Novartis Oncology

CAR-T regulatory and clinical development considerations: perspectives for today and the future

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BBS Seminar, October 4, 2023

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Plan

- Share experience and learning from the clinical development of the first CAR-T
- Outline development considerations and hurdles for the next wave of innovation, as existing CAR-Ts become standard of care
- Discuss potential ways to overcome challenges and advance next generation CAR-T development
- Closing remarks

Novartis journey of bringing the first CAR-T to approval

Aug 2012
Novartis enters collaboration with **University of Pennsylvania**

Dec 2012
Novartis purchases cell **manufacturing facility in Morris Plains (USA)**

July 2014
US FDA designates CTL019 as **Breakthrough Therapy** in (r/r) pediatric and adult acute lymphoblastic leukemia (ALL)

Jan 2015
Novartis enters into collaboration with the **Fraunhofer Institute (Germany)** enabling acceleration of global CTL019 clinical program

Jun 2016
EMA grants **PRIME** designation to CTL019

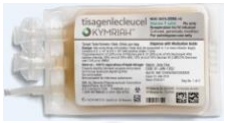
Feb 2017
Novartis submits **Biologics Licensing Application** (BLA) to FDA for CTL019 for pediatric/ young adult r/r ALL

April 2017
FDA grants CTL019 **Breakthrough Therapy** designation in r/r diffuse large B-cell lymphoma (DLBCL)

July 2017
US FDA **Advisory Committee** votes unanimously in favor of CTL019 approval

Aug 2017
FDA approves CTL019 (tisagenlecleucel) for patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse

Oct 2017 – April 2018
Regulatory filing in EU, Australia, Switzerland, Canada and Japan



01 May 2018
FDA approves tisagenlecleucel r/r large B-cell lymphoma after two or more lines of systemic therapy

Aug 2018
European Commission approves tisagenlecleucel for pediatric/young adult r/r ALL patients; and adult patients with r/r DLBCL after two or more lines of systemic therapy

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CAR-T therapies approved by FDA & EMA

Therapy	Disease[1]
Tisagenlecleucel (Kymriah)	Acute Lymphoblastic leukemia[2] Non-Hodgkin Lymphoma
Axicabtagene ciloleucel (Yescarta)	Non-Hodgkin Lymphoma
Brexucabtagene autoleucel (Tecartus)	Mantle Cell Lymphoma Acute Lymphoblastic leukemia[3]
Lisocabtagene maraleucel (Breyanzi)	Non-Hodgkin Lymphoma
Idecabtagene vicleucel (Abecma)	Multiple Myeloma
Ciltacabtagene autoleucel (Carvykti)	Multiple Myeloma

[1] Refer to product prescribing information and SmPC for exact indication wording for each therapy; all CAR-T therapies are approved only in the relapsed/refractory settings of the respective diseases
[2] Approved only in the pediatric and young adult population
[3] Approved only in the adult population

CAR-T clinical development learnings (1 of 2)

- **Execution of global, multi-center studies is complex**
  - Dedicated onboarding & training of clinical sites (e.g., learning curve in managing safety, patient selection, bridging therapy)
  - Establish logistics for global studies

- **There are unique clinical study design considerations**
  - Condensed development paradigm, often in Orphan designated diseases, late-stage indications with no effective standard of care available
  - Unique role of real world data to contextualize pivotal study results

- **Long-term follow-up (up to 15 years) may be needed for clinical trial patients**

CAR-T clinical development learnings (2 of 2)

- **Anticipate manufacturing challenges**
  - Autologous products require real-time individual manufacture for each patient
  - Potentially limited manufacturing capacity in early development phases
  - Align with HAs on comparability strategy throughout process development and for manufacturing changes
  - Technical transfer from academic settings to a robust commercial process requires iterative development cycles
    - impacted by variable patient starting material for autologous products, and limited product knowledge in early-phase clinical development

CAR-T regulatory & reimbursement learnings

- **Engage early to align on the development program with Regulators and Payers on critical aspects of the clinical program**
  - Analysis sets: Infused patients vs Enrolled patients
  - Importance of long-term data, e.g., duration of response
  - Endpoints: e.g., many payers do not accept progression free survival or response rates, but they are primary endpoints for regulatory approval
  - Importance of patient-level real-world evidence to contextualize pivotal data

Today: CAR-T becoming standard of care in certain hematological malignancies

- First CAR-Ts had impressive efficacy considering available therapy at the time, and resulted in a **major paradigm shift**[1]:
  - initial late-line development programs used one single arm trial
  - regulatory approvals granted thanks to outstanding efficacy

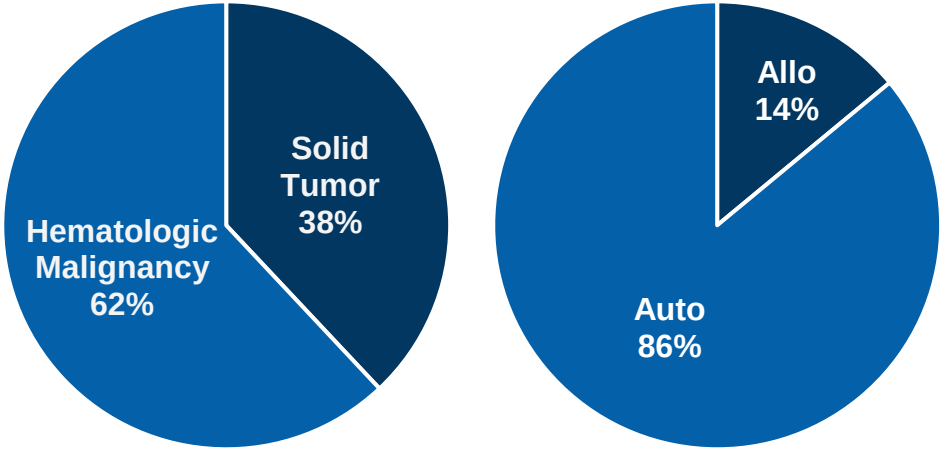
- Recent CAR-T approvals (2Q2022) in **second line** large B-cell lymphoma (2L LBCL)
  → new standards of care in US (NCCN guidelines)

- Great for many patients ... but can next generation CAR-Ts do better?

[1]Sehn and Salles, NEJM 2021.

CAR-T IND submissions to FDA

- There has been a relatively steady rise in new CAR-T IND and IND amendment submissions to the US FDA between 2015 and 2022
- A majority of CAR-T IND submissions are for hematological malignancies, and for autologous therapies



Peter Marks, FDA, March 2023, https://friendsofcancerresearch.org/event/the-next-generation-of-cellular-therapies-opportunities-to-accelerate-development/

The next wave: Rapid cycles of technical and scientific innovation in the CAR-T field aim at improving patient outcomes

- Improved product characteristics and introduction of new targets (e.g., T cell phenotype composition, fully human transgene, enhanced persistence, dual CAR-Ts to address antigen escape)
  - **potentially better efficacy (response, duration of response) + improved safety**
  - **expand to new indications or earlier lines of therapy**
- Improved/alternative manufacturing (e.g., turn-around time, reliability, allogeneic)
  - **better serve patients, especially those with rapidly progressing disease**

Questions and considerations for the development of the next wave of CAR-Ts

Compared with the “paradigm shift” impact of the first CAR-Ts on outcomes, more modest incremental benefits are expected for new CAR-Ts.	In indications where CAR-T is already standard of care, what are the expectations for, and feasibility of a randomized trial?
How can we deliver timely innovation?	Can existing data be leveraged to expedite the development of new CAR-Ts?
What is the effect on overall survival?	How can we ensure diversity?

Challenge of RCT 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) ~2-6 weeks

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

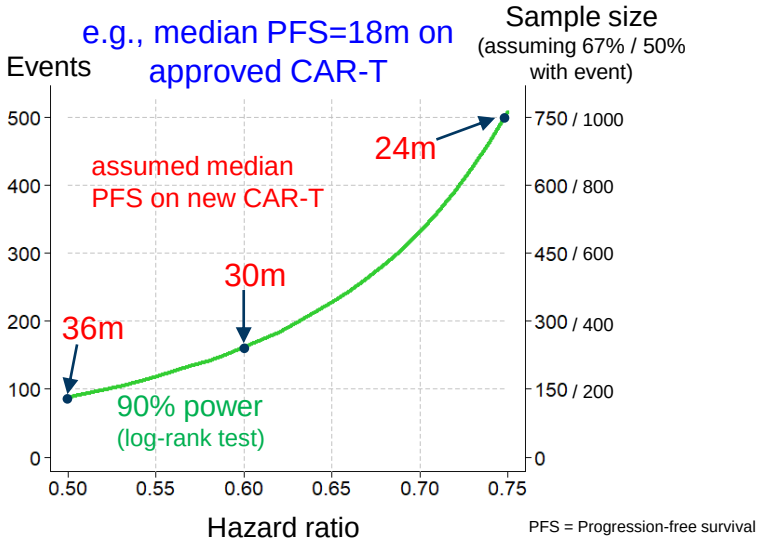
vs.

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

Delayed manufacturing of approved CAR-T could 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

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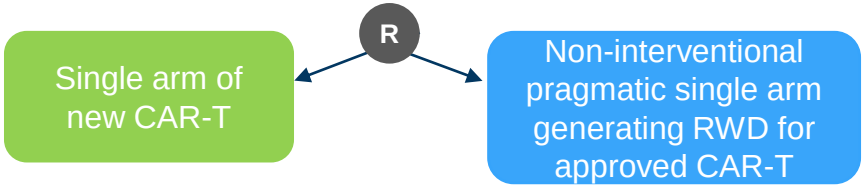
Randomized hybrid trial for CAR-T



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, RCT = randomized controlled trial.

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:
- can be attractive to both regulators (+) and payers (++)
- RW patients coming from RCT entry criteria
- could broaden population subject to accumulating data
- Limitations of design may include complexities for patients, sites, and sponsors, duration of trial, differences in response assessment in practice vs. trial settings

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Leverage real world data

- When there is a high unmet medical need, a lack of effective comparator therapies, or when initial phase I data of the investigational compound demonstrate a significant treatment effect over existing therapies, RCTs may not be warranted
- When treatment patterns are rapidly evolving after innovative treatments enter clinical practice, creating challenges of capturing newly emerging comparator therapies within RCTs while RWD can capture contemporaneous SOC
- High quality RWE (e.g. registries, electronic health records and chart reviews) can supplement pivotal single arm studies to support the benefit risk assessment
- Differences in assessment of endpoints in a clinical trial setting vs. practice setting must be considered

Consider earlier lines of disease

- Sponsors may consider a strategy of first developing CAR T-cell therapies in earlier line settings, whereby the unmet medical need is high, and CAR T-cell therapies are not the standard of care
- Sponsors to align with Health Authorities on the amount of safety and preliminary efficacy data needed to initiate trials in the earlier line settings

As part of the **US FDA's Project FrontRunner** initiative[1] FDA encourages drug sponsors to:

"Consider when it may be appropriate to first develop and seek approval of new cancer drugs for advanced or metastatic disease, in an earlier clinical setting rather than the usual approach to develop and seek approval of a new drug for treatment of patients who have received numerous prior lines of therapies or have exhausted available treatment options"."

[1]https://www.fda.gov/about-fda/oncology-center-excellence/project-frontrunner

Extrapolate data when appropriate

- Leveraging data from related product versions combined with prior platform technology knowledge can make the development and review processes more efficient
- Examples of different versions: altered CAR protein domain to enhance CAR T-cell activity, additional functional enhancements or co-stimulatory domains, a CAR-T cell derived from an alternative starting material, a more purified cell subtype
- Approaches for data extrapolation should consider the totality of evidence collected from preclinical research, clinical trials, and characterization of the manufactured product as well as any available published literature or post-marketing surveillance from related products to inform the safety and biological activity of iterative product versions

Closing remarks

- There is rapid innovation in the CAR-T field aiming to provide better patient outcomes
- For innovation to be sustainable and to reach patients in a timely manner, it is becoming less and less feasible to conduct large traditional development programs for advanced therapies such as CAR-T, when a CAR-T is the approved standard of care
- Novel designs that include the use of high-quality real-world data may need to play an increasingly important role in regulatory review and reimbursement decisions
- Timely patient access demands a close multi-stakeholder collaboration (Pharma - Biotech/Academia - Regulators - Payers) during all phases of development