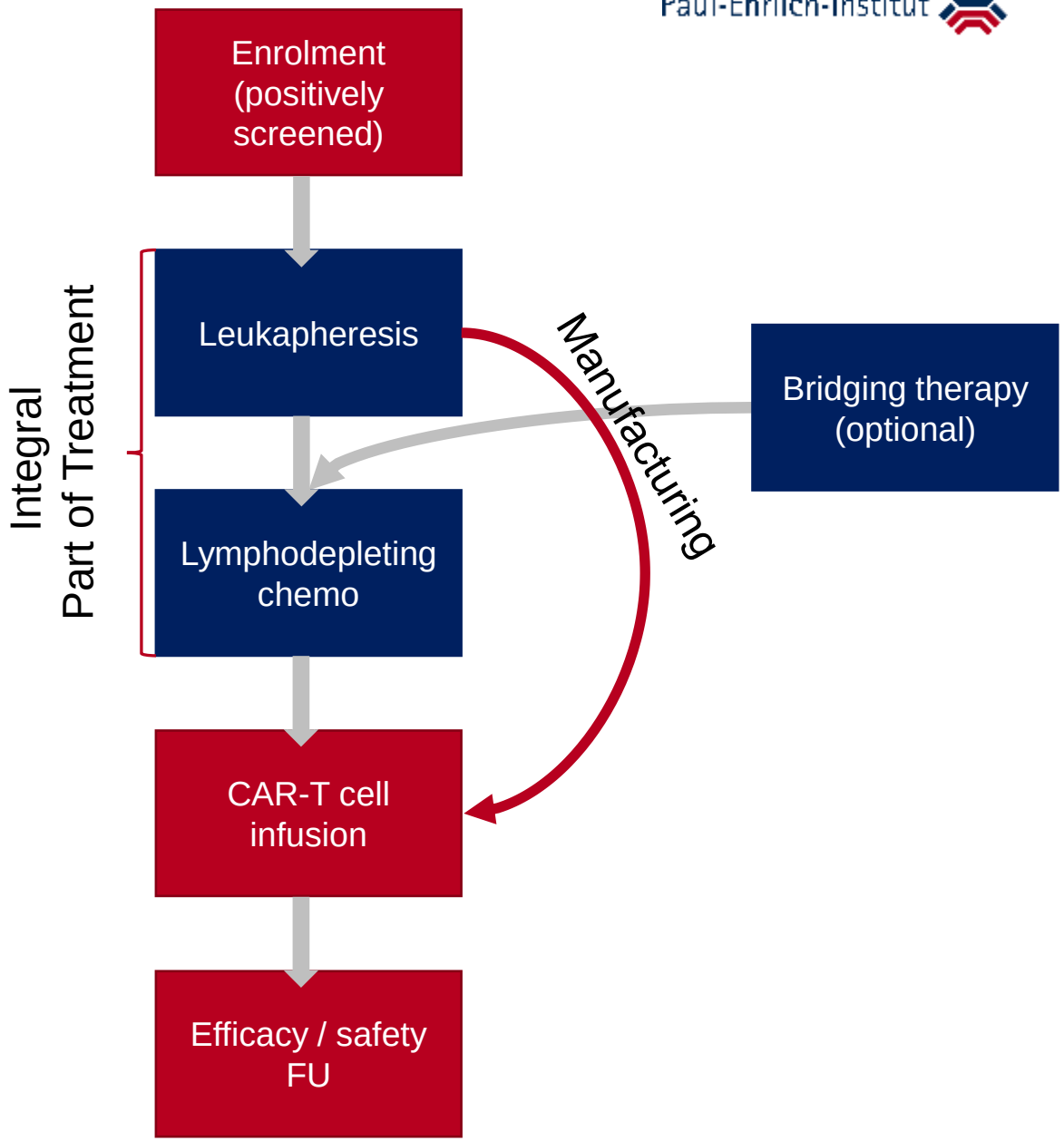
➢ Current approaches for dose finding / dose selection are very challenging for cell therapies, where multiple **product characteristics and patient characteristics** are strongly **correlated** and may affect the dose-response relationship

Analysis population
in single arm trials (SATs)

- **Primary analysis set per Applicant:**
  - All treated (with CAR-T cell product)

- No randomization and hence no classical ITT population.
- Nevertheless, all enrolled patients need to be considered for efficacy and B/R evaluation
- Also of key relevance for patients

- **Analysis sets in SmPC:**
  - All leukapheresed (≈ all enrolled; ITT)
    - Sometimes* only successfully leukapheresed subjects (≠ ITT principle)
  - Mostly also “all treated” as secondary analysis set (“mITT”)



*for Kymriah

SmPC
Lost in nomenclature

- Naming of analysis sets in SmPC varies greatly, sometimes even different names within one SmPC:

All subjects enrolled in trial
- Enrolled patients
- All leukapheresed (ITT)
- All leukapheresed
- All leukapheresed (FAS)
- Enrolled (leukapheresed)

All subjects treated with CAR-T cells
- Infused patients
- EAS*
- All treated
- All treated (mITT)
- Treated population
- Breyanzi-treated

➢ Unifying nomenclature would be helpful

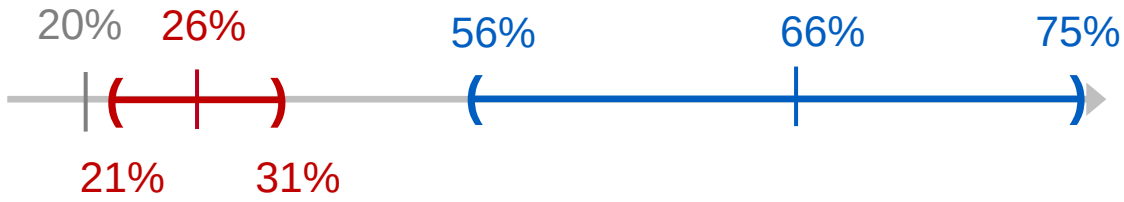
*Infused patients who had measurable disease at baseline per Independent Review Committee (IRC) and are included in the efficacy analysis set.

Single arm trials (SATs)
Definition of outstanding effect

- What threshold for ORR should we use to show that the treatment is working?
- What is the role (and issues) of RWD[1]?
  - Head-to-head comparison?
  - Used to contextualize the SAT data?
  - Used to derive threshold?
- How do we incorporate uncertainty of a derived threshold[1]?
- What is the adequate analysis population and treatment of intercurrent events? (see above)
- What do we need to show in terms of CR rate and other endpoints?

Example: Yescarta MAA for DLBCL[1]

Sketch of results



Prespecified threshold

ORR with CI (SCHOLAR-1)

ORR in ITT set (ZUMA-1)

Additionally a worst case analysis with selected external data was conducted leading to ORR of 30.1%

All fine here, but what if…

[1] Papadouli et al. (2020), EMA Review of Axicabtagene Ciloleucel (Yescarta) for the Treatment of Diffuse Large B-Cell Lymphoma, The Oncologist, https://doi.org/10.1634/theoncologist.2019-0646

Analysis population and study design


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 November 2020
EMA/CAT/GTWP/671639/2008 Rev. 1 - corr
Committee for Advanced Therapies (CAT)

Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

- "The design of the confirmatory study should follow a randomized controlled design, comparing CAR-T cell treatment to a reference regimen, unless otherwise justified."
- "The randomized controlled trial design should preferably be followed when appropriate also in such cases where late stage refractory disease settings are targeted or where reference therapies are not available (…). In such cases comparison to best care or treatment based on investigator's choice may provide the most convincing evidence of efficacy and is preferred over single arm trials, when appropriate."
- "In planning for main efficacy trials, whether randomised or not, care should be taken to adhere to the intention-to-treat (ITT) principle in assessing efficacy, and in defining the ITT population as all patients enrolled with the intention to initiate treatment, e.g. who have been randomized in a randomized controlled trial or who have signed informed consent in a single-arm trial should be included in the primary efficacy analysis."
- "Additional subgroup analyses can be defined in the CAR-T cell arm for e.g. the apheresed population, lymphodepleted population and treated/infused population."

Source: EMA/CAT/GTWP/671639/2008 Rev. 1 – corr, Annex I: Special clinical considerations on CAR-T-cells in haemato-oncology

Specifics of SATs


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2023
EMA/CHMP/564424/2021
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

Considerations on evidence from single-arm trials

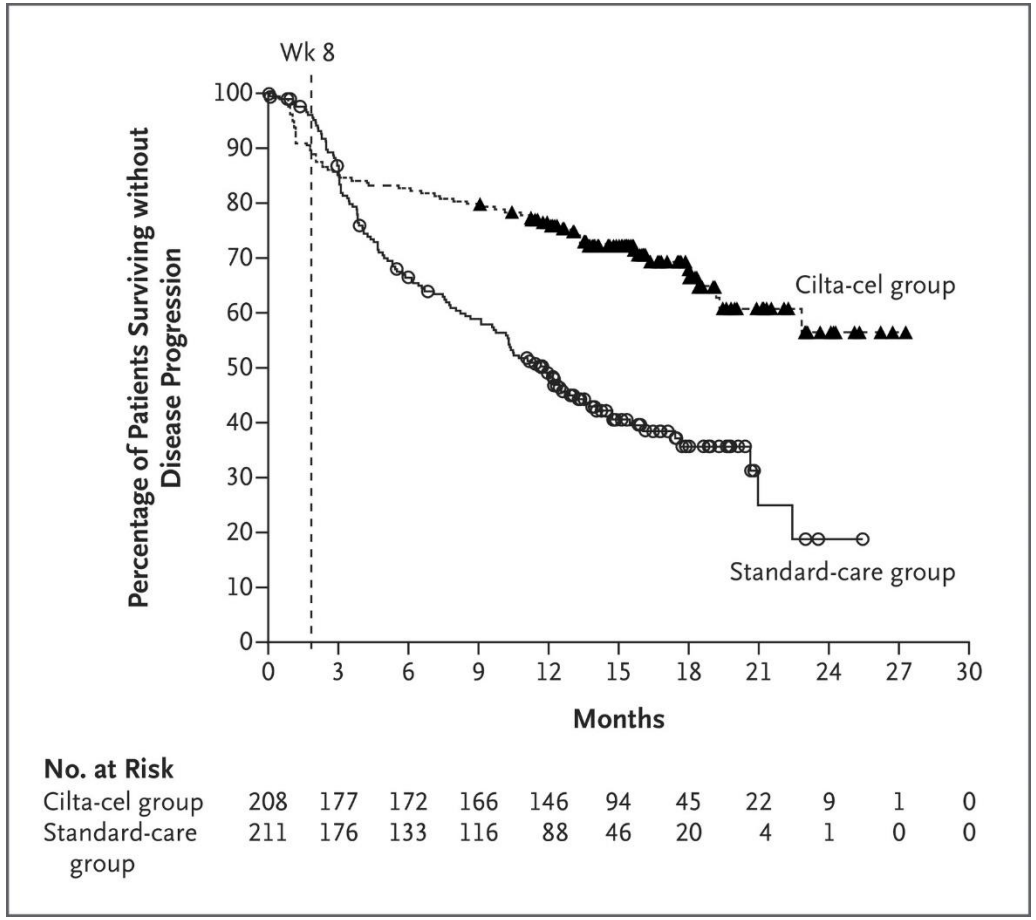
- Specific discussions around the isolation and estimation of a treatment effect
  - Possibly based on different endpoints
  - Isolation of a treatment effect often based on threshold crossing
  - Consider uncertainty of threshold
- Estimands are important but (usually) more difficult to derive
  - Analysis set usually FAS
- Causal interpretation of observed outcome difficult due to lack of control arm
- Issue of bias and measurement error increased due to lack of control arm
  - try to reduce or even avoid bias & measurement error as much as possible
  - discuss at submission

- For more see e.g. talk by Kit Roes @ EFSPI 2023

Source: EMA/CHMP/564424/2021

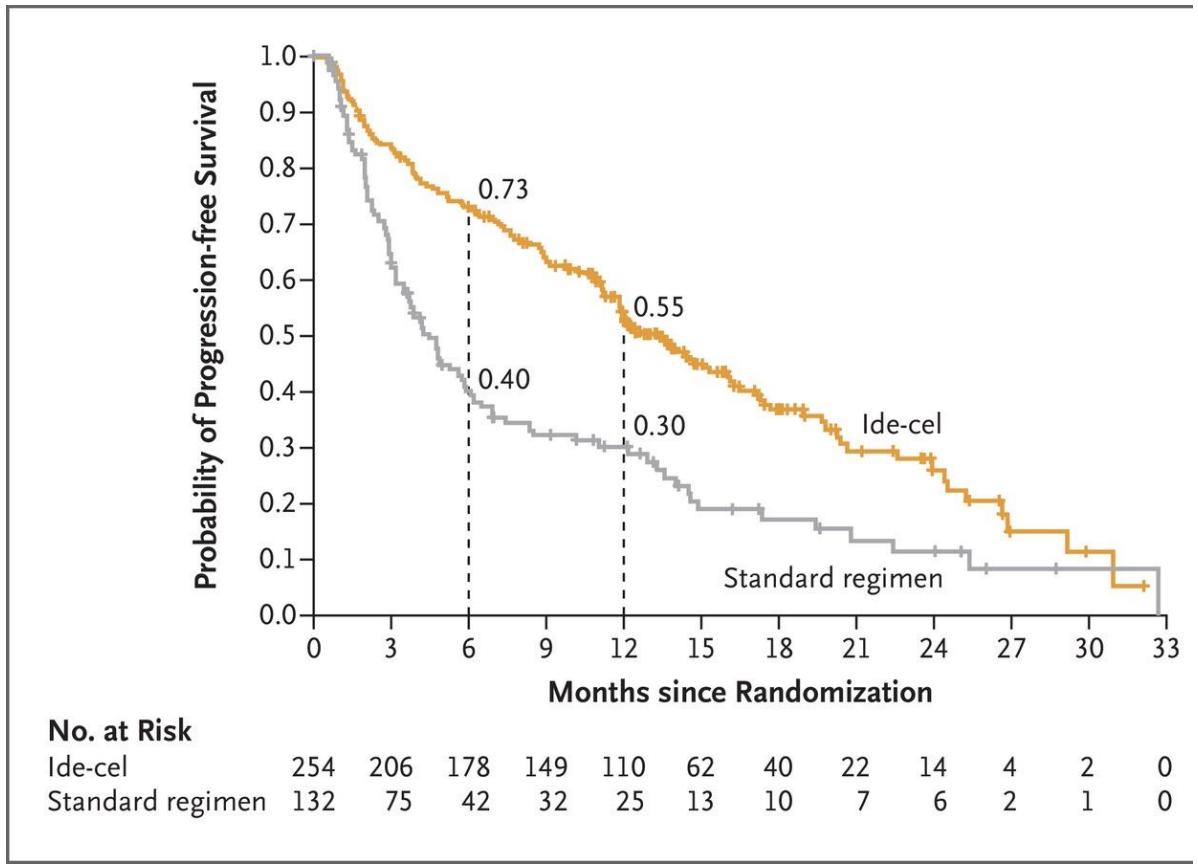
Crossing survival curves / late separation

Carvykti



Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2303379

Abecma



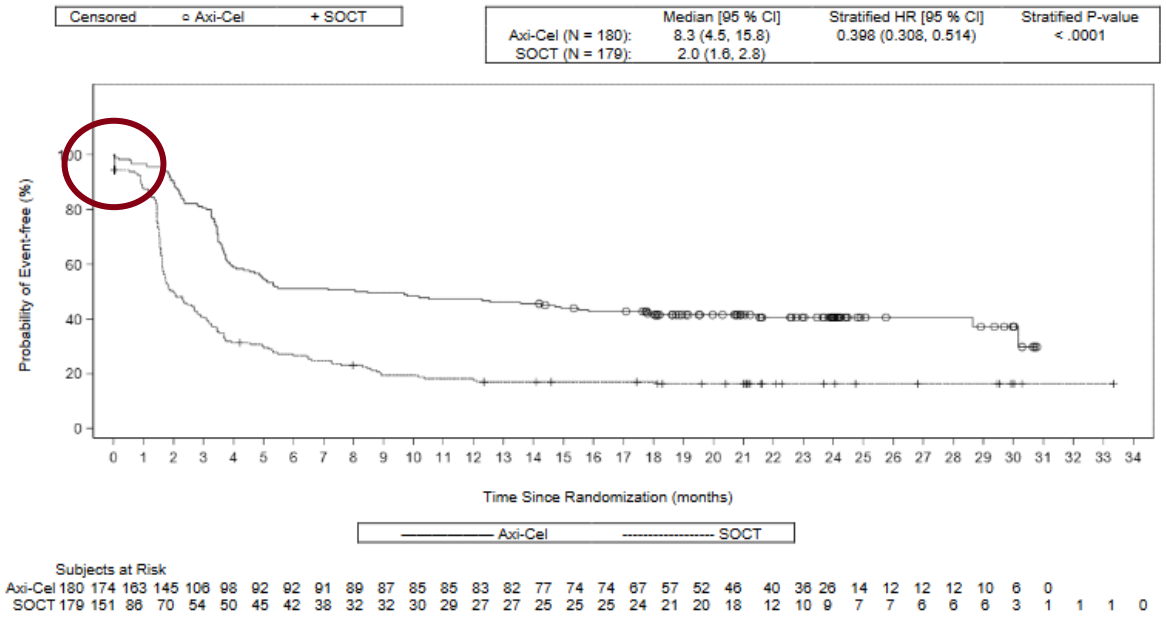
Source: https://www.nejm.org/doi/full/10.1056/nejmoa2213614

Reasons for crossing survival curves
in CAR-T cell RCTs

- Effect currently observed for PFS (in BCMA-targeted CAR-T cells)
  - What about OS, other trials / products and what about other treatment lines?
  - For checkpoint inhibitors: Pseudo progression and late response
- Here, currently not yet well understood
  - Is this only a (random) artefact?
  - Due to the bridging therapy (same for both arms)?
  - A mixture of populations?
  - A mixture of above reasons?
  - ➢ Requires further attention!
- Impacts statistical methods for effect estimation (PH assumption violated) **and** interpretation of derived effects and benefit/risk

EFS as endpoint in open-label RCTs
of CAR-T against SOC

Figure 1. Kaplan-Meier Plot of Event-Free Survival in ZUMA-7



- Early events due to treatment switching (supported by open-label nature of trial) may lead to earlier and more events in control arm
- Intolerance / toxicity with SOC may lead to earlier and more events in control arm
  - When no disease assessment prior initialization of new therapy was imputed as event at Day 0

➢ Anti-conservative estimate

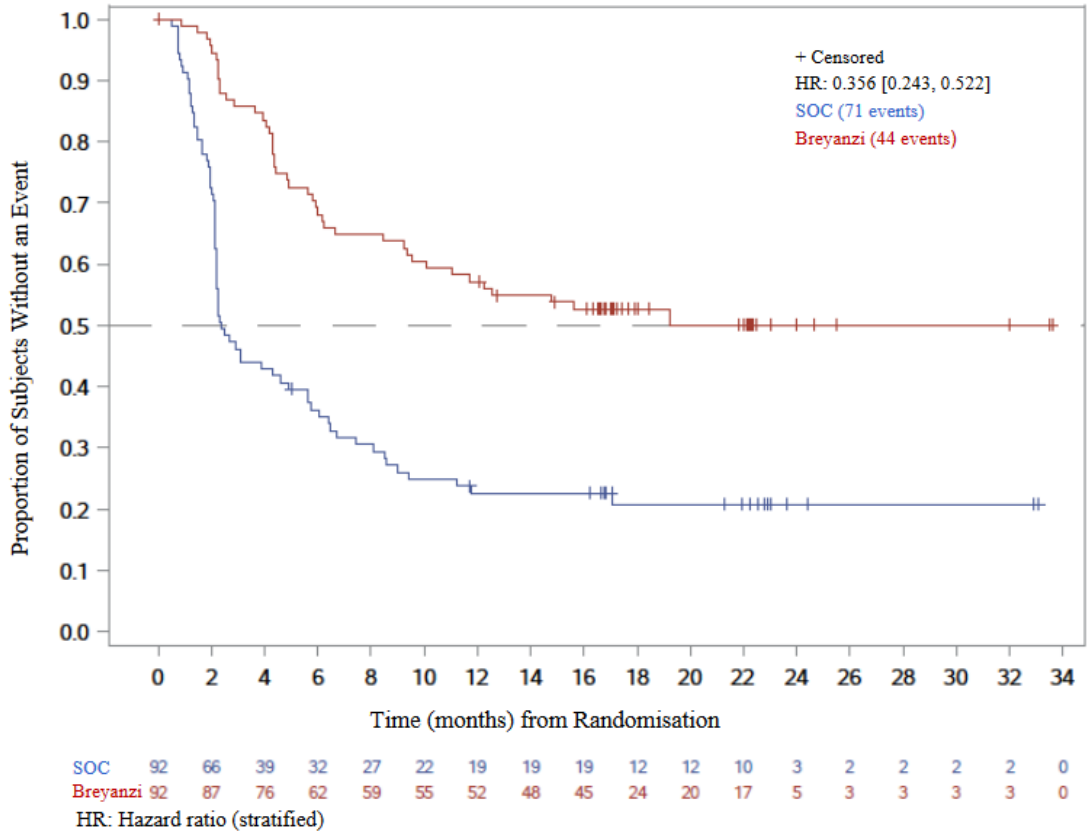
- But, not a <u>real</u> issue here as an effect is still evident and supported by other endpoints

- Is EFS a suitable endpoint (here)?

Source: EPAR II/46 EMA/804955/2022

EFS as endpoint in open-label RCTs
of CAR-T against SOC

Figure 1: Kaplan-Meier plot of event-free survival based on IRC Assessment (ITT analysis set)



- Issue not visible for Breyanzi
- Likely partially driven by definition of EFS
  - Initiation of new therapy without “efficacy concerns” (based on objective signs) was not considered an event and was to be censored
  - A switch within the 3 defined SOC regimen was allowed and not considered as a new antineoplastic therapy

- Is EFS suitable endpoint here?
- Or is at least a change/uniform definition of the estimand required?

Source: Breyanzi SmPC (accessed 25.09.2023); EPAR EMEA/H/C/004731/II/0005

Some further considerations

- Trials with CAR-T cells are (so far) open label trials:
  - Interim (efficacy) analyses problematic.
  - At least an independent DMC/DSMB should conduct the analyses with a clearly firewalled/independent statistician/programmer.
  - Central independent adjudication of endpoints important.

- Allogeneic CAR-T cells…
- Trials against licensed CAR-T cells…

… might impact clinical trial design and evaluation in the future.

RECURRING ISSUES

IN QUALITY DEVELOPMENT (*)

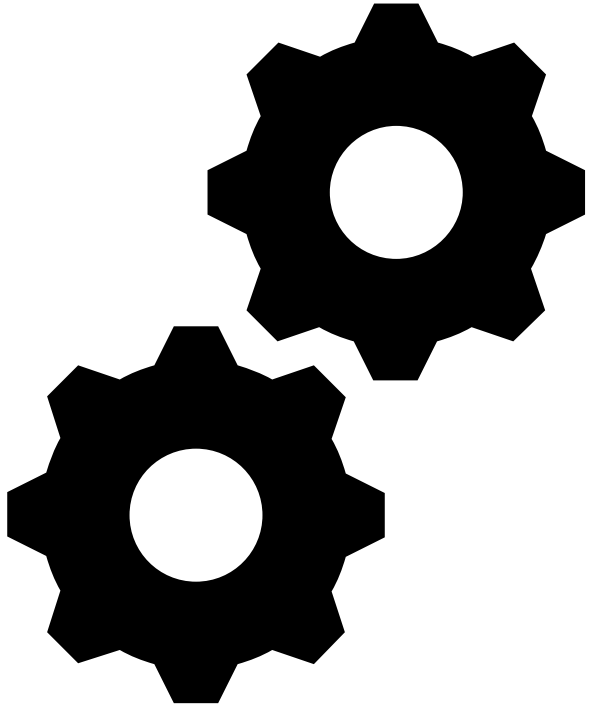
(*) not my main expertise

Deriving quality attributes and release criteria

- CAR-T cells are cell products based on human T-cells
  - **Allogeneic CAR-T cells** can be harvested from selected healthy, young donors
  - ➢ Specifications for harvested T-cells are possible (characterisation of starting material)
  - **Autologous CAR-T cells** might be additionally impacted by the underlying disease and pre-treatment regime of the patient
  - ➢ Specifications for cellular starting material not possible / sensible
  - ➢ Training / SOPs for leukapheresis centres might help to increase quality and consistency
- Variability is generally higher for cell products than for other biological products
- Process characterisation and validation often based on healthy donor material
  - Needs to be confirmed in clinical trials based on patient material
  - Confirmation needs to be repeated for each indication (see variability of starting material)

Optimization of existing CAR-T products

- Usually, manufacturing changes are assessed based on quality aspects (comparability)
  - (Only) if comparability cannot be shown and/or if observed differences cannot be sufficiently justified, clinical data might be relevant
- Definition of NAS[1] and hence the product (see Yescarta / Tecartus) impacts the need to collect clinical data
  - Platform approaches might be used to support development (see EMA toolbox GL; EMA/CHMP/BWP/QWP/IWG/694114/2019)
- If clinical data is needed to assess product changes
  - Type of clinical data depends on criticality and potential impact of change
  - Required data, endpoints and analyses depend on potential impact as well
  - Usually, descriptive analyses are sufficient



[1]new active substance

POINTS FOR DISCUSSION

Key Messages

- Specification of quality attributes and dose finding complicated
  - Autologous nature of (current) CAR-T cell products
  - “Living drug” (expansion in vivo)
- Guidelines exist for
  - trial design in CAR-T cell developments (EMA/CAT/GTWP/671639/2008 Rev. 1 – corr,)
  - SAT (EMA/CHMP/564424/2021)
- Estimands require more thoughts and could/should be improved
  - All infused vs. all leukapheresed
  - Intercurrent events in EFS
- Better nomenclature needed in communication of results
- Crossing PFS (and OS?) curves need to be further observed/discussed

Some Questions

- What would you suggest to establish efficacy beyond ORR/CR? Is DoR helpful?
  What else could one use to strengthen the evidence and derive patients' benefits?
  - I consider it very problematic as it is a subgroup defined based on a post-baseline event.
- Why are there subjects with "response" before being treated?
  - Is it the lymphodepleting chemotherapy or bridging chemotherapy? Carry-over effects? …?
- What is the current role of RWD in CAR-T cell trials (or in general in SATs)? What should be the role?
  - All sorts of bias and difficulties with attributing an effect to the treatment are self-evident.
- How should an estimand be defined for CAR-T cell trials when a comparison to an active control arm is planned?
  - Comparison of PFS / EFS very difficult due to the different nature of the products in trial arms
  - Differences might only be induced by differences in the treatment scheme
- How should the primary estimand be adequately defined in SATs for autologous CAR-T cells?