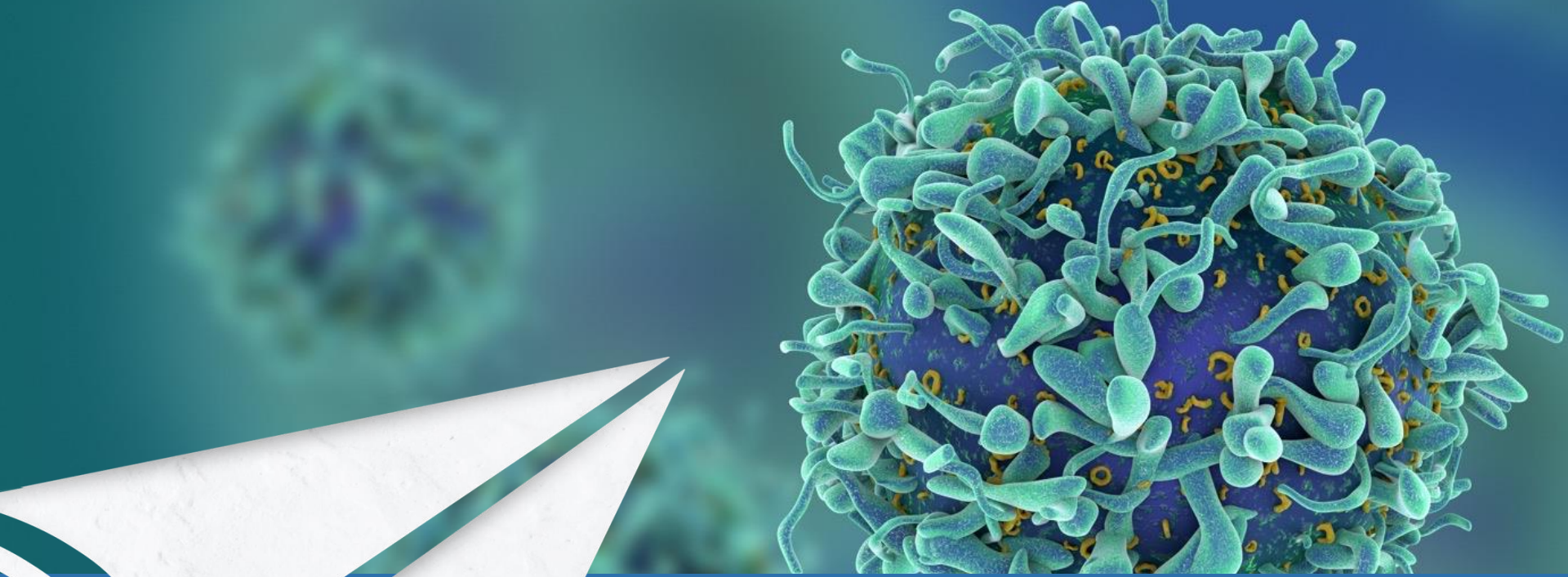

Data Extrapolation for Next Generation Cell-Therapies

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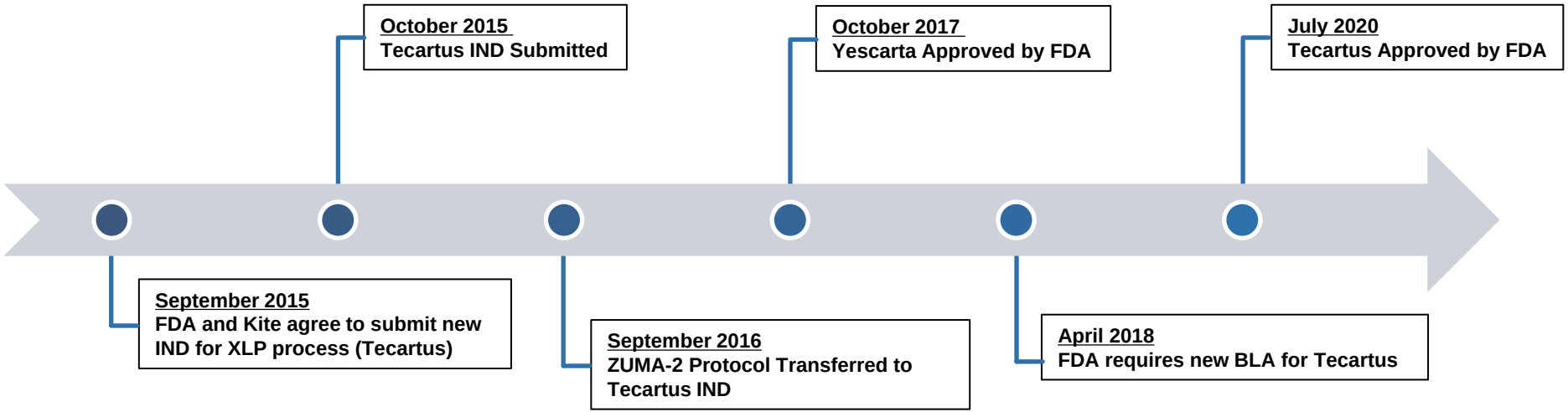
Case Study:

Brexucabtagene autoleucel (TECARTUS) development acceleration following axicabtagene ciloleucel (YESCARTA); two distinct CD19 directed CAR-T therapies

YESCARTA vs TECARTUS

- **Distinct Products:**
  - Same antigen, same vector
  - Change in manufacturing alters therapeutic effect
    - Lymphocyte vs T-cell enrichment
    - Modified T-cell activation media
  - Observed enhanced effectiveness against circulating tumor cells
  - *Guidance for Industry: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations (2021)*
- **Distinct Indications:**
  - Opportunity for extrapolation may have been greater if the indications were conserved (ie. replacement)

TECARTUS Development History



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Successful Data Extrapolation: What has worked

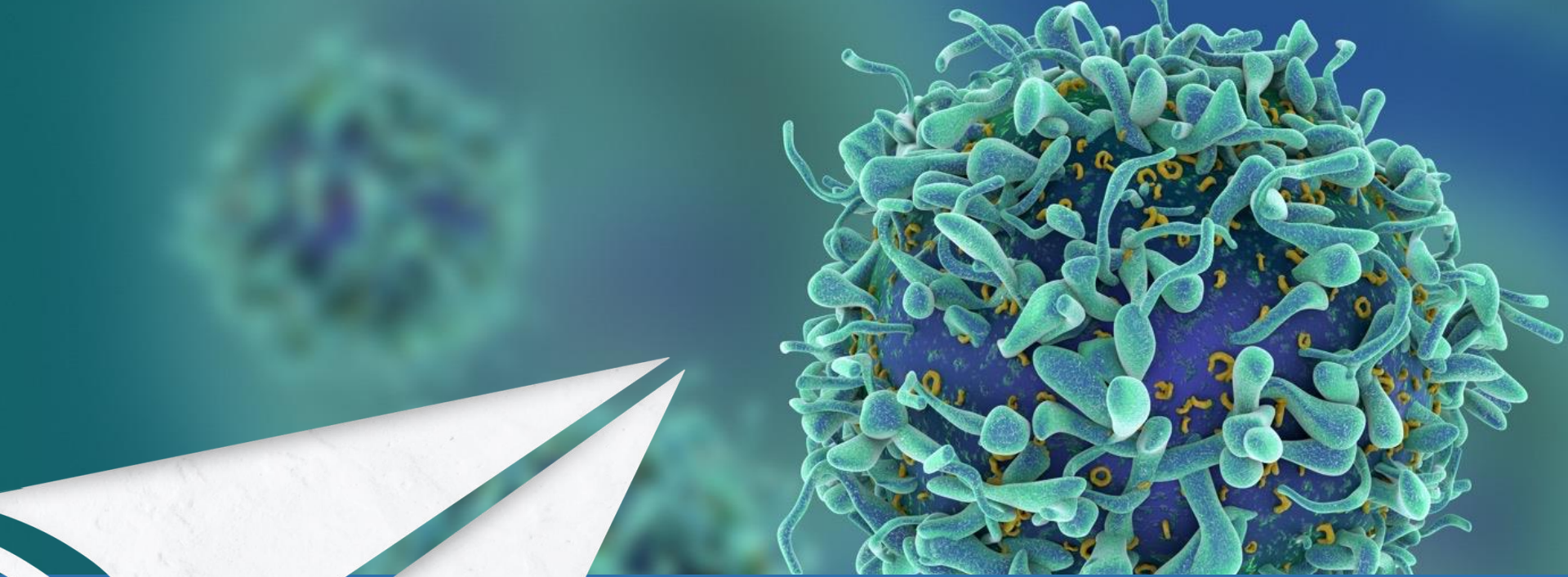
1. **Starting Dose**
   - Starting dose was chosen based on approved dose for Yescarta
   - 2 cohorts of dose exploration were conducted; no staggering, or other typical “FTIH” safety measures
2. **Stability Data**
   - Results from stress studies to confirm analytical methods, and CCI testing to support the stability program, but not long-term stability conclusions
3. **Safety Data**
   - FDA agreed to extrapolated the safety data from Yescarta and combine the REMS programs for both products

Next Generation Categories: Not all are the same

Change in Manufacturing
Same Antigen/Same Vector
New indications OR Same indications (ie. replacement)
Greatest opportunity for data extrapolation

Enhancements
Same Antigen/New Vector - ex. transgenes
New indications OR Same indications (ie. replacement)
Moderate opportunity for data extrapolation

New Target
New/Dual Antigen - Introduces new MoA
New indications - Replacement more challenging
Lesser opportunity for data extrapolation



Thank You

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