Cellular Gene Therapies: Regulatory Challenges

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CAR-T and the Rise of Cellicon Valley Penn Medicine-May 10, 2019
Viera Muzithras is an employee of Celgene
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)
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
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?
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
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?
Guidance

  https://www.fda.gov/.../guidancecomplianceregulatoryinformation/guidances/ucm078

- Guidance for Industry: CGMP for Phase 1 Investigational Drugs (July 2008, CDER, CBER)  


- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)  
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
Thank you