End of Treatment Peripheral Blood TCR Evaluation for Minimal Residual Disease Evaluation in Peripheral T-cell Lymphomas

Neha Mehta-Shah, MD, MSCI1, Todd A Fehniger, MD, PhD1, Eric D Jacobsen, MD2, Katrina Peterson1, Brad S. Kahl, MD1, Nancy L. Bartlett, MD1, Amanda F Cashen, MD1, Armin Ghobadi, MD1, Anne Fischer, BS1, Beth Reagan1, Alison J. Moskowitz, MD3, Fei Wan1, Natalie Hill4, Ying Huang, PhD4, Kasey Hutt, PhD4, Edgar Vigil4, Meredith Olson4, Austin Jacobsen4 and Steven M. Horwitz, MD3

1Washington University in St. Louis, St. Louis, MO; 2Dana Farber Cancer Institute, Boston, MA; 3Memorial Sloan Kettering Cancer Center, New York, NY; 4Invivoscribe, San Diego, CA
Disclosures

- **Mehta-Shah:** Institutional research funding from: Bristol Myers-Squibb, Celgene, Verastem, Corvus, Genetech/Roche, Innate. Consultancy for Kyowa Hakko Kirin, C4 Therapeutics, Daiichi Sankyo, Karyopharm, Ono: Consultancy

- **Fehniger:** Research funding from: HCW Biologics, Compass Therapeutics, ImmunityBio. Consultancy for Indapta, Nkarta, Kiadis, Orca, Biosystems, Wugen.

- **Jacobsen:** Research funding from Novartis, Pharmacyclics, F. Hoffmann-LaRoche, Consultancy from: Acerta, Astra-Zeneca, Merck; Honoraria from Takeda

- **Kahl:** Research Funding from ADC Therapeutics, Acerta, Beigene. Consultancy for AstraZeneca Pharmaceuticals LP, AbbVie, BeiGene, Acerta, Janssen, Celgene, Genentech, Roche, Pharmacyclics, ADC Therapeutics. Membership on an entity’s Board of Directors or advisory committees for AstraZeneca, ADC therapeutics, Janssen and BeiGene.

- **Bartlett:** Research funding from Seattle Genetics, Millennium, Merck, Affimed, Acerta, Janssen, Autolous, Roche/Genentech, BMS/Celgene, Pharmacyclics, Immune Design, Kite, Forty Seven, Consultancy for Seattle Genetics, BTG, ADC Therapeutics, Pfizer, WuGen, EUSA, Roche/Genentech, Bristol Myers Squibb, Kit, Membership on an entity’s Board of Directors or advisory committees for Seattle Genetics, Pfizer

- **Ghobadi:** Research funding from Amgen, Kite, Consultancy from Amgen, WuGen, EUSA, Bristol Myers Squibb, Kite

- **Moskowitz:** Research Funding from Merck, Incyte, Seattle Genetics, Bristol-Myers Squibb; Consultancy form Seattle Genetics, Imbrium Therapeutics, L.P, Miragen Therapeutics; Incyte; Merck:

- **Huang, Hutt, Vigil, A Jacobsen, Olson:** Employed by Invivoscribe

- **Horwitz:** Research Funding from Daiichi Sankyo, Corvus, Portola, Trillium, Seattle Genetics, Millenium/Takeda, Infinity, Verastem, Aileron, ADCT Therapeutics, Celgene, Forty Seven, Kiowa Hakka Kirin, Consultancy from: GlaxoSmithKline, Myeloid Therapeutics, Innate Pharm., Mundipharma, Beigene, Portola, Corvus, Trillium, Seattle Genetics, Millenium/Takeda, Kyowa Hakka Kirin, Forty Seven, Celgene, Aileron; ADCT Therapeutics, ASTEX, Affirmed, Miragen, Kura Oncology; Janssen; Vividion Therapeutics; Verastem, C4 Therapeutics
Background

- Peripheral T-cell lymphomas are a rare subtype of non-Hodgkin lymphoma
- High rate of relapse to standard therapy:
  - 80% overall response rate to anthracycline based chemotherapy
  - 5 year PFS approximately 20% for most subtypes
- Autologous transplant is considered in first remission
  - Benefits approximately 20% of patients
- Allogeneic transplant can be curative
  - Median survival from relapsed/refractory disease is 6-10 months
- Biomarkers would be critical:
  - To evaluate who is at highest risk of relapse
  - Who most benefits from a consolidative autologous transplant

| Outcomes By Intent to Consolidated with Auto-HSCT in Swedish Registry |
|----------------------------------------------------------|-----------------|-----------------|
|                                                          | Auto-SCT (n = 128) | No Auto-SCT (n = 124) |
| 5 yr OS                                                  | 48%             | 26%             |
| 5 yr PFS                                                 | 41%             | 20%             |

Ellin et al Blood 2014
Background

• Minimal residual disease markers are being studied to:
  – Predict relapse
  – Determine who benefits from maintenance or consolidative therapy
  – Promote early discontinuation of therapy

• T-cell receptor gene rearrangement (TCR) by next generation sequencing is able to detect a known TCR clonotype at $10^{-5}$
  • Highly specific and sensitive
  • Lends itself towards MRD evaluation in T-cell lymphomas

Shah et al AMP 2017

Courtesy of Maria Arcila (MSKCC)
Methods

- **Hypothesis:**
  - Next generation sequencing based TCR clonality assays is a feasible method of evaluating minimal residual disease

- **Primary Objective:**
  - To estimate the percentage of patients with a dominant tumor sequence identified from the pre-treatment tumor specimen.

- **Secondary Objectives**
  - To study whether a novel NGS-based TCR clonality assay to evaluate MRD (LymphoTrack) can prognosticate risk of relapse in PTCL, predict response to treatment
  - To evaluate whether the rate of decline of the tumor specific sequence or sequences predict duration of response.
  - To characterize the lead time from MRD positivity to subsequent clinical relapse.

- **Exploratory Objective**
  - To explore the ability of cfDNA sequencing analysis to assess MRD in PTCL.
Study Design

A prospective, multi-institutional, non-therapeutic cohort study

Eligibility:
- Untreated PTCL-NOS, AITL, ALK- ALCL, ALK+ ALCL, MEITL, EATL
- Pretreatment sample to evaluate tumor TCR sequence

Exclusion:
- CTCL, NK/T-cell, ATLL, HSPTCL

Chemotherapy with Curative intent (e.g. CHOPx6, CHOEPx6)

End of Treatment Response Assessment:

Surveillance*:
Blood Samples and PET/CT

MRD Blood Samples and Interim Scan

Cycle 1 2 3 4 5 6

PET/CT

3 6 9 12 15 18 21 24 mo

PET/CT and LymphoTrack assessment

LymphoTrack assessment

Cell Free DNA (cfDNA)

*Surveillance from End of Treatment PET or Day 0 Transplant

NCT03297697
Statistical Design

• Aim to demonstrate feasibility of evaluating for MRD by TCR clonotype (Lymphotrack) in peripheral blood at baseline
  – Feasibility: if TCR clonotype positive at baseline in >60% of cases

• Powered to detect 35% difference in 2 year PFS between those who have negative vs. positive peripheral blood MRD evaluation at end of treatment
  – 2 year PFS for End of Treatment PET
  – Negative: 60%, Positive 25%

• Sample size: 42 patients.
  – A one-sided log rank test with type I error of 0.1 will have power of 0.9 to detect a 35% difference in 2-year PFS
### Patient Characteristics

<table>
<thead>
<tr>
<th>Histology</th>
<th>N (%)</th>
<th>Therapy</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL</td>
<td>16 (42%)</td>
<td>CHOP</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>AITL</td>
<td>10 (26%)</td>
<td>CHOEP</td>
<td>10 (52%)</td>
</tr>
<tr>
<td>ALCL, ALK-</td>
<td>7 (18%)</td>
<td>BV-CHP</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>ALCL, ALK+</td>
<td>5 (13%)</td>
<td>CEOP</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>MEITL</td>
<td>1 (3%)</td>
<td>CHOP+ azacitidine</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Autologous Transplant</td>
<td></td>
<td></td>
<td>7 (37%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response to Therapy</th>
<th>Age</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td></td>
<td>61 (22-80)</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 38 patients enrolled
- 19 completed therapy and had end of treatment TCR available for analysis
Results

Baseline Tumor Tissue

15 (78.9%) TCR clonotype +
4 (21.1%) TCR clonotype –
• 3 PTCL NOS, 1 ALK+ ALCL

PET/CT CR (n=10)
8 (80%) TCR clonotype +
2 (20%) TCR clonotype –
At Median follow up 13.1 mo, 1 patient has relapsed

PET/CT PR/PD (n=5)
5 (100%) TCR clonotype +

End of Treatment Blood

13/15 (86.7%) TCR clonotype +
2/15 (13.3%) TCR clonotype –
Conclusions

• Measurement of peripheral blood TCR at the end of treatment is feasible in PTCL using next generation sequencing with a known tumor clonotype.

• Lack of radiographic CR was highly correlated with detectable TCR,

• Detectable TCR was also frequently seen in complete remission by PET/CT.

• Longer follow up is required to:
  – Determine if peripheral blood TCR clonotype at the end of CHOP-based therapy predicts likelihood of relapse
  – Evaluate the dynamics of TCR clonotype during and after completion of treatment
  – Evaluate if ASCT changes presence of minimal residual disease
Acknowledgements

Washington University in St. Louis
- Brad Kahl
- Todd Fehniger
- Nancy Bartlett
- Amanda Cashen
- Armin Ghobadi
- Obi and Malachi Griffith

MSKCC
- Steven Horwitz

DFCI
- Eric Jacobsen

Research Team:
- Anne Fischer
- Katrina Peterson
- Stephanie Myles
- Kim Trinkaus and Andy Ni

Funding Sources
- Lymphoma Research Foundation
- T-cell Leukemia Lymphoma Foundation
- Invivoscribe
- Paul Calabresi K12 Award