Oncology Biostatistics

# Challenges for new CAR-T therapies

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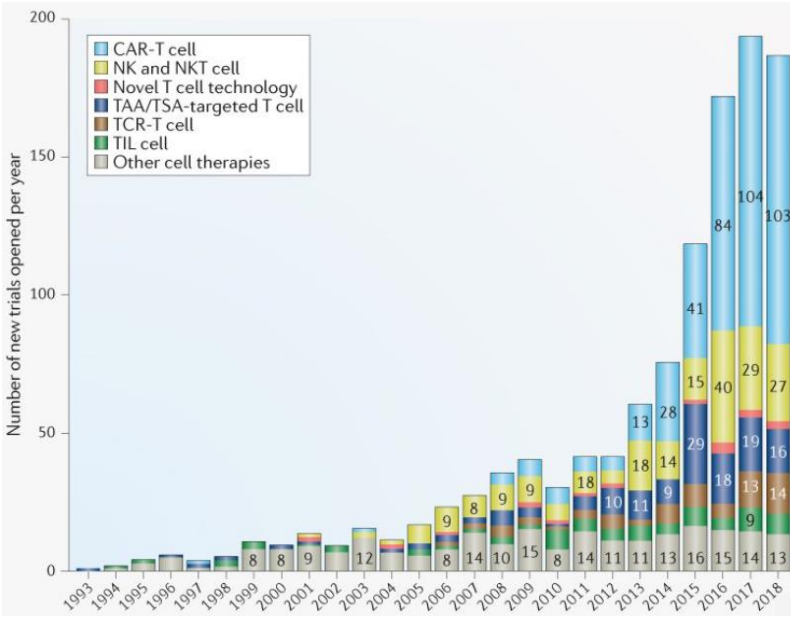
# Recent rapid growth in CAR-T development

New trials with CAR-T therapies:

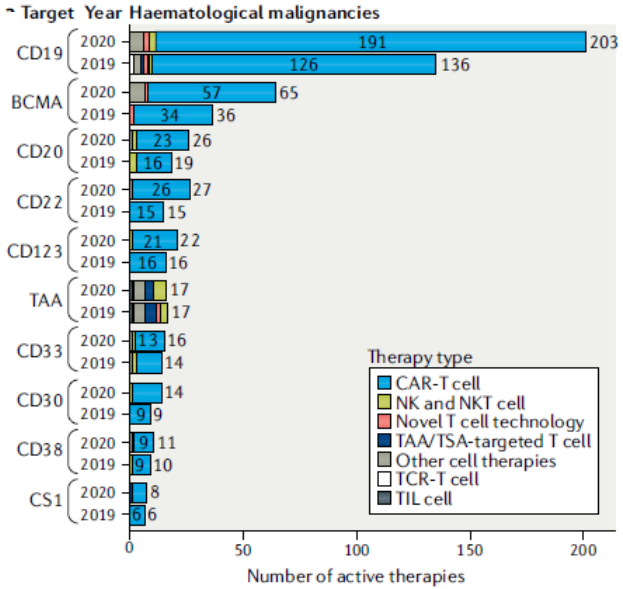
- 13 in 2013 vs. 103 in 2018




Yu et al., Nature Review Drug Discoveries (2019)

CAR-T therapies by target 2019 → 2020

- CD19: 126 → 191 +52%
- BCMA: 34 → 57 +68%




Yu et al., Nature Review Drug Discoveries (2020)



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Refs .....

# Approved CAR-Ts becoming standard of care

| CAR-T | Study | Indication | 1st approval |
|---|---|---|---|
| Kymriah® tisagenlecleucel | Eliana | 3L pedALL | 2017 |
| Yescarta® axicabtagene ciloleucel | Zuma-1 | 3L DLBCL | 2018 |
| Kymriah® tisagenlecleucel | Juliet | 3L DLBCL | 2018 |
| Tecartus® brexucabtagene autoleucel | Zuma-2 | 2L MCL | 2020 |
| Breyanzi® lisocabtagene maraleucel | Transcend | 3L DLBCL | 2021 |
| Yescarta® axicabtagene ciloleucel | Zuma-5 | 3L FL | 2021 |

all single arm pivotal trials
- rare populations (orphan designation)
- high unmet need in last line of therapy with no effective SOC
- highly promising early data impacting ethics/integrity of RCT

+ more expected in 2021 and beyond:
- 4L MM
- 2L DLBCL transplant eligible
- 3L aALL

"CAR-T ... represents **major paradigm shift** in ... r/r DLBCL" Sehn & Salles, NEJM 2021

Very encouraging for patients – but can we do better?

2L,3L,4L=second,third fourth line; pedALL=pediatric acute lymphoblastic leukemia; DLBCL=diffuse large B-cell lymphoma; MCL=mantle cell lymphoma; FL=follicular lymphoma; MM=multiple melanoma; aALL=adult acute lymphoblastic leukemia; SOC=standard of care; RCT=randomized controlled trial; r/r=relapsed/refractory



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# New CAR-Ts can further improve patient outcomes

- Rapid cycles of technical and scientific innovation are creating new CAR-T therapies to **further mprove patient outcomes** versus existing CAR-Ts:
  - improved product characteristics (e.g., T cell phenotype composition, fully human potent vector, enhanced persistence, dual CAR-Ts to address antigen escape)
    - ➢ **potentially better durability of response + improved safety**
  - improved/alternative manufacturing (e.g., turn-around time, reliability, allogenic)
    - ➢ **better serve patients, especially those with rapidly progressing disease**

- Compared with the “paradigm shift” impact of the first CAR-Ts on outcomes ...

  ... **more modest incremental benefits are expected for new CAR-Ts**

- What are implications on clinical development of new CAR-Ts?



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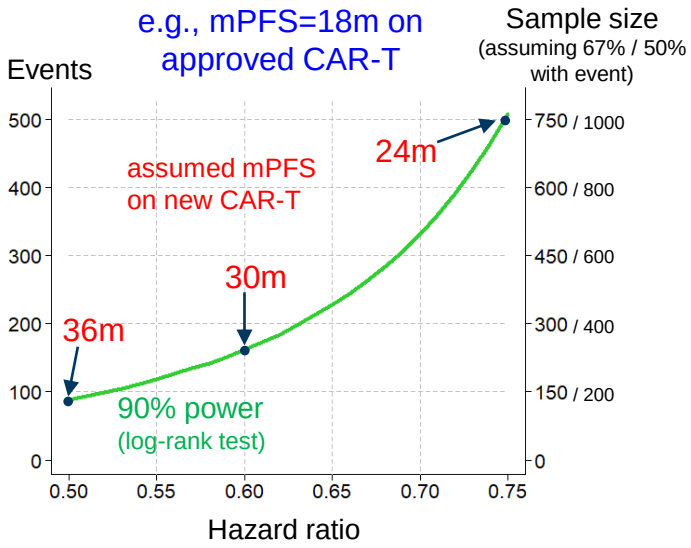
# Challenge of RCT: new CAR-T vs approved CAR-T

- Gold standard is RCT (e.g., Collins et al., NEJM 2020)
- Operational hurdles of CAR-T control arm
  - RCT could only enroll at limited number of qualified centers where control arm CAR-T is approved
    - ➢ some centers restrict number of CAR-Ts
    - ➢ others not able to participate (infrastructure, low patients)
  - manufacturing capacity of approved CAR-Ts still limited
    - ➢ could impact control arm slot availability
    - ➢ risk of long turn-around times on control arm (bias?)
- Likely large sample size / lengthy development time
  - delays patient access to potentially better therapy
  - possibly beyond capacity of any single manufacturer


R=randomization; mPFS=median progression-free survival; 18m=18 months



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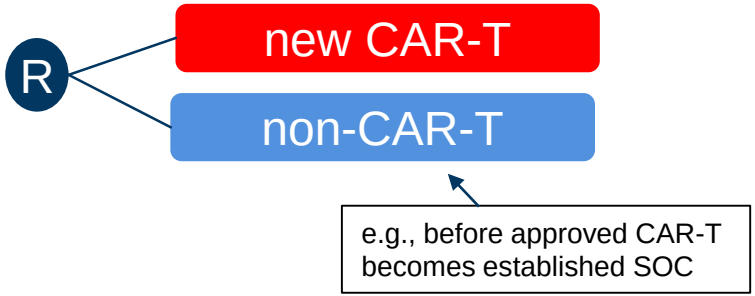
# Challenge of RCT: new CAR-T vs. non-CAR-T

- Blinding not possible → risk of bias
  e.g., control arm patients withdraw consent
  - compromises trial credibility, renders ITT analysis uninterpretable e.g., Checkmate-37 (2015), not treated: 1.5% vs. 23% (active vs. control)
  - can be mitigated by offering cross-over
    - however, this compromises comparison of OS




- Choice of control arm may be difficult in rapidly evolving indications
  - e.g., for 4L MM, current approved therapies include belantamab and selinexor, but:
    - many BCMA-directed therapies in clinical development: 2 ADCs, 13 CAR-Ts, 6 bispecifics (Yu et al., JHemOnc (2020)), plus additional 2 (non-BCMA) bispecifics at ASH2020
  - regional differences in SOC
- Success probably requires (1) positive trial + (2) favorable results of indirect comparison between new CAR-T arm and published data on approved CAR-T

ITT=intention to treat; OS=overall survival; ADC=antibody-drug conjugate; ASH=American Society of Hematology



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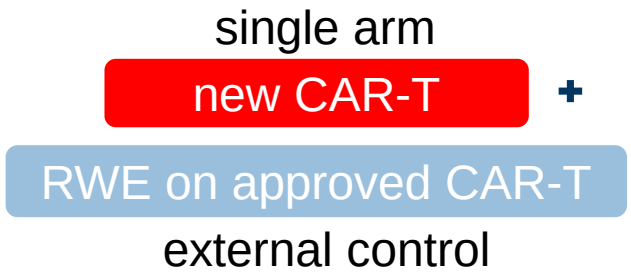
# Opportunity for RWE?

- Avoids operational hurdles of CAR-T control arm in RCT
- Likely shorter development time
  - quicker access to patients
  - more attractive to manufacturers, encourages innovation
- RWD can capture contemporaneous SOC, including newly emerging comparators
  - obtained prospectively in similar time-frame to single arm trial
- May be only possibility in rare indications, e.g., MCL

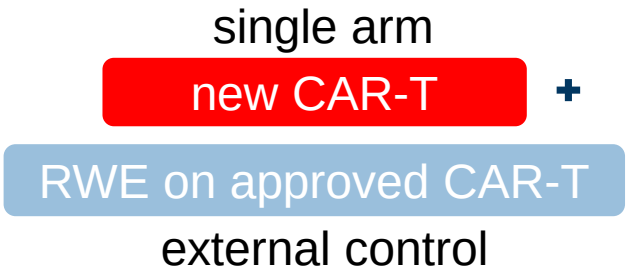



How?

- Single arm trial with hypothesis test
  - efficacy threshold based on historical benchmark
- Patient-level RWD to contextualize
  - indirect comparison vs single arm to estimate treatment effect
  - also to support choice of efficacy threshold used in single arm trial

RWE=real world evidence; RWD=real world data; MCL=mantle cell lymphoma

# Challenge of RWE external control




- Data quality, provenance and completeness
- Selection bias and confounding
  - possibly present even if selecting all patients who meet incl./excl. criteria of trial
  - lack of randomization means cannot guarantee comparable populations, could be differences in known (or unknown) prognostic factors
- RWE analysis set – best matched or all meeting incl./excl. of trial?
- Differences in real-world vs. trial-based endpoints (e.g., response criteria)
  - subjective measures may be unreliable (absence of blinding)
- Availability of index time in RWE?
  - e.g., date of leukapheresis? date leukapheresis product accepted at manufacturing facility?



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# Guiding principles for high quality RWE

- Pre-specification of a study protocol and SAP for a prospective RWE study
  - use of target trial framework (Hernan & Robins, AmJEpi (2016)) - similar to estimand framework - to identify the causal question of primary interest and align RWD selection with this in a transparent and structured way
  - prospectively engage with regulators, show not cherry-picking favorable data
- Obtain high-quality patient-level data from reliable and traceable sources
- Appropriate cohort selection based on matching inclusion/exclusion
- Suitability of real-world endpoints
- Fit-for-purpose analytical methodologies

SAP=statistical analysis plan



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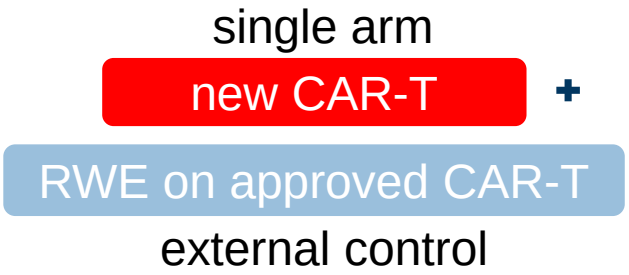
# Challenges for new CAR-Ts


- Operational hurdles (for approved CAR-T control arm)
- Time/resource heavy


- Risk of bias due to consent withdrawal in control arm
- Choice of SOC may not be relevant at end of study
- Likely also need favorable result from indirect comparison vs. approved CAR-Ts




- Data quality
- Risk of bias
- Regulator/payer skepticism



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# Closing remarks

- Other challenges for new CAR-Ts
  - Non-proportional hazards – as CAR-Ts are yielding long term responders
    - analysis by weighted log-rank, RMST, landmark?
  - Heterogeneity in requirements of regulators/payers
    - single arm trials in rare diseases more frequently acceptable to FDA/PMDA compared with EMA and EU payers
    - many HTA bodies do not accept PFS, although it is often primary endpoint for regulatory approval

- More dialogue in future between all stakeholders
  - aim to bring transformative new CAR-Ts to patients as soon as possible

RMST=restricted mean survival time; FDA=Food and Drug Administration; PMDA=Pharmaceuticals and Medical Devices Agency; EMA=European Medicines Agency; EU=Europe; HTA=Health Technology Assessment; PFS=progression-free survival



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