Cellular Gene Therapies: Regulatory Challenges

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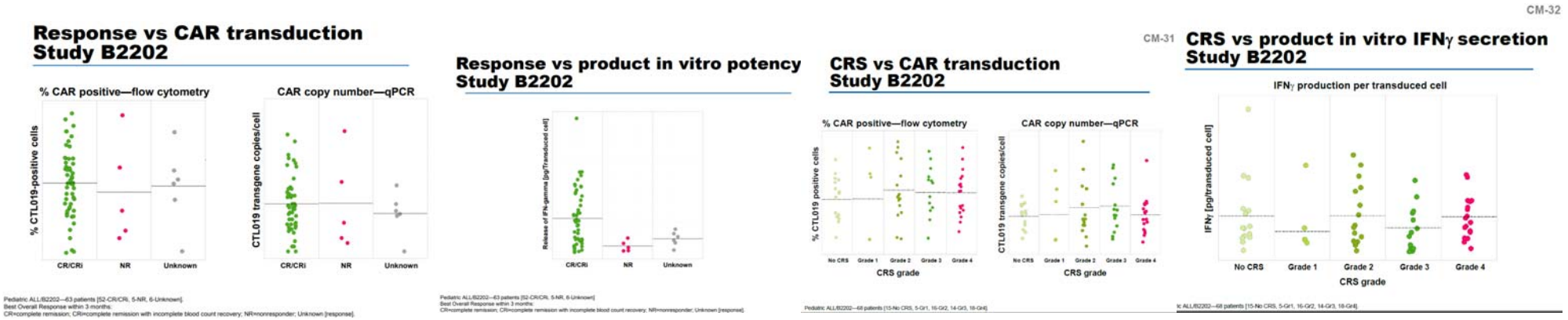
CAR-T and the Rise of Cellicon Valley Penn Medicine-May 10, 2019

Disclosure

- Viera Muzithras is an employee of Celgene

Approved CAR Ts

- To date, CAR T therapies in leukemia and lymphoma have achieved regulatory approval
  - Data presented at Kymriah® ODAC showed no clear correlation with product quality attributes and response or CRS



Example from Kymriah (ODAC)

Cellular Immunotherapy Product Development Will Be Rapid and Complex

- Sponsors are engaged to develop new technologies innovations
- Manufacturing improvements and next generation of manufacturing pose regulatory challenges
- New technologies will accelerate and challenge the current process of development; raising the need for clarity on new development pathways
- Currently no harmonized guidance on demonstrating product comparability

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Challenges for Clinical Development of Cellular Immunotherapies

- When do process improvements require clinical evaluation?
  - Is a safety assessment sufficient?
  - Clinical comparability data requiring time to event analyses hinder rapid implementation of serial process improvements: PK, biomarker and safety data should suffice
- No informative nonclinical models
- Cost and time to repeat clinical development
  - Randomized vs approved cellular therapies may not be feasible
  - How many patients need to be treated to demonstrate comparability?

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Advances in cancer immunology

- Emerging technologies
  - Tumor infiltrating lymphocytes (TILs)
  - Engineered T-cell receptors (TCR)
  - Chimeric Antigen Receptor (CAR) T cell (autologous and allogeneic)
- Have potential to change treatment landscape beyond hematologic cancers

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How do we get there?

- Which technology is the best?
  - Nonclinical models not sufficient to guide technology choice
- Small Human studies in patients
  - Small exploratory clinical studies to differentiate best technology
  - Potential to better understand biology and product attributes driving efficacy and safety of the different technologies
- Is a basket protocol under a single IND an option?

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Guidance

- Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies (January 2006, CDER) *https://www.fda.gov/.../guidancecomplianceregulatoryinformation/guidances/ucm078*
- Guidance for Industry: CGMP for Phase 1 Investigational Drugs (July 2008, CDER, CBER) *https://www.fda.gov/downloads/drugs/guidances/ucm070273.pdf*
- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013) *https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf*
- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015) *https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf*

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Next Steps

- Harmonized guidance on comparability
- More timely interactions to answer questions (CMC, nonclinical, clinical)
- Flexible approach to evaluating different T-cell based products in basket protocols

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Thank you