T-CELL LYMPHOMAS TREATMENTS AND PITFALLS IN THE ERA OF PRECISION MEDICINE

JASMINE ZAIN, MD
CITY OF HOPE NATIONAL MEDICAL CENTER
• **Relevant Financial Relationship(s)**

  Speakers bureau Seattle Genetics

  Advisory board for Celgene and Spectrum

• **Off Label Usage**

  • Gemcitabine, Lenalidomide, Bortezomib, Bendamsutine, Penotstatin, Mogamulizumab, Alisertib, Rituximab, Duvelisib
Three Big Strategic Questions

- Where Are We Now?
- Where Do we Want to Go?
- How Will We Get There?
WHO CLASSIFICATION OF MATURE TCELL AND NK/T CELL LYMPHOMAS 2016

- Classification based on the most up-to-date knowledge of different clinical subtypes utilizing immunohistochemical, genetic, and molecular tools, as well as the clinical course. Improved diagnostic accuracy
- Needed to develop a management plan for the patient
- Recognition of the heterogeneity of different disease types and complexity of diagnosis
51% had nodal disease
No clear standard of therapy in the US for PTCL
Anthracyclins remain important in upfront therapy at least for nodal disease

Carson et al: Cancer 2017
T-CELL DEVELOPMENT

Central lymphoid tissue

Precursor T-cells

- Bone marrow
  - Progenitor T-cell/Prothymocyte
  - Subcapsular cortical thymocyte
  - Common thymocyte
  - Medullary thymocytes
  - CD4
  - CD8

Thymus

- T lymphoblastic lymphoma/leukemia

Peripheral lymphoid tissue

Peripheral (mature) T- and NK-cells

- Spleen
  - Mucosa
  - Peripheral blood
  - Skin

- γδ T-cell
- Naive T cell
- T-blast
- Effector T-cell
- Memory T-cell
- TFH

- AG (Adaptive Immune System)

Follicle

- FDC

Blood. 2008;112:4384.
PATHOGENESIS OF PTCL

INTRINSIC
- TCR/CD3 signaling
- Notch signaling
- Jak/Stat pathways
- PI3K-AKT pathways
- Epigenetic alterations
- Transcription factors

MICROENVIRONMENT
- Decreased tumor immunogenicity
- Environmental signals
- intra tumoral non-neoplastic cells

VIRUS MEDIATED ONCOGENESIS
- EBV
- HTLV1
SIGNALLING PATHWAYS
VIRUS MEDIATED PATHOGENESIS

**Viral Infection**
- Oral epithelium route

**Transmission**
- Maternal
- Sexual
- Blood

**Infectious cycle**
- Clonal expansion

**TAX expression**
- Low grade
- Aggressive ATLL

**HBZ expression**
- Latency period (decades)

**Pathological Effects**
- Proliferation
- Antiapoptosis
- Immortalization
- Inflammation
- Proliferation
- Genomic instability
- Inflammation
- Invasion and metastasis
- Immune evasion
- Drug resistance
Figure 3(a): GEP defined molecular diagnostic signatures for PTCL

Figure 3(b): Sub groups with in PTCL-NOS

Figure 3(c): Clinical outcome in TBX21 and GATA3 subgroups.
Table 4. Summary of recurrent mutations in nodal peripheral T-cell lymphomas

<table>
<thead>
<tr>
<th>Gene</th>
<th>AITL (%)</th>
<th>PTCL with TFH phenotype (%)</th>
<th>PTCL, NOS (%)</th>
<th>ALK+ ALCL (%)</th>
<th>ALK- ALCL (%)</th>
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</thead>
<tbody>
<tr>
<td>RHOA</td>
<td>53-72</td>
<td>62</td>
<td>18-26</td>
<td>---</td>
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</tr>
<tr>
<td>TET2</td>
<td>33-82</td>
<td>---</td>
<td>20-49</td>
<td>0</td>
<td>0-50</td>
</tr>
<tr>
<td>IDH1</td>
<td>0</td>
<td>---</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>IDH2 R172</td>
<td>13-32</td>
<td>---</td>
<td>&lt;1</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>23-38</td>
<td>---</td>
<td>27,36</td>
<td>---</td>
<td>16</td>
</tr>
</tbody>
</table>
### MUTATIONS ASSOCIATED WITH DERANGED PATHWAYS

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Mutations/Proteins</th>
<th>Effect</th>
<th>VIRUS MEDIATED ONCOGENESIS</th>
<th>THERAPEUTIC IMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCR pathways</td>
<td>Mutations PLCγ1, CARD11, Fusion Protein ITK-SYK</td>
<td>• Reduced immunogenicity (B2M, HLA, HLB mutations) • Altered cell to cell interactions –CD58 and LFA1 mutations</td>
<td>EBV pathogenic in a minority of cases</td>
<td>Activity noted with PI3 kinase inhibitors</td>
</tr>
<tr>
<td>JAK/STAT pathway</td>
<td>Fusion proteins, PCM1-JAK2</td>
<td></td>
<td></td>
<td>CD47 antibodies may be effective therapies</td>
</tr>
<tr>
<td>Notch pathway</td>
<td>Gene loss LEF-1 TCF-1</td>
<td>• Altered response to proapoptotic signals and immune regulation (cFLIP and CD47 overexpression) • TAM mediated immune modulation • PD-L1 overexpression</td>
<td></td>
<td>Check point inhibitors</td>
</tr>
<tr>
<td>PI3K- AKT pathway</td>
<td>Hyperactivation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epigenetics</td>
<td>TET2, DNMT3A mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

**MUTATIONS ASSOCIATED WITH DERANGED PATHWAYS**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCR pathway</td>
<td>Mutations in <em>CD28</em>, <em>VAV1</em>, <em>PLCy-1</em>, <em>CTNNB1</em>, <em>GTF21</em>, <em>PI3K</em> Fusion CTL1-CD28</td>
</tr>
<tr>
<td>Rho A pathway</td>
<td><em>RHOA</em> mutations, fusion <em>VAV1</em>-STAP2</td>
</tr>
<tr>
<td>Epigenetics</td>
<td><em>TET1</em>, <em>IDH2</em>, <em>DNMT3A</em></td>
</tr>
</tbody>
</table>

**MICROENVIRONMENT**

- Reduced immunogenicity (*B2M* mut)
- Increased proliferation signaling (*CD28* mut)
- cFLIP overexpression and altered response to proapoptotic signals
- Cytokine, T reg and endothelial mediated immune modulation,
- Immune check point modulations (*PD-L1* over expression)

**VIRUS MEDIATED ONCOGENESIS**

Intratumoral EBV found in some cases. EBV positive large B cells found in the infiltrate

**THERAPEUTIC IMPLICATIONS**

Epigenetic therapies are effective

- Belinostat - 66% ORR
- Romidepsin – 33-50%
- Ongoing trials of PDL-1 inhibitor
- Rituximab, lenalidomide, cyclosporin, low dose methotrexate can be effective in some cases
### Aik POSITIVE

<table>
<thead>
<tr>
<th>MUTATIONS ASSOCIATED WITH DERANGED PATHWAYS</th>
<th>MICROENVIRONMENT</th>
<th>THERAPEUTIC IMPLICATIONS</th>
</tr>
</thead>
</table>
| TCR and CD30 pathways                      | Activation by alk fusion protein | • cFLIP overexpression and altered response to proapoptotic signals  
• Treg and TAM mediated immune response  
• PD-L1 overexpression | CD30 targeted therapies are effective  
 i.e Brentuximab Vedotin has a RR of 87%  
Alk inhibitors are effective Crizotinib |
| Jak/Stat pathway                           | Loss of gene PTPase |                          |
| Notch pathway                              | Activation by alk fusion proteins |                          |
| AP-1 pathway                               | Activation by alk fusion proteins |                          |

### Aik NEGATIVE

<table>
<thead>
<tr>
<th>MUTATIONS ASSOCIATED WITH DERANGED PATHWAYS</th>
<th>MICROENVIRONMENT</th>
<th>THERAPEUTIC IMPLICATIONS</th>
</tr>
</thead>
</table>
| TCR and CD30 pathways                      | Fusion proteins DUSP22-FRA7H  
Tp63-TBLiXR1 | • cFLIP overexpression and altered response to proapoptotic signals  
• Treg and TAM mediated immune response  
• PD-L1 overexpression | CD30 targeted therapies are effective  
 i.e Brentuximab Vedotin has a RR of 87%  
DUSP-22 mutations associated with improved outcomes  
TP63 mutations associated with a worse outcome |
| Jak/Stat pathway                           | JAK1, STAT3 mut  
Fusion proteins NCOR2-ROS1, NF-kB1-ROS1  
Gene loss PTP-ase |                          |
| Notch pathway                              | Constitutive activation |                          |
| Epigenetics                                | DNMT1 and TET2 mutations |                          |
ALK NEGATIVE ALCL

- ALK+ Systemic
  - 100% ALK rearr.
  - STAT3 key effector

- ALK- Cutaneous
  - Rearrangements: IRF4/DUSP22, TP63, tyrosine kinases,
    Overexpression: ERBB4
  - Mutations: JAK1/STAT3

sALCL ALK+
sALCL ALK-
cALCL

BREAST IMPLANT ASSOCIATED ALCL (bi-ALCL)

Associated with breast implants
Median time to presentation is 8 years
Arise in the seroma associated with the implant
Can be aggressive and have invasive features
ALK NEGATIVE
Remove the seroma and the implant
Radiation or chemotherapy based on extent of disease

PATHOGENESIS

- Malignant cells are derived from Th1/Th17 cells
- Mutations in JAK/STAT signaling, SOCS1 TP53 and DNMT3
- Chronic inflammation is thought to play a role. Bacterial biofilm-gram negative bacteria leading to T cell stimulation via toll like receptors. Preponderance of Ralstonia found in bi-ALCL samples
1. **EATL** - associated with Celiac disease and gluten sensitivity. αβ subtype, invasion of intestinal mucosa and surrounding villous. Derives from small intestinal intraepithelial lymphocytes (innate lymphocytes)

2. **MEITL** - formerly EATL type II. No association with Celiac disease. γδ origin, CD8 and CD56 positive. Surrounding mucosa intact

3. **INDOLENT T CELL LYMPHOPROLIFERATIVE DISORDER OF GIT**. Small mature lymphoid cells that are mostly CD8+. Indolent clinical course but symptomatic

4. **INTESTINAL INVOLVEMENT OF PTCL**
• Presence of high risk HLA alleles associated with CD, serologic evidence of gluten sensitivity and decreased risk of lymphoma in patients on a gluten free diet.

• RCD – precursor to EATL-
  – RCD1—IEL normal phenotype and polyclonal
  – RCD2--- IEL is aberrant, and clonal, IL15

### MUTATIONS ASSOCIATED WITH DERANGED PATHWAYS

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Mutation/Condition</th>
<th>Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCR pathway (EATL-1)</td>
<td>Activation by gluten</td>
<td>• Reduced immunogenicity (loss of HLA class II)</td>
</tr>
<tr>
<td>Jak/Stat pathway</td>
<td>Mutations STAT-5b</td>
<td></td>
</tr>
<tr>
<td>Epigenetics</td>
<td>TET2, SETD2</td>
<td></td>
</tr>
</tbody>
</table>
NK/T CELL LYMPHOMAS- NASAL TYPE

EBV associated, common in Asia, Central and South America as well as Native American populations

Hemophagocytic syndrome -negative prognostic value

- Express MDR associated p-glycoprotein – MTX and asparaginase effective
- EBV driven upregulation of PD-L1

### MUTATIONS ASSOCIATED WITH DERANGED PATHWAYS

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<th>VIRUS MEDIATED ONCOGENESIS</th>
<th>THERAPEUTIC IMPLICATIONS</th>
</tr>
</thead>
</table>
| Jak/Stat pathway                            | Mutations in jak3, STAT3 and STAT5 | • Treg and TAM-mediated immune dysregulation  
• PD-L1 overexpression likely driven by EBV infection | EBV pathogenic  
Immune check point inhibitors are highly effective in relapsed/ref disease |
| Epigenetics                                 | Mutations MLL2, ARID1a, EP300, ASXL1 |                           |                         |
PRINCIPLES OF THERAPY

- Upfront therapy
- Role of high dose therapy and ASCT
- Maintenance
- Relapsed disease – therapeutic options
- Allogeneic stem cell transplant
- CART cell therapy?
OPTIMAL UPFRONT THERAPY

- CHOP based therapies remain the back bone of upfront therapy
- Role of Etoposide if the upfront regimen continues to be debated. Best data is by Schimdt et al. < 60, normal LDH, improved OS. CHOEP followed by high dose ASCT has been used by several groups.
- CHOP+ Romdepsin (Ro-CHOP)- Initial results ORR 78% including 66% CR .randomized phase 3 ongoing
- CHOP+ Belinostat – ORR 86%,67%CR, 19% PR
- CHOP+Pralatrexate- ORR 89%, CR 67%
- CHP+Brentuximab Vedotin- in CD30+ , 3 year OS is 80%, median PFS not reached, No SCT. Await results of randomized study ECHELON 2
- CHOEP+Revilimid-88% ORR and 38% CR. Len maintenance arm
- CHEP+BV- Ongoing . Possible EPCH+BV ??
### EFFECT OF UPFRONT TRANSPLANT IN PTCL

<table>
<thead>
<tr>
<th></th>
<th>ALCL ALK+</th>
<th>ALCL ALK-</th>
<th>PTCL-NOS</th>
<th>AITL</th>
<th>NK/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr OS rate % - Int T cell Project</td>
<td>70</td>
<td>49</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>5 year OS rate % - Abouyabis et al</td>
<td>56 (all subtypes)</td>
<td>34</td>
<td>36</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>3 year OS - Schmitz et al</td>
<td>88.8</td>
<td>63</td>
<td>53</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>5 year OS % - D’Amore et al</td>
<td>Not included</td>
<td>70</td>
<td>47</td>
<td>52</td>
<td>44</td>
</tr>
</tbody>
</table>
ASCT is performed in PTCL

- As consolidation in CR1 (for nodal histologies - PTCL-nos, AITL and ALCL alk-ve) – No randomized control studies to support this approach
- Relapsed setting if no prior auto and if patient has achieved a CR
NEED FOR NEW APPROACHES TO ASCT FOR PTCL

- No consensus on specific conditioning regimen
- Avoid TBI based regimens due to long term toxicity
- BEAM/BEAC are the most common regimens
- Modify conditioning regimen to improve transplant outcomes
- Consider post transplant maintenance
IMPROVING OUTCOMES OF UPFRONT THERAPIES

• Incorporate targeted therapies in upfront regimes

• Non transplant consolidation and maintenance- lenalidomide, BV, other Pralatrexate

• Improve conditioning regimens — Phase I study of the yttrium-\(^{90}\) labeled anti-cd25 monoclonal antibody plus beam for autologous hematopoietic cell transplantation in patients with mature t-cell non-Hodgkin lymphoma, the A-TAC-beam regimen- phase 1 completed.

• Post transplant maintenance strategies- Romidepsin, Pembrolizumab, other targeted agents

BV+CHP; 6 cycles q 3 wk- Median fu is 59.6 months
28 patients > 1% CD30 expression
ORR 100% and CR 88%
5 year OS is 80%, median PFS 52%, No SCT.

Fanale et al abstract 2790, ASH 2017
RELAPSED DISEASE

**Treatment Goals**

- Bridge to transplant - if allogeneic transplant is an option
- Palliation

**Challenges**

- Rare and heterogenous diseases
- Limited interest from pharmaceuticals
- Lack of adequate tumor models to study the disease
<table>
<thead>
<tr>
<th></th>
<th>Pralatrexate</th>
<th>romidepsin</th>
<th>Belinostat</th>
<th>Brentuximab vedotin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>29</td>
<td>25</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>PTCL-nos</strong></td>
<td>31</td>
<td>29</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td><strong>AITL</strong></td>
<td>8</td>
<td>30</td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td><strong>ALCL</strong></td>
<td>29</td>
<td>24</td>
<td>15</td>
<td>86</td>
</tr>
</tbody>
</table>
TARGETING THE PI3K PATHWAY

Duvelisib (IPI-145)
- ORR 53% (8/15) in phase I trial of patients with relapsed/refractory PTCL
- Exhibits in vitro synergy with romidepsin (HDACi approved for PTCL)

- Combinations in TCL
  - Bortezomib
  - Romidepsin

Constitutive activity of pAKT TCL cell lines predicts sensitivity to duvelisib

Duvelisib Clinical Activity in TCL

<table>
<thead>
<tr>
<th></th>
<th>Best Response, n (%)</th>
<th>Median Time to Response, months (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>n</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>CTCL</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>PTCL</td>
<td>16</td>
<td>2 (18.8)</td>
</tr>
</tbody>
</table>

Includes evaluable patients = at least 1 on-treatment response assessment or PD without assessment
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
ORR = CR + PR

- Clinical activity observed across CTCL and PTCL subtypes
  - CTCL: PRs in 4 MF, 1 Sézary syndrome, and 1 MF-LCT
  - PTCL: CRs in 1 EATCL and 1 PTCL NOS
  - PRs in 2AITCL, 2 SPTCL, 1 PTCL NOS, 1 ALC (ALK-negative)

Horwitz et al, Blood in press 2017
Romidepsin+DUV).
- 8 are evaluable for efficacy.
- No dose limiting toxicities.
- Overall response rate (ORR) and median time to response (TTR) were 4/8 (50%) and 51 (range 49-54) days.

(bortezomib+DUV), 15 pts are evaluable for efficacy.
- ORR, complete response (CR), and median time to response (TTR), were 8/15 (53%), 3/15 (20%), and 52 (range 47-57) days.
- 1 experienced DLT (pneumonia), other SAEs included Gr 3 infectious colitis and Gr 4 AST/ALT elevation.
COMBINATION STRATEGIES

**Parallel Phase I studies of duvelisib plus romidepsin or bortezomib**

**3+3 Design with Dose Expansion at MTD**

- **Arm A**: Duvelisib with Romidepsin
- **Arm B**: Duvelisib with Bortezomib

**ROMIDEPSIN+DUV**
- 8 evaluable for efficacy.
- No DLT
- ORR - 50%
- TTR 51 days (49-54)

**Bortezomib+DUV**
- 15 evaluable for efficacy
- 1 experienced DLT (pneumonia)
- ORR-53%, CR 20%
- TTR 52 days (47-57)
## DOUBLETS AND TRIPLETS

<table>
<thead>
<tr>
<th>Combination</th>
<th>n</th>
<th>Results</th>
<th>Main toxicity/DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pralatrexate + Romidepsin</td>
<td>14</td>
<td>ORR 71%</td>
<td>Mucositis, thrombocytopenia</td>
</tr>
<tr>
<td>Duvelisib + Romi</td>
<td></td>
<td>ORR 50%</td>
<td></td>
</tr>
<tr>
<td>Duvelisib + Boretezomib</td>
<td></td>
<td>ORR 53%</td>
<td></td>
</tr>
<tr>
<td>Alisertib + Romidepsin</td>
<td>3</td>
<td>ORR 25%</td>
<td>Hematologic, fatigue, infection</td>
</tr>
<tr>
<td>Chidamide + thalidomide + Cyclophosphamie</td>
<td>12</td>
<td>ORR 83%, CR 41%, PR 33%</td>
<td></td>
</tr>
<tr>
<td>Romidepsin + Azacitidine</td>
<td>5</td>
<td>ORR 80%, CR 40%</td>
<td>Neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Lenalidomide + vorinostat</td>
<td>8</td>
<td>ORR 25%</td>
<td>hematologic</td>
</tr>
<tr>
<td>Romidepsin plus lenalidomide</td>
<td>11</td>
<td>ORR 50%</td>
<td>Neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Romidepsin + lenalidomide + carfilzomab</td>
<td>16</td>
<td>ORR 45%, CR 36%, PR 9%</td>
<td>Hematologic, DVT, infection</td>
</tr>
<tr>
<td>Panobinostat + boretezomib</td>
<td>23</td>
<td>ORR 43%</td>
<td>Thrombocytopenia, diarrhea, neuropathy</td>
</tr>
</tbody>
</table>
### Novel Targeted Therapies

<table>
<thead>
<tr>
<th>PI3 KINASE</th>
<th>R/R PTCL</th>
<th>Main toxicity</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP6530-γ/γ inhibitor (tenalisib)</td>
<td>Phase 1 completed 800mg bid</td>
<td>ORR 45%</td>
<td>Mainly elevated AST and ALT</td>
</tr>
<tr>
<td>Jak/Stat inhibitor-Ruxolitinib</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EZH2 inhibitor-Tazemetostat – Histone modification</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCR4 - Magamulizumab</td>
<td>Approved in Japan for ATLL and PTCL</td>
<td>Phase 3 completed for ATLL and CTCL</td>
<td>Skin rashes</td>
</tr>
</tbody>
</table>
ALLOGENEIC STEM CELL TRANSPLANT IN T-CELL NHL

A

5-year OS: 57%
5-year EFS: 53%

Time (months)
Probability

B

AIITL (n = 11): 80%
PTCL (n = 27): 63%
AAlCL (n = 27): 55%
Other (n = 12): 33%

Le Gouill et al 2008

OVERALL SURVIVAL

Time (Year) from Date of Transplant
Survival Probability

DISEASE FREE SURVIVAL

Time (Year) from Date of Transplant
Survival Probability

Zain et al 2011
Update of allogenic stem cell transplant in PTCL

- Large US bases multicenter retrospective study
- 301 patients
- 2 yr OS 61%, PFS 48.9%
- TRM at 1 year is 12.8%
- Dz status at the time of transplant was associated with PFS

<table>
<thead>
<tr>
<th>Disease subtype</th>
<th>2 yr PFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL-Nos 82</td>
<td>56.48 (44-69)</td>
</tr>
<tr>
<td>AITL 50</td>
<td>60.3% (44-87)</td>
</tr>
<tr>
<td>NK/t 35</td>
<td>39.6% (23-58)</td>
</tr>
<tr>
<td>HSTCL 29</td>
<td>46.07 (26-84)</td>
</tr>
<tr>
<td>ALK+ ALCL 13</td>
<td>36.9 (12-51)</td>
</tr>
<tr>
<td>Alk (unk) ALCL 12</td>
<td>36.9 (12-51)</td>
</tr>
<tr>
<td>ALK-ve ALCL 10</td>
<td>25 (4-54)</td>
</tr>
<tr>
<td>EATL 5</td>
<td>40% (7-28)</td>
</tr>
</tbody>
</table>

Neha et al. TCLF 2017
MAJOR TURNING POINT IN NK/T CELL LYMPHOMAS

High expression of PD1 seen in NK-T cell lymphomas driven by EBV
High response rates to PD1 blockade in RR disease
Disappearance of EBV from responding tumors
Treatment was safe even in post allogenic transplant patients

Kwong et al: Blood 2017
Designing CAR-T cells for PTCL

TARGETING DILEMMAS

- Fratericide- shared expression of target antigens between T effector cells and Tcell malignancies results in fratricide, or self-killing, of CAR-T cells

- Harvesting adequate number of autologous T cells without contamination with tumor

CD-30 CAR-

CD5 – CAR targeting, spare normal T cells (Mamonkin et al Blood 2005)

CD7 genomic disruptions with CD7 CAR to stop fratricide (Brenner et al ASH 2016)

Targeting CD4 or CD8 depending on tumor sub type (Pinz et al Leukemia 2016)

• CD7 is expressed in T cell malignancies

• CD7 is expressed by normal T cells including CAR-T cells

• Deletion of CD7 and TCR alpha chain (TRAC) by CRISPR/Cas 9 from CAR-T

• Efficient targeting of malignant T cells without fratricide. Efficient expansion of cytotoxic CD8 cells

• Blockage of T cell mediated signaling permits the use of allogeneic T cells without GVHD
Targeting the T cell receptor β-chain constant immunotherapy of T cell malignancies

Paul M Maciocia¹, Patrycja A Wawrzyniecka¹, Brian Philip¹, Ida Ricciardelli², Ayse U Aka Shimobi C Onuoha³, Mateusz Legut³, David K Cole¹, Andrew K Sewell⁴, Giuseppe Grifoni⁵, Miguel A Piris⁶, Karl S Peggs¹, David C Linch¹, Teresa Marafioti¹ & Martin A Pule¹,³,⁷

Table 1 Summary data of TRBC1 expression in primary samples of TCR⁺ malignancies

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>TRBC1⁺ (%)</th>
<th>TRBC1⁻</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic large cell lymphoma⁸</td>
<td>5 (42)</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Angioimmunoblastic T cell lymphoma⁸</td>
<td>2 (40)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral T cell lymphoma, NOS⁸</td>
<td>8 (44)</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>NKT cell lymphoma⁹</td>
<td>0 (0)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sézary syndrome⁸</td>
<td>1 (33)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>T acute lymphoblastic leukemia/lymphoma⁹</td>
<td>2 (25)</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Adult T cell leukemia/lymphoma⁹</td>
<td>2 (100)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>T prolymphocytic leukemia⁹</td>
<td>1 (33)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>T large granular leukemia⁹</td>
<td>1 (25)</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

![Diagram of TRBC1 and TRBC2 expression in T cells](image)

Anti-TRBC1 CAR T cells are specific and effective in mouse models of disseminated T cell malignancy
- **Use of NK cells** for CD5 targeted CAR expression - NK cells do not express CD5

- Generate CD5 negative T cells for CD5 CAR expression using CRISPR-Cas9 to knockout CD5 expression
CITY OF HOPE ALGORITHM FOR TREATING PTCL/EXCLUDING NK/T CELL LYMPHOMA

CLINICAL TRIAL
CHOEP X6
CHOP X6 IF ELDERLY
ICE/IVAC FOR HSTCL
IVE+MTX FOR EATL

CR

PR/SD/POD

CLINICAL TRIAL
AUTOLOGOUS STEM CELL TRANSPLANT
ALLOGENEIC TRANSPLANT FOR HSTCL, GAMMAL DELTA TCL, AGGRESSIVE

RELAPSE/PROGRESSION

CR/PR

POD

CLINICAL TRIAL
ICE- TRANSPLANT CANDIDATE
HDACI- AITL
BRENTUXIMAB VEDOTIN- ALCCL, CD30 POSITIVE
PRALATREXATE

ALLOGENEIC STEM CELL TRANSPLANT
OBSERVATION

PROGRESSION

CLINICAL TRIAL SECOND LINE THERAPY
CONCLUSIONS

- PTCL – not a single disease
- Treatments are now being defined for specific subtypes
- Current upfront treatments are not curative
- Improved molecular pathology will define specific subtypes that can benefit from unique therapeutic approaches
- Single agents have limited efficacy and combination therapies will likely improve outcome
- Continued need for collaboration and well designed clinical trials to make progress
“I go home today. They cured me using this new miracle drug. I’m afraid it’ll be years before it’s approved for humans.”