Clinical Updates and Issues: T-Cell Lymphomas

Susan McCall, ANP-BC, AOCNP
Memorial Sloan Kettering Cancer Center

Faculty Biography

Susan McCall, ANP-BC, AOCNP is a Research Nurse Practitioner in the Lymphoma Service at Memorial Sloan Kettering Cancer Center in New York, New York.

Ms. McCall received her Bachelors of Science in Nursing and Masters of Science in Nursing from the University of Pennsylvania School of Nursing in Philadelphia, Pennsylvania.

As a nurse practitioner on Memorial Sloan Kettering’s Lymphoma Service, Ms. McCall works with adults undergoing treatment for Hodgkin and non-Hodgkin lymphoma. In collaboration with physicians, she coordinates the care required for patients who will be receiving high-dose chemotherapy and autologous stem cell transplants and cares for patients during the post-transplant period.

Ms. McCall is a member of several professional societies including The Oncology Nursing Society, Nurse Practitioner Association of New York, and Sigma Theta Tau International.
Lymphoma 101

- Of all cancers, lymphomas represent 4.9% cases in US
  - 81,000 new cases in US in 2015
  - Most common hematologic malignancy
- Neoplasms arising from cells of the lymphoid lineage
- Based on pathologic and clinical features
  - REAL classification
  - NHL v. HL
  - Aggressive v. indolent
- Risk factors not fully understood
- There are >70 types of lymphoma
  - Majority are NHL

Peripheral T-Cell Lymphomas

- Represent ~10-15% of all cases of NHL
- Broadly classified as systemic or cutaneous
  - Heterogenous group of lymphomas
  - Treatment plan depends on extent of involvement
- Typically aggressive
- Making the diagnosis can be challenging
- 5 yr OS ranges, depending on risk factors
  - 6-74%

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**T-Cell neoplasms**

"**Systemic T-cell Lymphoma**"
- Peripheral T-cell lymphoma NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic Large Cell-ALK-1 negative
- Anaplastic Large Cell-ALK-1 positive
- Enteropathy-type intestinal lymphoma
- Extranodal NK/T-cell lymphoma-nasal
- Adult T-cell leukemia/lymphoma (HTLV-1)
- Hepatosplenic T-cell lymphoma (may be derived from an immature T-cell)

"**CTCL**"
- Mycosis Fungoides
- Sezary syndrome
- Subcutaneous panniculitis-like
- Primary cutaneous ALCCL
- Lymphomatoid papulosis
- Primary cutaneous small/medium CD4+
- T-cell lymphoma
- Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

Cancers of Immature T-cells
- ALL (Precursor T cell)
- lymphoblastic lymphoma/leukemia

**Distribution of subtypes among 1,314 cases**

- Peripheral T-cell Lymphoma: 25.9%
- Angioimmunoblastic: 9.6%
- Natural killer/T-cell lymphoma: 6.6%
- Adult T-cell leukemia/lymphoma: 10.4%
- Anaplastic large cell lymphoma, ALK+: 4.7%
- Anaplastic large cell lymphoma, ALK-: 6.6%
- Enteropathy-type T-cell: 1.7%
- Primary cutaneous ALCCL: 1.4%
- Hepatosplenic T-cell: 0.9%
- Subcutaneous panniculitis-like: 12.2%
- Unclassifiable PTCL: 2.5%
- Other disorders: 4.7%

International T-Cell Lymphoma Project JCO 2008;26:4124-4130
Making that diagnosis...

- **Biopsy** is the golden ticket
  - More than a FNA
  - Discuss clinical context with pathologist
  - Expert review is essential
  - Agreement is not universal

- **Morphology**
  - Small, medium, or large cells
  - Cytoplasm/nucleoli

- **Phenotype**
  - CD2, CD3, CD4, CD5, CD7, CD8 as pan T markers
  - EBV
  - ALK-1
  - Proliferation index

- **Genotype**
  - Looking for T-cell receptor (TCR) chain rearrangement

- **Objective quantification**
  - mSWAT
  - PET/CT
  - Bone marrow biopsy
  - HTLV-1 serology

- **International Prognostic Index (for NHL)**
  - Age
  - LDH
  - Performance status
  - Ann Arbor Stage
  - # extranodal sites

- **Prognostic Index for PTCL-U (PIT)**
  - Age
  - LDH
  - Performance status
  - BM involvement

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Pathology example

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Cutaneous T-Cell Lymphomas

- Mycosis fungoides (MF) and Sezary syndrome (SS) are most common subtypes
- Accumulation of atypical memory T cells in epidermis and dermis
- Median OS 24 years\(^1\)
  - 140 advanced MF/SS patients with median OS 2.47 years\(^2\)
  - Presence of patches, plaques, and/or LN correlate with prognosis

CTCL: skin lesions

Mycosis Fungoides


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**MF/SS Therapy: Skin-directed**

<table>
<thead>
<tr>
<th>Limited</th>
<th>Generalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Steroids</td>
<td>• Steroids</td>
</tr>
<tr>
<td>• Topical chemotherapy (mechlorethamine)</td>
<td>• Topical chemotherapy (mechlorethamine)</td>
</tr>
<tr>
<td>• Local radiation</td>
<td>• Phototherapy (UVB/PUVA)</td>
</tr>
<tr>
<td>• Topical retinoids (bexarotene)</td>
<td>• Total skin electron beam therapy (TSEBT)</td>
</tr>
<tr>
<td>• Phototherapy (UVB/PUVA)</td>
<td>• Topical tacrolimus</td>
</tr>
<tr>
<td>• Topical immune response modifiers (imiquimod, resiquimod)</td>
<td></td>
</tr>
</tbody>
</table>

**MF/SS: Systemic Therapy**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Biologic response modifiers</td>
<td>• Targeted therapy</td>
</tr>
<tr>
<td>– interferon (IFN-α2a)</td>
<td>– brentuximab vedotin</td>
</tr>
<tr>
<td>– Oral retinoids (isotretinoin, bexarotene)</td>
<td>– denileukin diftitox</td>
</tr>
<tr>
<td>• HDAC inhibitors</td>
<td>• Chemotherapy</td>
</tr>
<tr>
<td>– Vorinostat</td>
<td>– gemcitabine</td>
</tr>
<tr>
<td>– romidepsin</td>
<td>– liposomal doxorubicin</td>
</tr>
<tr>
<td>• Extracorporeal photopheresis (ECP)</td>
<td>– pralatrexate</td>
</tr>
<tr>
<td>• Methotrexate</td>
<td>– chlorambucil</td>
</tr>
<tr>
<td>• Steroids</td>
<td>– pentostatin</td>
</tr>
<tr>
<td></td>
<td>– Bortezomib</td>
</tr>
<tr>
<td></td>
<td>• Allo transplant?</td>
</tr>
</tbody>
</table>
### MF/SS: newer agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>N</th>
<th>ORR</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>Anti-CD52 MoAb</td>
<td>various</td>
<td>86-100%</td>
<td>several</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>HDAC inhibitor</td>
<td>139</td>
<td>17.3%</td>
<td>Duvic et al, 2012</td>
</tr>
<tr>
<td>Belinostat</td>
<td>HDAC inhibitor</td>
<td>29 CTCL (24 MF/SS)</td>
<td>13.8%</td>
<td>Foss et al, 2014</td>
</tr>
<tr>
<td>Forodesine</td>
<td>PNP inhibitor</td>
<td>101</td>
<td>11%</td>
<td>Dummer et al, 2014</td>
</tr>
<tr>
<td>Mogamulizumab</td>
<td>Anti-CCR4 MoAb</td>
<td>38</td>
<td>36.8% (SS 47.1%, MF 28.6%)</td>
<td>Duvic, et al 2015</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>immunomodulatory</td>
<td>32</td>
<td>28%</td>
<td>Querfeld, et al 2014</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>Alkylating agent</td>
<td>3</td>
<td>67%</td>
<td>Zaja, et al 2013</td>
</tr>
</tbody>
</table>

### CTCL treatment map

### Agents in the pipeline

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>NCT identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-3475 (Pembrolizumab)</td>
<td>PD-1 inhibitor</td>
<td>02243579</td>
</tr>
<tr>
<td>SGX301 (Synthetic Hypericin)</td>
<td>topical photosensitizing agent</td>
<td>02448381</td>
</tr>
<tr>
<td>NM-IL-12 (rHuIL-12) + TSEBT</td>
<td>immunotherapy</td>
<td>02542124</td>
</tr>
<tr>
<td>MRG-106</td>
<td>miR-155 inhibitor</td>
<td>02580552</td>
</tr>
<tr>
<td>Intratumoral IL12 Plasmid</td>
<td>Intratumoral immunotherapy</td>
<td>01579318</td>
</tr>
</tbody>
</table>

### Systemic T-Cell Lymphomas
Systemic T-Cell lymphomas

- Peripheral T-Cell lymphoma, not otherwise specified (PTCL, NOS) is the most common subtype
  - Median age of onset is 57 yrs
- Other common subtypes:
  - Angioimmunoblastic T-Cell lymphoma (AITL)
  - Natural killer/T-cell, nasal type (NK/T)
  - Anaplastic large cell lymphoma (ALCL)
    - CD30+ T-cell neoplasm
    - ALK pos v. ALK neg


Swedish Registry: Population- based PTCL cohort

Frontline treatment

- Most histologies:
  - Clinical trial
  - Chemotherapy (CHOP-like)
    - 4-6 cycles
    - +/- involved site radiotherapy (ISRT)
  - If complete response
    - Clinical trial
    - Consolidative high dose therapy + autoSCT (if eligible)
    - There are trials using maintenance therapy after autoSCT
- ALCL, ALK +
  - Chemotherapy (CHOP-like)
  - If early stage, add ISRT

CHOP: The regimen of choice

<table>
<thead>
<tr>
<th>Citation</th>
<th>Regimen</th>
<th>Population</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>PFS/EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savage, et al.</td>
<td>CHOP (retrospective)</td>
<td>PTCL-NOS</td>
<td>117</td>
<td>84%</td>
<td>64%</td>
<td>29% (5 yr)</td>
</tr>
<tr>
<td>Reimer, et al.</td>
<td>CHOP → ASCT</td>
<td>PTCL/AITL/ALCL</td>
<td>83</td>
<td>79%</td>
<td>39%</td>
<td>36% (3 yr), with ASCT</td>
</tr>
<tr>
<td>Simon, et al.</td>
<td>CHOP v. VIP-rABVD</td>
<td>PTCL/AITL/ALCL</td>
<td>43</td>
<td>62%</td>
<td>39%</td>
<td>42% (2yr)</td>
</tr>
</tbody>
</table>

**CHOP-based therapy for Peripheral T/NK Lymphomas**

**Always**
- Anaplastic Large Cell-ALK-1 positive

**Sometimes**
- Peripheral T-cell lymphoma NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic Large Cell-ALK-1 negative
- Enteropathy-type intestinal lymphoma
- Subcutaneous panniculitis-like T-cell

**Never**
- Mycosis Fungoides
- Sezary syndrome
- Primary cutaneous CD30+ disorders
  - Primary cutaneous Anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- T-cell large granular lymphocytic
- Extranodal NK/T-cell lymphoma-nasal
- Hepatosplenic T-cell lymphoma
- NK/T-cell leukemia/lymphoma
- Adult T-cell leukemia/lymphoma
- T-cell prolymphocytic leukemia

**Improving upon CHOP**

**Swedish Lymphoma Registry**

<table>
<thead>
<tr>
<th></th>
<th>CHOP (n=145)</th>
<th>CHOEP (n=107)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>70%</td>
<td>81%</td>
<td>0.052</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>30%</td>
<td>47%</td>
<td>ns</td>
</tr>
<tr>
<td>5 yr PFS</td>
<td>23%</td>
<td>40%</td>
<td>ns*</td>
</tr>
</tbody>
</table>

In patients 60 or younger, addition of etoposide was associated with improved PFS (HR 0.49, p=0.008)

### Additional attempts to improve CHOP

<table>
<thead>
<tr>
<th>Citation</th>
<th>Regimen</th>
<th>N</th>
<th>%ORR / CR</th>
<th>PFS / EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallamini A, et al.</td>
<td>Alectuzumab + CHOP</td>
<td>24</td>
<td>75 / 71</td>
<td>48% (2 yr)</td>
</tr>
<tr>
<td>Kim SJ, et al.</td>
<td>Bortezomib + CHOP</td>
<td>46</td>
<td>76 / 65</td>
<td>35% (PTCL 31%)</td>
</tr>
<tr>
<td>Simon A, et al.</td>
<td>VIP-rABVD</td>
<td>43</td>
<td>58 / 44</td>
<td>45% (2 yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ND than CHOP</td>
</tr>
<tr>
<td>Dupuis J, et al.</td>
<td>Ro-CHOP</td>
<td>18</td>
<td>78 / 66</td>
<td>57% (12 mo)</td>
</tr>
<tr>
<td>Mahadevan D, et al.</td>
<td>PEGS</td>
<td>20</td>
<td>39 / 24</td>
<td>14% (2 yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In untreated</td>
</tr>
<tr>
<td>Advani, RH, et al.</td>
<td>CEOP + PDX</td>
<td>33</td>
<td>70 / 52</td>
<td>48% (1 yr), 39% (2yr)</td>
</tr>
</tbody>
</table>

Brentuximab vedotin plus CHOP/CHP for CD30+ PTCL – Phase I

<table>
<thead>
<tr>
<th>Treatment schema</th>
<th>Patients</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sequential treatment:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BV x2 -&gt; CHOP x6 -&gt; BV x8</td>
<td>13 ALCL</td>
<td>85%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Combination treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BV plus CHP x6 -&gt; BV x 10</td>
<td>19 ALCL 7 non-ALCL</td>
<td>100%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Notable grade ≥3 adverse events in combination arm:
- Febrile neutropenia 31%
- Peripheral sensory neuropathy 8%
- Cardiac failure 8%

Fanale et al. JCO 2014;32:3137-3143

Studies building upon CHOP in PTCL

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT</th>
<th>Study Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECHELON-2</td>
<td>01777152</td>
<td>A Comparison of Brentuximab Vedotin and CHP With Standard-of-care CHOP in the Treatment of Patients With CD30-positive Mature T-cell Lymphomas</td>
</tr>
<tr>
<td>Ro-CHOP</td>
<td>01796002</td>
<td>Phase 3 Multi-center Randomized Study to Compare Efficacy and Safety of Romidepsin CHOP (Ro-CHOP) Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma</td>
</tr>
<tr>
<td>A-CHOP-14</td>
<td>00725231</td>
<td>Immunotherapy in Peripheral T Cell Lymphoma - the Role of Alemtuzumab in Addition to Dose Dense CHOP</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>01420679</td>
<td>Study of Pralatrexate Versus Observation Following CHOP-based Chemotherapy in Previously Undiagnosed Peripheral T-cell Lymphoma Patients</td>
</tr>
<tr>
<td>RADCHOP</td>
<td>01198665</td>
<td>RAD001 (everolimus) Combined With CHOP in Newly Diagnosed Peripheral T-cell Lymphomas</td>
</tr>
</tbody>
</table>
Upfront consolidation with autologous transplant

Swedish Lymphoma Registry¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Auto-SCT ITT (n=128)</th>
<th>Non-auto-SCT (n=124)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year PFS (%)</td>
<td>41</td>
<td>20</td>
<td>0.002</td>
</tr>
<tr>
<td>5 year OS (%)</td>
<td>48</td>
<td>26</td>
<td>0.004</td>
</tr>
</tbody>
</table>

MSKCC series – PTCL patients with intent for front-line transplant²

<table>
<thead>
<tr>
<th>Patients (n=65)</th>
<th>4 year PFS</th>
<th>4 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All: 32 PTCL-NOS, 21AITL, 12 ALK-neg ALCL</td>
<td>38%</td>
<td>52%</td>
</tr>
<tr>
<td>Auto-SCT (n=34)</td>
<td>55%</td>
<td>66%</td>
</tr>
<tr>
<td>Allo-SCT (n=5)</td>
<td>30%</td>
<td>67%</td>
</tr>
<tr>
<td>No transplant</td>
<td>16.5%</td>
<td>27%</td>
</tr>
</tbody>
</table>


Prospective phase II study: Up-front auto-SCT

CHOP x 4-6
N=83
ORR 79%, CR 39%

BEAM or ESHAP
N=65 (78%)

HDT (Cy/TBI) and auto-SCT
n=55 (66%)

3 yr OS 48%
3 yr PFS 36%

Reimer et al. JCO 2009;27:106-113
CHOEP followed by auto-SCT - Nordic Lymphoma Group Trial 1

CHO(E)P-14 x 6
n=160
ORR 82%
CR 51%

BEAM or BEAC
auto-SCT
n=115 (72%)

ORR 82%
CR 51%

5 yr OS 51%
5 yr PFS 44%

d'Amore et al. JCO 2012;30:3093-3099

Relapsed/Refractory PTCL

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Treatment Strategy for Relapsed/Refractory Disease

Relapsed PTCL (PTCL-NOS, AITL, ALCL)

- Transplantation soon (Donor known, patient eligible)
  - Combination chemotherapy (ICE, other combinations)
  - Allogeneic stem-cell transplantation

- Transplantation unclear (Donor unknown, patient may or may not be eligible)
  - Inadequate response
  - Donor available

- Transplantation never (Physician or patient determines patient ineligible)
  - Clinical trial or single agent

CIBMTR: PFS excluding pt in CR1 (Most patients ALCL)

- CIBMTR
- Stanford

Stanford

CIBMTR, Center for International Blood and Marrow Transplant Research
Smith S, et al. JCO 2013;31:1922-1927
Allogeneic stem cell transplant

- Data on allo-SCT is limited
- OS curves reach a plateau at > 50%
- Small numbers raise questions about patient selection and general applicability

Single-agent activity in Relapsed/Refractory PTCL

<table>
<thead>
<tr>
<th>Agent</th>
<th>n</th>
<th>ORR</th>
<th>CR</th>
<th>DOR (mo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romidepsin</td>
<td>130</td>
<td>25%</td>
<td>15%</td>
<td>17</td>
<td>Coiffer, et al. JCO 2012</td>
</tr>
<tr>
<td>Belinostat</td>
<td>129</td>
<td>26%</td>
<td>10%</td>
<td>8.3</td>
<td>O’Connor, et al. JCO 2015</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>111</td>
<td>29%</td>
<td>13%</td>
<td>10.5</td>
<td>O’Connor, et al. JCO 2011</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>60</td>
<td>50%</td>
<td>28%</td>
<td>3.5</td>
<td>Damaj, et al. JCO 2013</td>
</tr>
<tr>
<td>Brentuximab vedotin (ALCL)</td>
<td>58</td>
<td>86%</td>
<td>57%</td>
<td>12.6</td>
<td>Pro, et al. JCO 2012</td>
</tr>
<tr>
<td>Brentuximab (non-ALCL)</td>
<td>35</td>
<td>41%</td>
<td>23%</td>
<td>7.6</td>
<td>Horwitz, et al. Blood 2014</td>
</tr>
</tbody>
</table>
### Recent promising studies in PTCL

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>N</th>
<th>ORR</th>
<th>N in CR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duvelisib</td>
<td>PI3-kinase, γδ</td>
<td>33</td>
<td>47% (PTCL)</td>
<td>2</td>
<td>Horwitz, et al. ASH 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38% (CTCL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR</td>
<td>16</td>
<td>44%</td>
<td>1</td>
<td>Witzig, et al. Blood 2015</td>
</tr>
<tr>
<td>Alisertib</td>
<td>Aurora kinase</td>
<td>37</td>
<td>30% (PTCL)</td>
<td>2</td>
<td>Barr, et al. JCO 2015</td>
</tr>
<tr>
<td>Romidepsin/Lenalidomide</td>
<td>HDAC/immune-modulatory</td>
<td>21</td>
<td>53% (PTCL/CTCL)</td>
<td>2</td>
<td>Mehta-Shah, et al. ASCO 2015</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multikinase inhibitor</td>
<td>12</td>
<td>42% (PTCL/CTCL)</td>
<td>4</td>
<td>Gibson, et al 2014</td>
</tr>
<tr>
<td>Plitidepsin</td>
<td>Cyclic depsipeptide</td>
<td>29</td>
<td>20.7% (PTCL)</td>
<td>2</td>
<td>Ribrag, et al 2013</td>
</tr>
</tbody>
</table>

The Future....
PTCL: Gene expression signatures - towards more precise classification

- 372 PTCL cases analyzed
- 37% PTCL-NOS re-classified based upon gene-expression signature

PTCL-NOS molecular subgroups

**GATA3**
- 33% of cases
- TH2 Transcription factor
- 5 yr OS = 19%
- Poor clinical outcome
- PI3K and mTOR pathways

**TBX21**
- 49% of cases
- TH1 Transcription factor
- Plasma cell-like gene signature (good outcome)
- 5 yr OS = 38%
- Cytotoxic cell-like gene signature (poor outcome)
- NFκB and STAT3
- 18% unclassifiable
Distinct molecular signatures

ALK(−)ALCL is molecularly distinct from PTCL-NOS and ALK(+)ALCL.

Iqbal et al. Blood 2014;123:2915-2923

ALK negative ALCL: Prognostic impact of DUSP22 and TP63 rearrangements

**SYK as a target in PTCL**

- 94% cases PTCL over express SYK
- 38% with ITK-SYK rearrangement
- Inhibition of SYK = inhibition of proliferation + cell death


**Pathways and potential targets in PTCL**

T-cell lymphoma - Summary

Looking Back
• **Classification** - morphologically based, leaving many cases un-classified
• **Up-front transplant** - still the standard of care, if possible for your patient disease
• **Relapsed/Refractory disease** - choice of treatment mostly empiric

Looking Ahead
• **Genetic-based classification** – better precision will ultimately translate into more specific treatments
• **New targets** - Correlative studies will inform future combination studies through identification of predictors of response and resistance

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