Lifecycle Management: Challenges and Lessons Learned from Kymriah™ (CD19 CAR T)

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Agenda

Kymriah™ (CD19 CAR T) Overview
Early Development and Transfer
Characterization and Process Development
Process Validation and Launch
Challenges / Lessons Learned
The Next Chapter of Kymriah™
Novartis CTL019 CAR-T Cell Therapy

1. Patient relapse or refractory to prior therapy
2. Patient identified as CTL019 candidate
3. Patient’s T cells harvested at apheresis center
4. T cells activated and transduced with lentiviral vector
5. CTL019 infused into patient and CRS* monitoring
6. Patient disease state evaluated +28 days after infusion

*Cytokine Release Syndrome: common CART therapies’ side effect, may require hospitalization

Morris Plains (Novartis)

- CTL019 controlled before quality release
- CTL019 packaged and cryopreserved (reprogrammed T cells)
- Modified T cells expanded and harvested
- T cells activated and transduced with lentiviral vector

Hospital / Infusion / Apheresis Centers

- Patient’s T cells transferred to Morris Plains
- CTL019 cells transferred to infusion center
- CTL019 packaged and cryopreserved (reprogrammed T cells)
Early Development and Transfer
## Early Clinical Development

### Historical Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Learning</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>CD3/CD28-bead costimulation for CD4+ T cells</td>
<td>Levine et al. JI 159:592</td>
</tr>
<tr>
<td>1998</td>
<td>Large scale production of CD3/CD28 costimulated CD4+ T cells</td>
<td>Levine et al. J Hematotherapy 7:437</td>
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<td>2011</td>
<td>Autologous CAR+ T cells for anti-leukemic memory</td>
<td>Kalos et al. Sci Transl. Med 3:1</td>
</tr>
<tr>
<td>2011</td>
<td>CAR+ T cells in CLL</td>
<td>Porter et al. NEJM 265:725.</td>
</tr>
<tr>
<td>2012-2014</td>
<td>Tech transfer from UPenn to Novartis</td>
<td>Novartis documents</td>
</tr>
</tbody>
</table>
Key Considerations in Kymriah™ During Transfer

• Transfer + Process Improvements

• Open systems to closed where feasible
  – Water bath to Plasmatherm
  – Open Product Transfers to Luer Connections
  – Open bead wash step to closed process
  – Replace Luer Connections wherever possible with tube welding

• Manual to automatic
  – Manual Ficoll to automated Sepax
Process Transfer

Evaluation
- Feasibility (Process A)
- Quality Risk Assessment
- Alternatives
- Selection of Receiving Site

Planning
- Team formation and kickoff
- Regulatory assessment
- Manufacturing process transfer protocol

Preparation
- Documentation packages
- Training
- Incorporation of Process Improvements
Process Transfer (cont)

Execution
- Feasibility Runs (test)
- Engineering Runs (confirm)
- Comparability Runs (regulatory)

Assessment
- Analysis of results
- Submission of comparability data
- Manufacturing process transfer report

Post-transfer
- Lessons learned
- Initiate monitoring
- Phase 2 clinical trial at Morris Plains
- Begin process characterization (Process B)
Characterization and Process Development
Process Characterization Approach

- Historical UPenn clinical data (used to set initial ranges)
- Clinical data from Morris Plains
- PC data with healthy donors (normal process and atypical process conditions)

**Historical data (UPenn and MP Runs)**

- Control Space

**Process Characterization Test Range**

- CPP, KPP, NKPP definition and ranges
- CQA definition and ranges
- Data evaluation from clinical lots

- Feasibility Studies
- Data Summaries
- PC Protocols
- Confirmation Studies PC Protocols
- Confirmation Studies PC Reports
- PC Summary Report

- FMEA
- PC Master Plan
PC Implementation
Process Validation and Launch
## Initial Development Thru Qualification

<table>
<thead>
<tr>
<th>Activity</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
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</thead>
<tbody>
<tr>
<td>Tech Transfer</td>
<td>UPenn -&gt; Novartis</td>
<td></td>
<td>Novartis -&gt; CMO 1</td>
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<tr>
<td>Clinical Manufacturing</td>
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<td>Training and Readiness</td>
<td>CMO 1 Clin Mfg</td>
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<tr>
<td>PD</td>
<td>Proc. A-&gt;B</td>
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<tr>
<td>Process Validation</td>
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<td>Proc. B-&gt;C</td>
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<td></td>
<td>Process Characterization Phase I</td>
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<td>Process Qualification Process C</td>
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Initial Process Validation Approach

CTL019 Process Performance Qualification Strategy

<table>
<thead>
<tr>
<th>Clinical Phase</th>
<th>Commercial Manufacturing Phase</th>
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<tr>
<td><strong>Stage 1: Process Design</strong></td>
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<tr>
<td>Healthy Donor Starting Material</td>
<td>Patient Starting Material</td>
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<tr>
<td>- Process Transfer</td>
<td>- Clinical Manufacturing batches demonstrating patient manufacturing conditions</td>
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<tr>
<td>- Develop unit operations</td>
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<td>- Process Characterization and process parameters and ranges</td>
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<tr>
<td>Finalization of process parameters and ranges (CPPs, etc.)</td>
<td>Justification of Specifications Report (CQAs)</td>
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| **Stage 2: Process Performance Qualification** | | |
| Patient Starting Material | | |
| PPQ Protocol Pathway 1 | PPQ Final Report Pathway 1 |
| PPQ Protocol Pathway 2 | PPQ Final Report Pathway 2 |
| PPQ Protocol Pathway 3 | PPQ Final Report Pathway 3 |
| Manufacture Batches | Manufacture Batches |

| **Stage 3: Continued Process Verification** | | |
| Patient Apheresis Processing | Routine monitoring of validated process pathways |

Justification of Specifications Report (CQAs)
Finalization of process parameters and ranges (CPPs, etc.)
# Continued Development and Launch

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<td><strong>Clinical Manufacturing</strong></td>
<td>CMO 1 Clin Mfg</td>
<td>Morris Plains Clin Mfg</td>
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<tr>
<td><strong>Commercial Manufacturing</strong></td>
<td>Morris Plains pALL (Process C)</td>
<td>Morris Plains pALL/DLBCL (Process D)</td>
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<tr>
<td><strong>PD</strong></td>
<td>Proc. C-&gt;D</td>
<td>Proc. D-&gt;E (planned)</td>
</tr>
<tr>
<td><strong>Process Validation</strong></td>
<td>Process Characterization Phase II</td>
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<tr>
<td></td>
<td>Process Qualification (Process D)</td>
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<td>Process Qualification (Process E Planned)</td>
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# Current Process Validation Approach

## CTL019 Process Performance Qualification Strategy

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| **Stage 2: Process Performance Qualification** | |
| Patient Apheresis Processing | |
| Routine monitoring of validated process | |

| **Stage 3: Continued Process Verification** | |
| | Process Monitoring Using CQAs |
Challenges / Lessons Learned
Consistent CTL019 T-cell product from individual patient material

Incoming leukapheresis material

Transduced viable T cell product (CTL019) ~97% T cells
Continual Learnings on Cell Growth
The Next Chapter of Kymriah™
Near Term Process Improvements

• Additional steps moved from luer to tube weld connections
• More pre-assembled components
• Earlier introduction of cells to the WBR
• More robust cell selection
• Move to automation, particularly around de-beading, harvest and formulation
• Switch to vector produced via more robust/scalable methods
• Additions of secondary sources for key raw materials
Next Gen Manufacturing

• Automated, closed system, minimized footprint

![Diagram of manufacturing process]

PATIENT CELLS → APHERESIS → ENRICHMENT → SFM → VESSEL → VECTOR → HARVEST-FILL-FINISH

Manufacturing Devices (6) → Manufacturing Devices (4)
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