Breaking Through the Barriers to Cell and Gene Therapies

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ARM Cell & Gene State of the Industry Briefing
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Overview

• Update on CAR T cell therapeutics
• Rare disease therapeutics
• State of the field of rare disease gene therapy
• How FDA plans to help address challenges
U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)
- Casgevy (2023)
- Lyfgenia (2023)
CAR-T Cell Update
Examples of CAR-T Cell Results

Tisagenlecleucel (Kymriah) in relapsed refractory pediatric and young adult acute lymphoid leukemia

Remission rate at 3 months of 81%

Maude SL, Laetsch TW, Buechner J et al. NEJM. 2018;378:439-448

Axicabtagene Ciloleucel (Yescarta) in relapsed refractory adult non-Hodgkin lymphoma

Neelapu SS, Locke FL, Bartlett NL et al. NEJM. 2017;377:2531-2544
Safety Concerns for CAR-T Cells

• Cytokine release syndrome (CRS) - common
• Cell-mediated encephalopathy syndrome/immune effector cell associated neurotoxicity syndrome (CRES, ICANS)
• Others: low blood counts, transient heart dysfunction, low immunoglobulin levels
• Long-term follow up necessary to fully define
Safety Concerns for CAR-T Cells

- T Cell Malignancies (Safety alert on 28 Nov 2023)
  - T cell lymphoma, large granular lymphocytosis, others
  - 22 cases reported as of December 31, 2023, with over 27,000 individuals treated in the United States
  - Investigation ongoing: sequencing not available for all
    - Onset within 2 years reported to date (when date known)
    - Presence of CAR construct documented in a few cases
Addressing T Cell Malignancies

• Patients and clinical trial participants should be monitored life-long for new malignancies
• If a new malignancy occurs following treatment, contact the manufacturer to report the event and obtain instructions to test for the presence of the CAR transgene
• The overall benefits of these products continue to outweigh their potential risks for all approved uses
Gene Therapy for Rare Diseases
Importance of Therapies for Disorders that are Rare

• Out of thousands of rare hereditary and acquired diseases there are hundreds of disorders affecting one to thousands per year that could be addressed with novel therapies
  – Addressing molecular defects may reduce some more common diseases to very rare diseases
Potential Rare Disease Therapeutics

• Small molecules
• Protein therapeutics
• Antisense oligonucleotides
• Gene therapy
Gene Therapy

Advantages
• Generally, administration of only one dose is required
• High possibility of success based on design
• Many different diseases can be addressed
• Long-term disease benefit or even cure possible

Disadvantages
• Complexity and cost of manufacture
• Potential for irreversible side effects
• Special expertise required for administration
• Presents challenges of a new business model
FDA Approved Systemic Directly-Administered Gene Therapy

- **Onasemnogene abeparvovec-xioi (Zolgensma):** for the treatment of patients less than two years of age with spinal muscular atrophy (SMA) with confirmed biallelic mutations in the *survival motor neuron 1 (SMN1)* gene
  - SMA Type 1 commonly presents with muscle weakness that is evident at birth or within the first few months of life


Evelyn with documented SMA1 treated with onasemnogene, now age 3 running around, something never seen in untreated children
Current Challenges

• Gene therapy is currently at a critical juncture due to a combination of factors
  – Manufacturing challenges
  – Clinical development timelines
  – Different global regulatory requirements
Actions at Center for Biologics

- Advancing manufacturing technologies for cell and gene therapy through research
- Application of platform technology provision
- Work to more clearly define the use of accelerated approval for gene therapy
- Exploring concurrent submission and product review with other regulatory authorities
- Communication pilot for rare diseases
Manufacturing

Current manufacturing platforms limit gene therapy production

Issues: Capacity Cost

Sweet Spot

Technologic Advances Needed

Approximate Treatment Population Per Year

1-100  >100-10,000  >10,000
Manufacturing Solutions

• Harmonization of manufacturing protocols
  – Standardized protocol use by academics and small companies would more easily facilitate transfer of process to contract manufacturing organizations

• Automation of manufacturing process
  – Development of automated or semi-automated fabrication devices for gene therapies based on a manufacturing machine-disposable paradigm
The small batch gene therapy manufacturing platform of the future may be a vector fabrication device that uses consumables and disposables.
Premise

• In appropriate situations, non-clinical data and manufacturing information from one product may be able to be leveraged to another
Omnibus Appropriations Act of 2023

• Section 2503. Platform Technologies
  – Sponsors may also “reference or rely upon data and information” from a previous application for a drug or biological product that incorporates or uses the same platform technology
  – Data must be submitted by the same sponsor or the sponsor relying on the data received permission from the sponsor who originally submitted the data
  – FDA will issue guidance relating to the program
CRISPR: Poster Child of a Platform

From: Zhou et al. Trends in Biotechnology. 2023; 41:1000-1012
Leveraging Accelerated Approval

- The science inherent in the development of many gene therapies potentially facilitates the use of biomarkers as endpoints that are *reasonably likely* to predict clinical outcomes
  - Enzyme activity levels, structural protein levels can be measured and correlated with clinical endpoints in model systems or even in humans
Connecting Biomarkers with Gene Therapy Clinical Outcomes

**Animal Models**
- Disease model reflects aspects of human pathology
- Administration of therapy associated with achievement of a specific protein level ameliorates disease

**Human Observations**
- Disease state is associated with protein levels above or below a certain range
- Certain protein levels are associated with disease absence or minimal disease

Demonstrate that equivalent protein levels can be achieved in humans affected by the disease
Collaboration on **Gene Therapies Global (CoGenT Global) Pilot**

- Initial participation by Standing Regulatory Members of ICH
- Partners may participate in internal regulatory meetings and meetings that include the sponsor
- Specific regulatory reviews are shared and discussed with partners
- All meetings conducted and information shared under strict confidentiality agreements
- Goal is to increase the efficiency of the regulatory process, reducing time and cost for agencies and sponsors
Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot

• Further accelerate pace of development for products intended to address unmet medical needs in rare diseases or conditions likely to lead to significant disability or death

• Three CBER eligible products in the initial iteration to receive enhanced communications when selected for the pilot
  – An initial meeting to review features of the pilot program
  – Additional ad hoc email or live interactions on an as needed bases
  – Applications for requests to participate accepted through March 1, 2024

Summary

• The Center for Biologics Evaluation and Research aims to make 2024 a breakout year addressing key challenges to the development of cell and gene therapies, especially for rare disorders