Hematology Analytics

Challenges in developing next generation CAR-T

Nigel Yateman

BBS Seminar, July 15, 2022

NOVARTIS | Reimagining Medicine

Plan

- CAR-T is becoming standard of care in certain hematological malignancies
- Next generation CAR-Ts can further improve patient outcomes
- May need innovative trial designs
  - Traditional development program may not work for next generation CAR-T
- Example design incorporating real world data into a randomized trial
- Closing remarks

CAR-T: Chimeric antigen receptor T cell therapy.

CAR-T becoming standard of care in certain hematological malignancies

- First CAR-Ts had very impressive efficacy: "major paradigm shift" (Sehn and Salles, NEJM 2021)
  - initial late-line development programs used one single arm trial
  - regulatory approvals granted thanks to outstanding efficacy

- Recent approvals based on randomized controlled trials of CAR-T vs. standard of care in second line large B-cell lymphoma

- Great for patients ... but can we do better?

NEJM: New England Journal of Medicine.

NOVARTIS | Reimagining Medicine

New CAR-Ts can further improve patient outcomes

- Next generation CAR-T therapies can **further improve patient outcomes**
  - 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, allogeneic)
    - ➢ **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?

in indications where CAR-T is already standard of care:
need for **randomized trial** vs approved CAR-T ?

NOVARTIS | Reimagining Medicine

Challenge of new CAR-T vs. approved CAR-T

Operational hurdles with an approved CAR-T

CAR-T is a personalized medicine
- manufacturing is patient-specific, using patient's own blood
- manufactured in real-time (after randomization) ~3-6 weeks

Sponsor has full control over experimental arm (in-house)
- can plan manufacturing capacity according to study needs

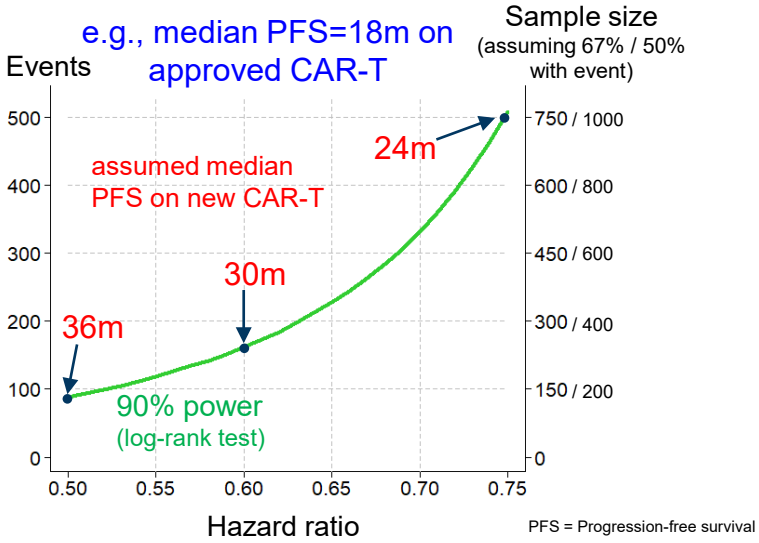
vs.

No control over manufacturing for approved CAR-T in control arm
- subject to commercial manufacturing availability, risk of delays

Delayed manufacturing can negatively affect clinical outcomes
- could seriously confound interpretation of treatment effect

	New CAR-T	Approved CAR-T
Manufacturer	Sponsor	Competitor
Manufacturing process	Clinical trial	Commercial
Planned manufacturing slots	Yes	Unlikely
Likelihood of delays	-	++

Lengthy development: due to more modest incremental benefits (vs. approved CAR-T)



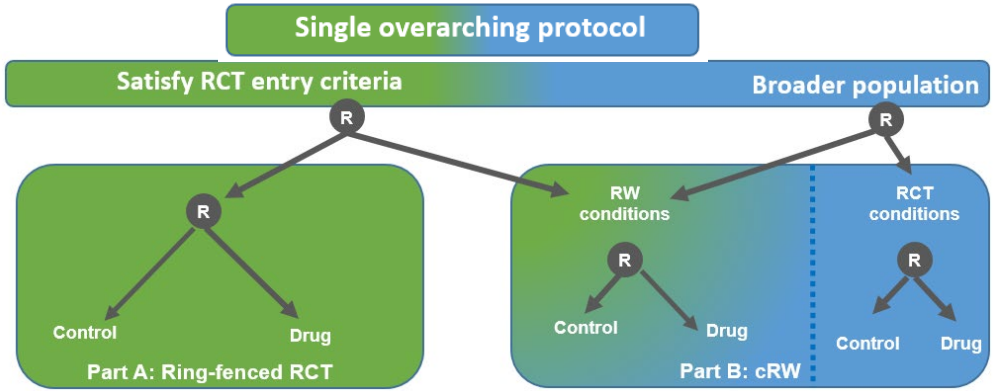
- delays patient access to potentially better therapy
- possibly beyond capacity of any single manufacturer

NOVARTIS | Reimagining Medicine

Need for innovation: opportunity for real world data?

Borrow from recent novel idea on augmenting a registration randomized controlled trial (RCT) with concurrent real-world data (cRWD)?

developed by Cornelia Dunger-Baldauf, Byron Jones and Frank Bretz, in collaboration with Chris Holmes



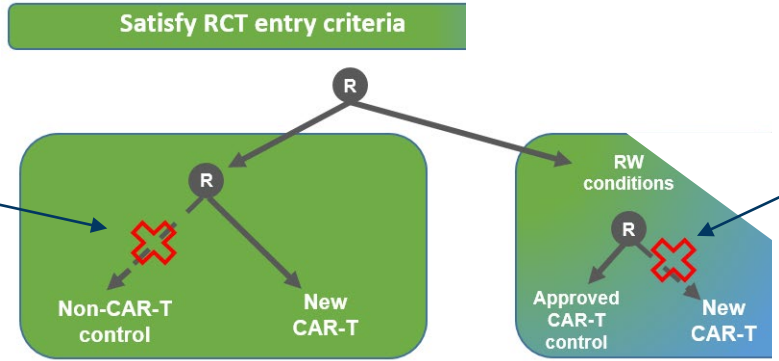
RCT drug effect
Internal validation ++
→ more for registration

RW drug effect
External validation ++
→ more for payers

... propose to use a part of this highly complex strategy

R = randomization; RCT = randomized controlled trial; cRWD = concurrent real world data; RW = real world

Example application to new CAR-T



Cannot randomize to non-CAR-T if SoC = approved CAR-T

Cannot randomize until after 1st approval

R

Single arm of new CAR-T

Non-interventional pragmatic single arm generating RWD

Remains highly beneficial to randomize

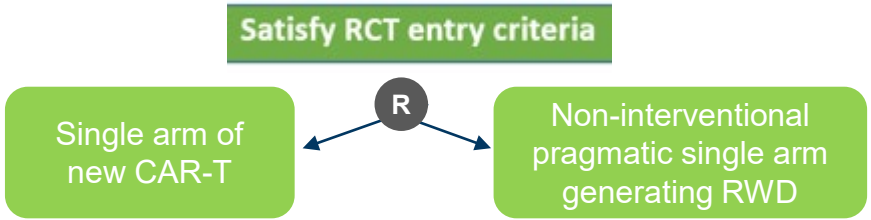
i.e., investigator choice – but expected mainly **approved CAR-T** as study would need to be conducted in CAR-T centers

In some geographies (e.g., US) the 2 arms could be aligned on eCRFs, visit schedule, independent review of response

SoC = standard of care; eCRF = electronic case report form

NOVARTIS | Reimagining Medicine

Randomized hybrid trial for CAR-T



Data analysis

- Single arm of new CAR-T: hypothesis test on appropriate response based endpoint (e.g., at landmark time). Test would use efficacy threshold based on historical benchmark (e.g., published results on approved CAR-Ts)
- Single arm of RWD on approved CAR-Ts to contextualize
  - estimation of treatment effect
  - also to contextualize choice of efficacy threshold used in test on single arm of new CAR-T
- Alternatively: could also consider going beyond contextualization, and test between the two arms

SAP = statistical analysis plan

Guiding principles for high quality RWD:

- Pre-specificied in protocol and SAP ✓
- Patient data from reliable/traceable source ✓
- Collected prospectively ✓
- Minimized selection bias ✓
- Suitability of real-world endpoints ✓
- Unambiguous index date ✓

Note: this design more adapted to regulators than payers
- RW patients coming from RCT entry criteria
- could broaden population subject to accumulating data

NOVARTIS | Reimagining Medicine

Closing remarks

- For innovation to be sustainable and to reach patients in a timely manner, less and less feasible to conduct large traditional development programs for advanced therapies such as CAR-T

- Novel designs that include the use of high-quality real world data may need to play increasingly important role in regulatory review and reimbursement decisions