Leveraging Existing Data to Benefit Cell Therapy Programs- An Academic Perspective

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- **Focus on First-in-Human Pilot and Phase I T cell-based cellular therapies**
- **Single Manufacturer- UPenn Clinical Cell and Vaccine Production Facility (CVPF)**
  - Supported manufacturing of approximately 28 T cell product INDs since 2000
- **Standardized CAR T cell manufacturing platform**
  - DMF allows for FDA to see comprehensive programmatic data; streamlines IND submissions
- **Standardized lentivirus production platform**
  - Packaging plasmids identical across vector lots
  - Transgene vector backbone consistent across programs
- **Several instances where a single product used in multiple disease indications**
- **CCI Safety and Pharmacovigilance team reviews and monitors safety across all of our programs**

This centralized, consistent structure has allowed us to leverage programmatic data to help advance individual programs or justify reduction in regulatory burden

Successes and Works in Progress

- Have leveraged programmatic product stability data to reduce/streamline our testing program ✓
- Used clinical data to justify doses, determine expected safety concerns, and develop toxicity grading and management algorithms ✓
- Reduced or eliminated RCL testing of product and patient ✓
- Using persistence and safety of modified cells to reduce patient follow-up duration

Replication Competent Retrovirus/Lentivirus (RCR/L)

- **Program-wide data on RCL testing of vector lots, cell products and post-infusion patient monitoring published in Marcucci et al. 2018, affirming no evidence of RCL.**
- **This, and other data informed the January 2020 Guidance, "Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up"**
  - "If you have accumulated manufacturing and clinical experience that demonstrates that your transduced cell product is consistently RCR-negative, we recommend that you provide this data to support reduction or elimination of testing ex-vivo genetically modified cells for RCR."
  - "After you have accumulated patient monitoring data with your product, you may provide a rationale to discontinue all active testing of patient samples for RCR in the safety monitoring section of your clinical protocol."

RCL- Justifications for removing testing

- **Product testing**
  - Per Marcucci et al, RCL was not detected in any products manufactured by CVPF (17 different vector lots under 8 INDs, 375 T cell products tested by qPCR or biological assay)
  - At the time of request to FDA (July 2020) the number of products was up to approximately 705
  - Additional justification in Cornetta et al 2018, reporting 460 transduced T cell products across 26 clinical trials were RCR/L negative
- **Patient Monitoring**
  - In Marcucci et al, evaluation of 308 patients (almost 194.8 years cumulative test follow-up) we estimate using a Poisson probability model that a single patient, or group of patients would need to be followed for 52.8 years to observe 1 positive RCL event, highlighting the unlikelihood
  - Cornetta et al 2018 published their findings of no RCL events in 296 clinical trial subjects monitored post-infusion
  - To date, there have been no reports of confirmed RCR/L reported in the literature.

RCL testing- Current Status = no routine testing

- **Products**
  - RCR/L is not a required test for release of most standard CAR T products in CVPF
  - Final product sample is archived indefinitely, but could qualify for disposal if trial has been ended for more than 5 years, or patient has died (whichever comes latest)
- **Patient Monitoring**
  - Post-infusion blood samples are collected and archived at pre-infusion baseline, and months 3, 6 and 12 post-infusion
  - In the event an RCL is suspected, the archived product and post-infusion samples are available for use in an investigation

FOLLOW UP DURATION

Patient Safety Follow up

Primary

- **Looking at safety of a new CAR/product and it's activity**
  - Toxicity
  - Off target effects
  - Dose relationship

LTFU

- **Looking at safety of the approach/integration**
  - Integration site concerns/implications
  - PDAEs
    - New malignancy(ies)
    - New incidence or exacerbation of a pre-existing neurologic disorder
    - New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
    - New incidence of a hematologic disorder.
    - New incidence of infection (potentially product-related)

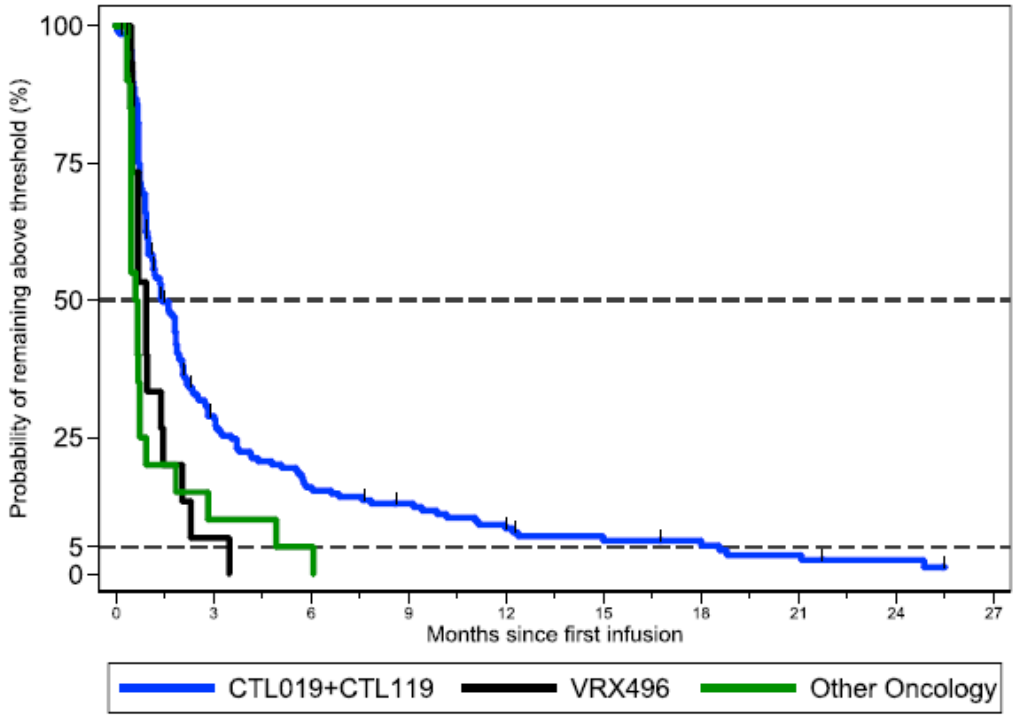
Long Term Follow up Duration

- **LTFU After Administration of Human Gene Therapy Products Guidance, January 2020**
  - "We consider the assessment of risk to be a continuous process; as more data accumulates, we recommend that you reassess the risk to your subjects and, if appropriate, revise your existing LTFU observations study protocol…"
  - "Preclinical and clinical experience with your product or similar products may be considered relevant in the assessment of the risk for delayed adverse events. For example, experience with GT products in the same vector type, administered by a similar route, or given for the same clinical indication may contribute helpful information."
  - "To reduce the unnecessary burden to study subjects and to you as the study sponsor, it may be appropriate to modify the duration of the LTFU observation based on your ongoing assessment of product persistence, transgene expression, and clinical findings."

LTFU Duration

- **One concern of FDA is development of leukemias and premalignant conditions (clonal expansion) due to lentiviral vector or gammaretroviral vector integration**
  - They recommend analysis of vector integration sites if ≥1% of surrogate sample is positive for vector sequence by PCR
  - Marcucci et al reports estimated median time for LV-modified T cell products to fall below 1% were 1.4 months in hematologic malignancies, 0.66 months in solid tumor and 0.92 months in HIV, indicating such events would be captured well before the end of current recommendation for LTFU duration

Currently exploring compiling comprehensive safety and persistence data to support reducing LTFU follow up duration

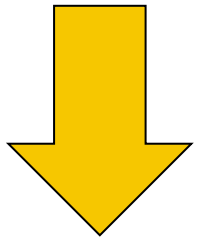


LTFU Duration

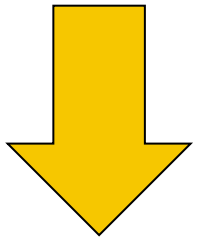
- We have been able to close 2 INDs for HIV lentivirus-modified cell therapies prior to 15 years based on lack of persistent cells and favorable safety profile/ lack of PDAE
- Recently amended Adult ALL protocol, now performing only annual visits via phone/telemedicine after Month 24 if CAR T cells are no longer detectable (reduced from 5 years)
- Leveraged previous CAR T data for a new study in breast cancer where total length of follow up is 5 years post infusion
- Currently amending an HIV CD4 CAR-CCR5 ZFN trial to conclude LTFU after 5 years based on previous CD4 CAR trial 15 year safety data and 2 CCR5 ZFN trials with data out 5-10 yrs.
- Working on a manuscript detailing our comprehensive programmatic data

Goal- Finding a Balance

Long/15 year follow up



Shorter Follow up



- More data being generated, but is it informative?
- Is there an active concern being addressed?
- How much safety data is needed to inform on next gen?

- How long is long enough?
- Risk consideration?
- Value of impact on cost, resources, and patient burden?

Thank you