University of Washington Comprehensive
Hematology Oncology Board Review Course

# Non-Hodgkin Lymphoma:
# T-cell Lymphomas

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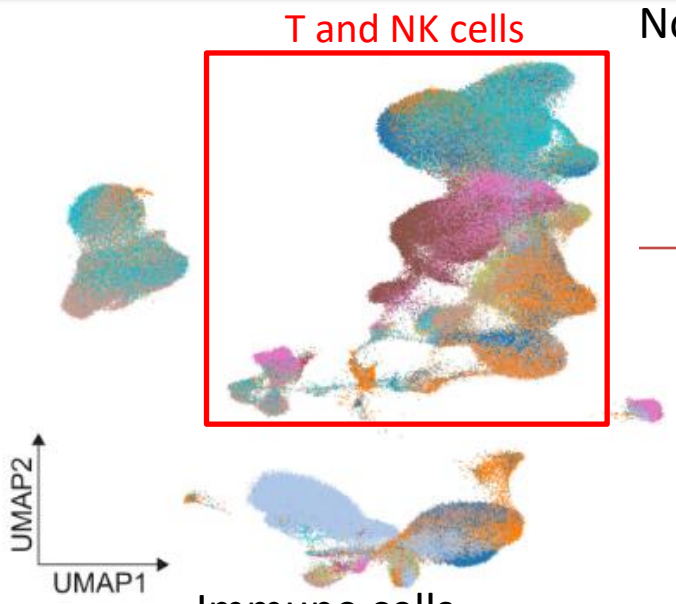
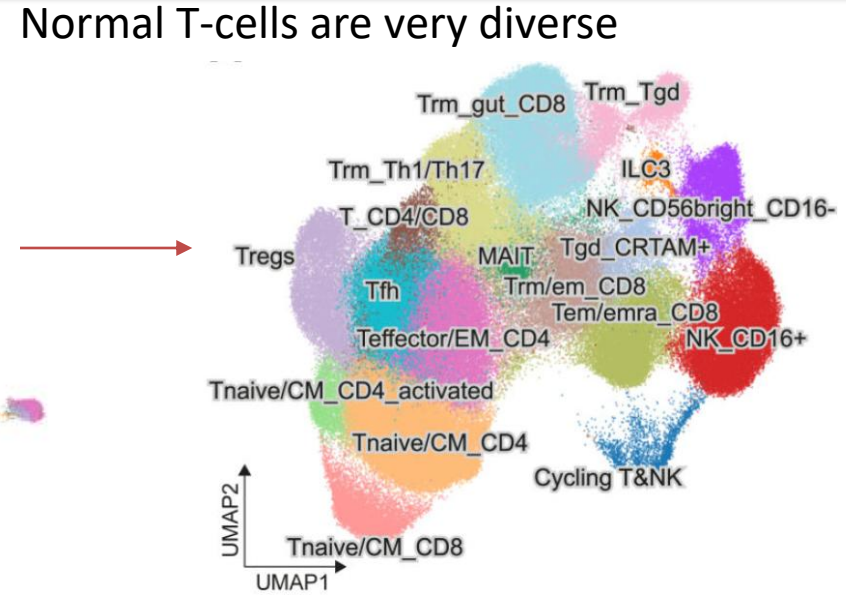
# T-cell Lymphomas

- 10% of non-Hodgkins lymphoma
- 39 subtypes (2022 WHO)

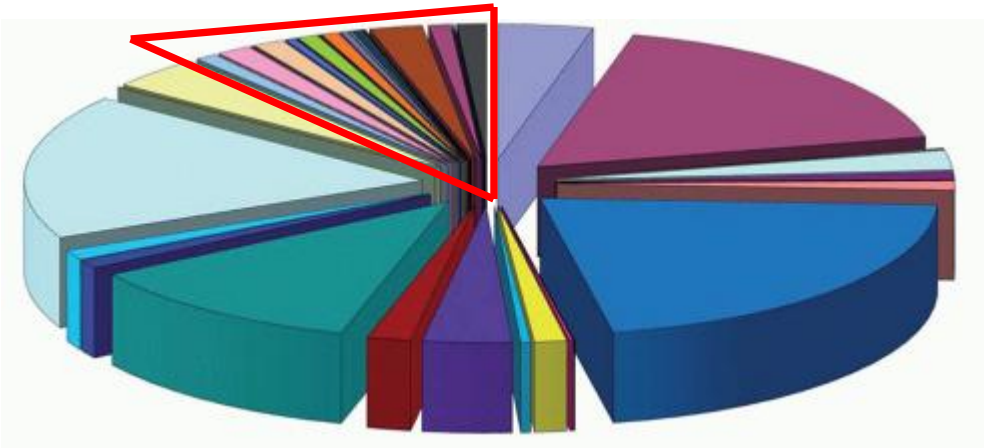
- We will cover 10 types

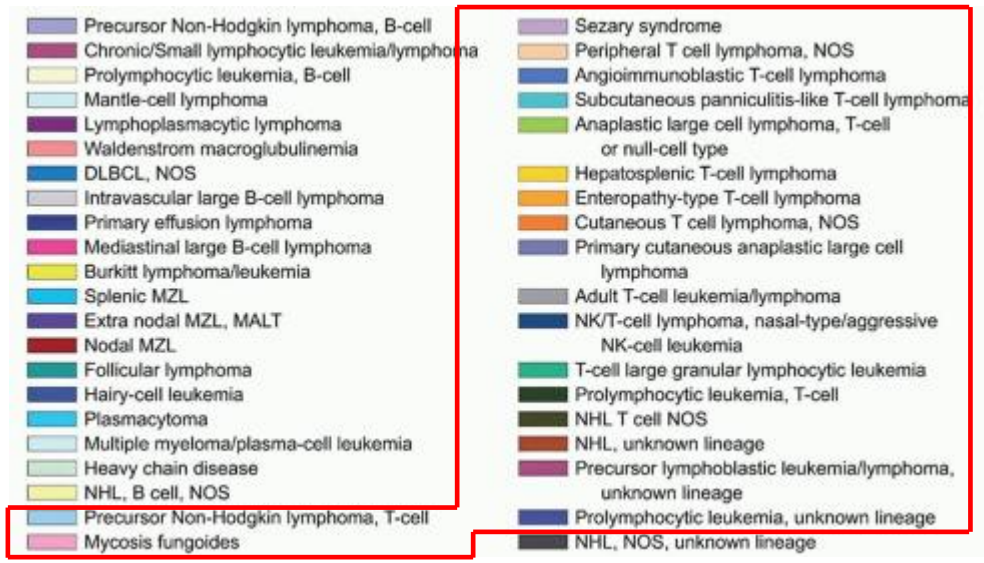



Dominguez Conde et al. Science 2022

Non-Hodgkins lymphoma incidence





# Outline – High yield and Board focus

## Diagnostic

- Clinical presentation
- Key diagnostic tests
- Key genomics

## Treatment

- Frontline treatment selection
- Relapsed/refractory
  - Mechanism of action
  - Key toxicities

## Important Pearls for Management

## Common nodal types

- ALCL
  - ALK+
  - ALK-neg
  - Breast Implant
- Follicular helper T-cell
  - AITL
- PTCL-NOS

## Rarer subtypes

- NK/T cell lymphoma
- Adult T-cell leukemia/lymphoma
- T-large granular lymphocytic leukemia
- T-prolymphocytic leukemia
- Hepatosplenic gamma delta T-cell lymphoma
- Intestinal lymphomas
- Cutaneous T-cell lymphomas

# Nodal T-cell lymphomas

## 1. ALCL

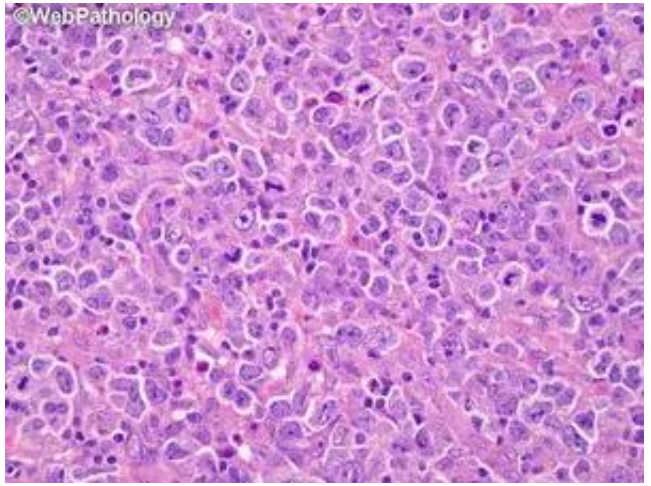
- ALK+
- ALK-negative

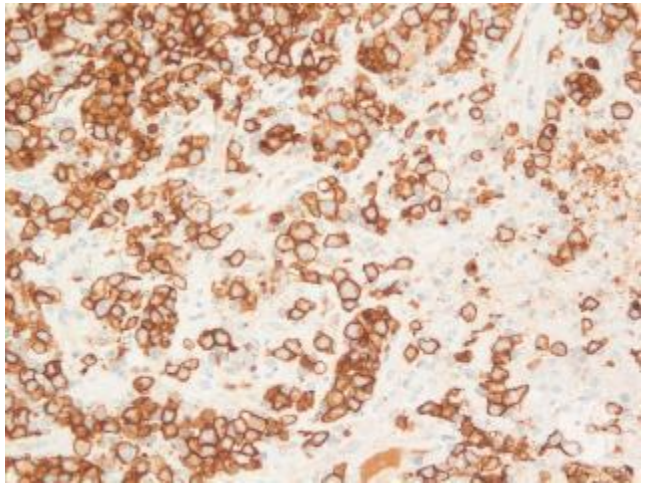
## 2. Follicular helper T-cell

## 3. PTCL-NOS

# Anaplastic Large Cell Lymphoma

- Diffuse, large cells with T-cell marker (CD2, CD4, CD5)
  - Often negative for CD3 and TCR
- Clinically aggressive, often extranodal. High SUV
- Diffusely positive **CD30**. Must distinguish from Hodgkins



CD30

| ALK positive | ALK negative | Breast implant |
|---|---|---|
| 5 year PFS: 87% | 49% | >80% Early stage<br>~50% Advanced |

*Textured surface*
Breast implant capsule

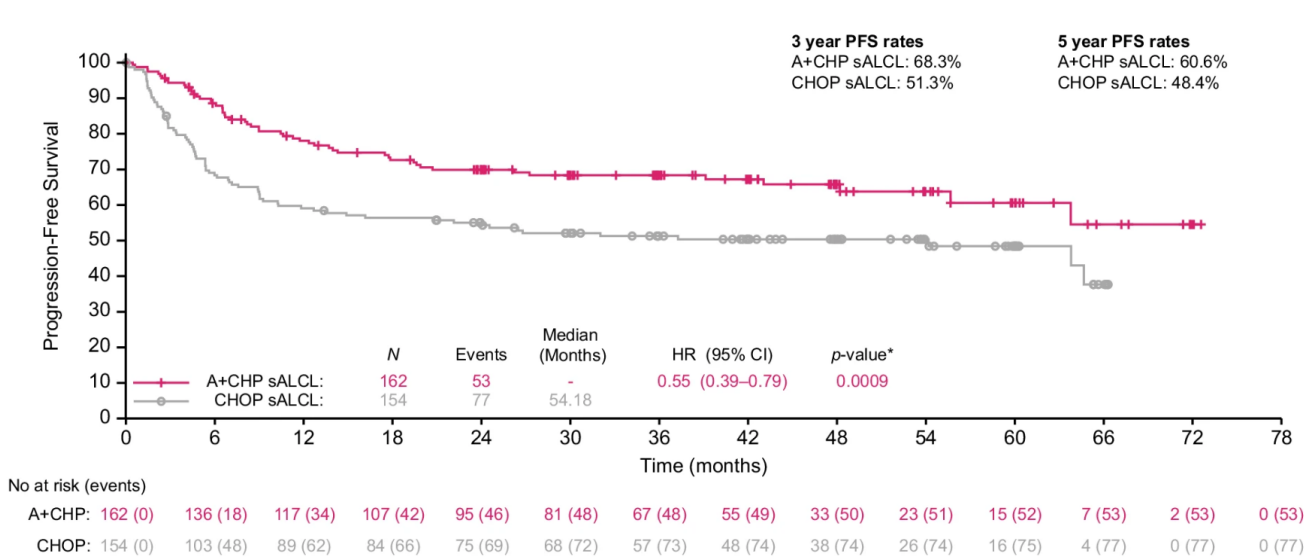
Rearrangements:

| | |
|---|---|
| NPM1-ALK<br>Very good | DUSP22 (~45%) – maybe good<br>TP63 (<5%) – very bad |

Domingo-Domenech et al. Blood Cancer Journal. 2025

# Anaplastic Large Cell Lymphoma -Treatment

- **BOARD QUESTION:**
  - How do you treat newly diagnosed ALCL (whether ALK+ or ALK-neg)?
  - Answer: **Brentuximab*-CHP x 6 cycles**
    - Better ORR, PFS
    - Almost significant OS
    - ECHELON-2 trial, randomized phase 3
- For breast implant
  - If just capsule can start with just removal
  - If advanced, then brentuximab alone or with CHP




*Brentuximab is anti-CD30 antibody drug conjugate

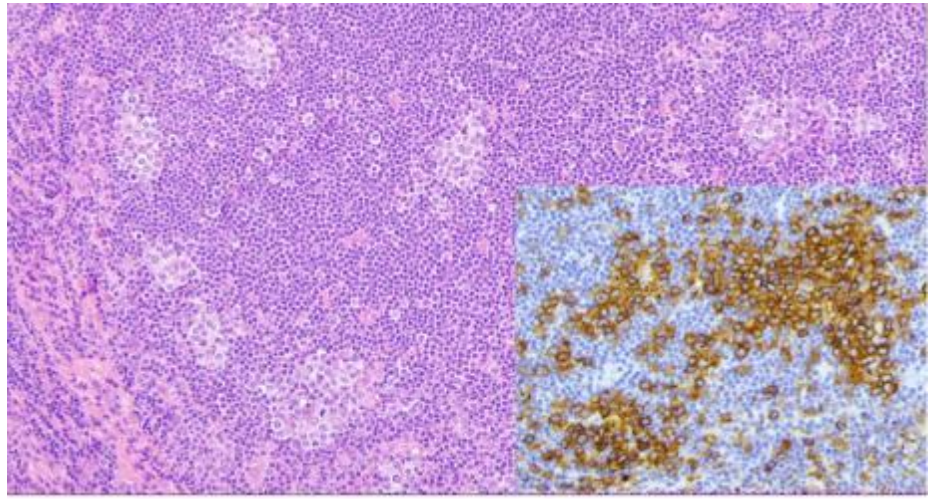
Horwitz et al. Lancet. 2019; Domingo-Domenech et al. Blood Cancer Journal. 2025

# T-follicular helper lymphoma

- We used to call angioimmunoblastic, now:
  - Nodal T-follicular helper cell lymphoma, angioimmunoblastic type
  - Nodal T-follicular helper cell lymphoma, follicular-type
  - Nodal T-follicular helper cell lymphoma, NOS

- Named for the markers on the T cell.  Need to have 2 expressed to be diagnosed
  - **PD1**
  - ICOS
  - CXCR5
  - CXCL13
  - CD10 (not reliable like follicular lymphoma)
  - BCL6

- Interesting biology that is informing treatments

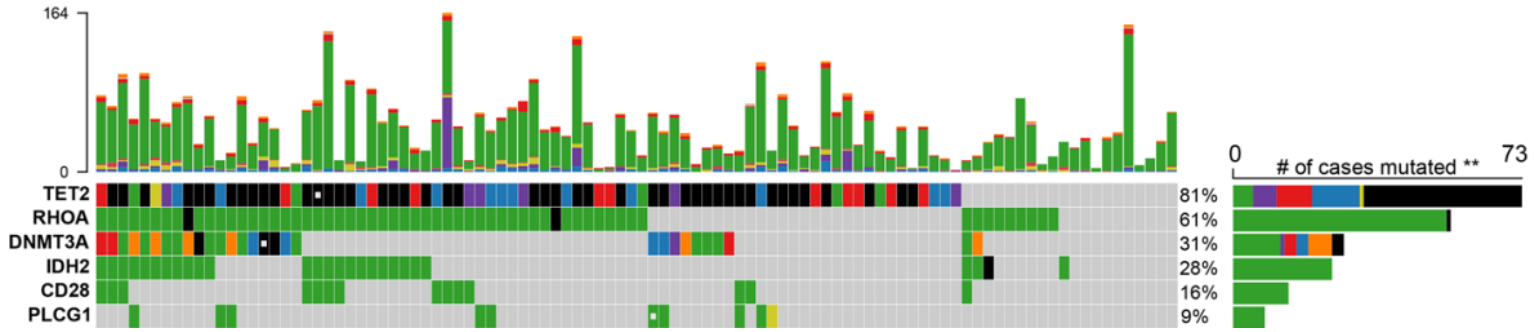


PD1

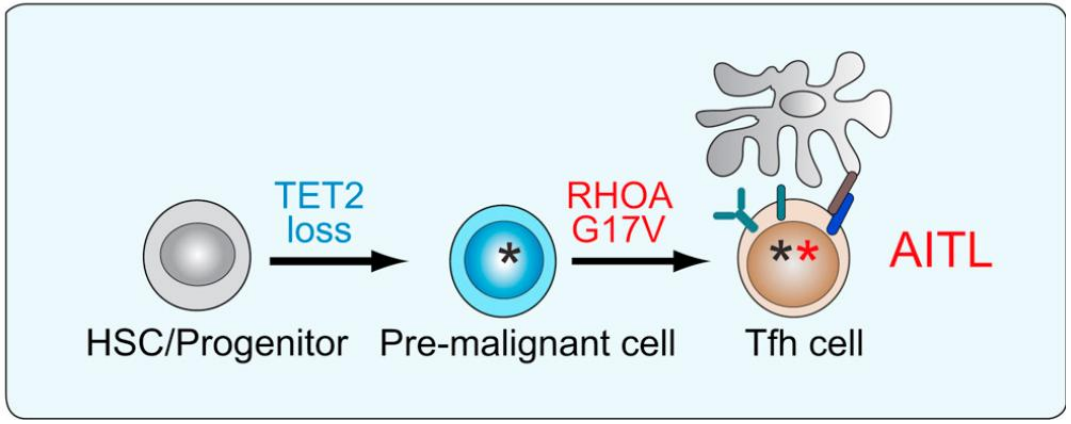
# T-follicular helper lymphoma – Genomics

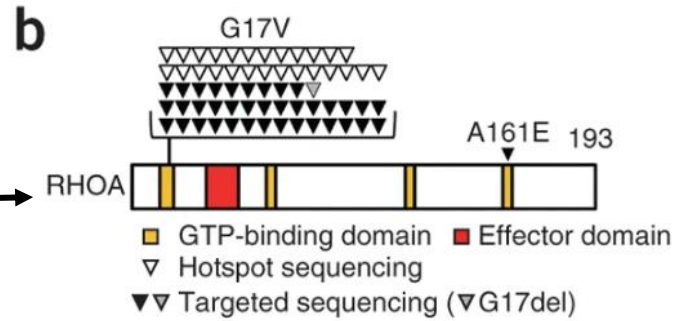
Most common mutations

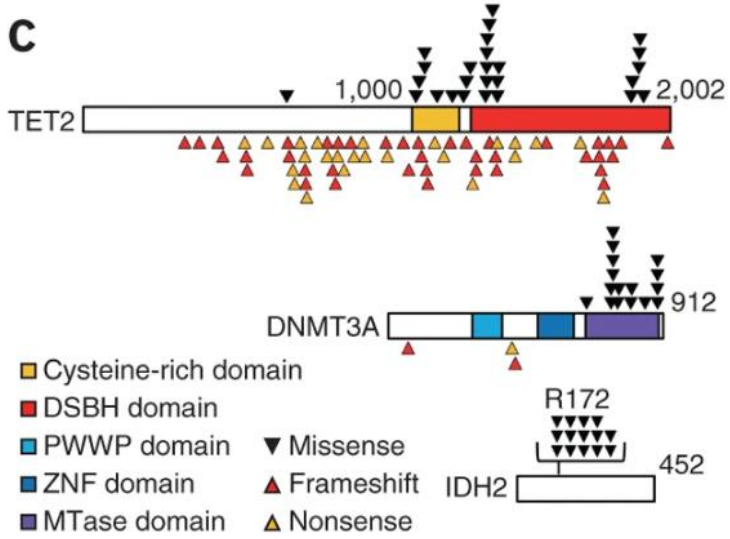
1. **TET2** (often biallelic)
2. **RHOA** $^{G17V}$
3. DNMT3A
4. IDH2 $^{R172}$




**RHOA** $^{G17V}$ **= Tfh lymphoma**



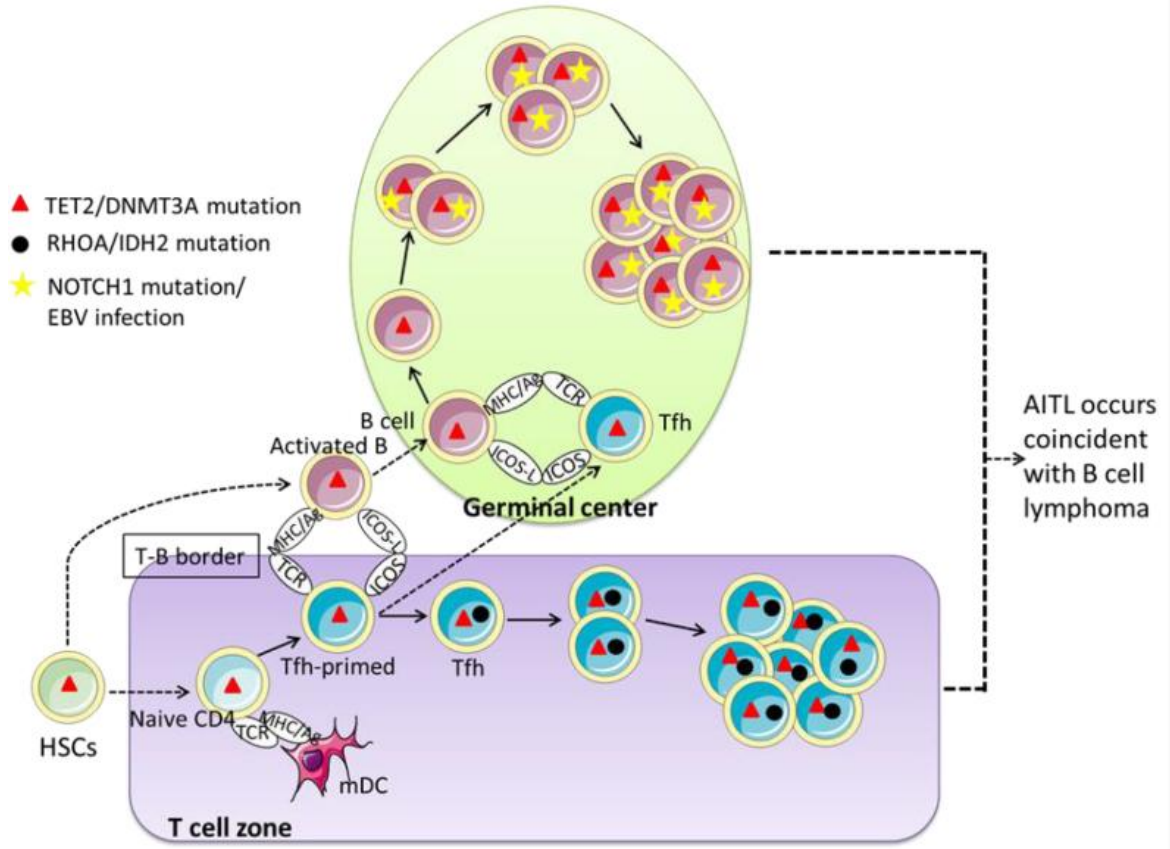




**TET2** and DNMT3A mutations are in the HSC!

Cortes et al. Cancer Cell. 2018; Sakata-Yanagimoto et al. Nat Genet. 2014

# T-follicular helper lymphoma – Genomics – why it matters: Reason 1




**TET2** and DNMT3A mutations are in the HSC

TET2 mutations are in the myeloid and **B-cell** compartments

Plus Tfh cells *help* B-cell development

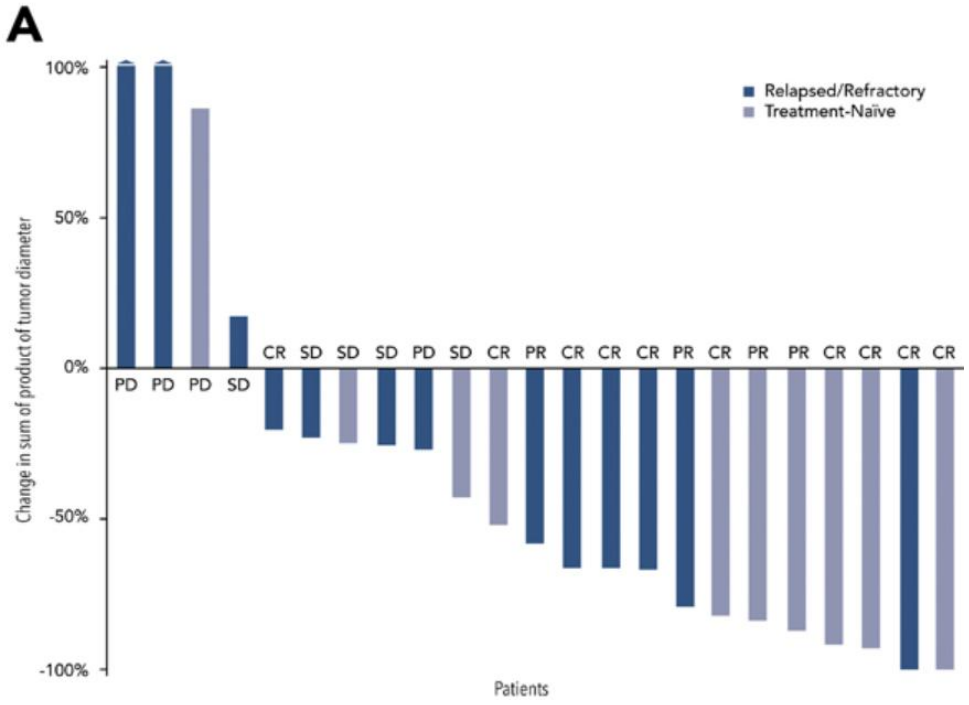
There is a high risk of a concomitant TET2-mutated **B-cell lymphoma** with Tfh lymphomas, often EBV+

**Pearl for Tfh:** You must have a high suspicion of a secondary B-cell lymphoma in Tfh: Biopsy, biopsy, biopsy

Hu et al. Cancers. 2022

# T-follicular helper lymphoma – Genomics – why it matters: Reason 2

| Non-TFH vs TFH phenotype | P value |
|---|---|
| ORR to HDACi and HDACi combinations<br>29% (19% CR) vs 56% (29% CR) | .003 |
| Logistic regression model<br>TFH independent predictive factor of ORR to HDACi | .009 |




Tfh lymphoma biology has marked chromatin dysregulation

Tfh lymphomas are the ones that response best to **histone deacetylase inhibitors** (HDACs): e.g. belinostat, romidepsin

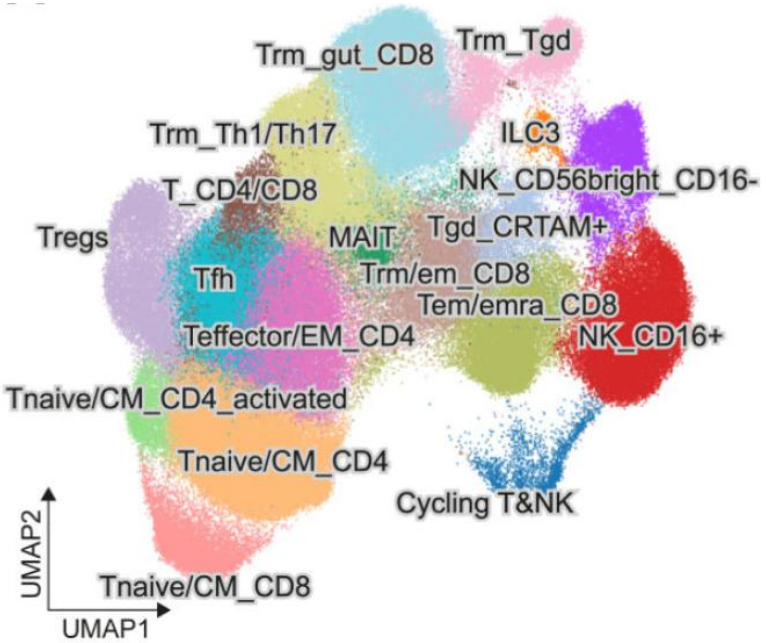
Tfh lymphoma also respond to **hypomethylating agents**: e.g. azacytidine

Combination HDAC + hypomethylating: **80% ORR** in relapsed Tfh

Ghione et al. Blood. 2020; Falchi et al. Blood 2021.

# Peripheral T-cell Lymphoma – Not Otherwise Specified

- PTCL-NOS is the “other” category that do not fit well into any T-cell subtype
- This not really one entity and phenotype and behavior vary widely
- Although we lump these into one group, management of these can/should be more nuanced



# Treatment of Nodal T-cell lymphomas – initial treatment

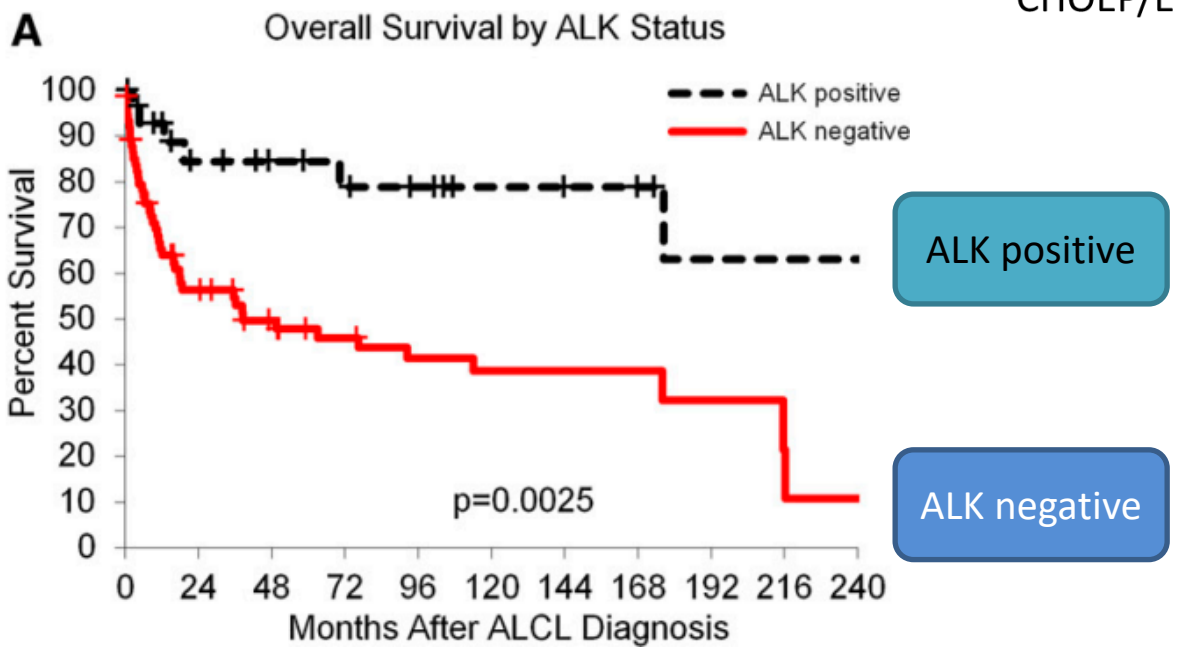
Prognosis: Good Okay to bad

** for “CD30-positive”

ALK positive | ALK negative | Tfh | PTCL-NOS

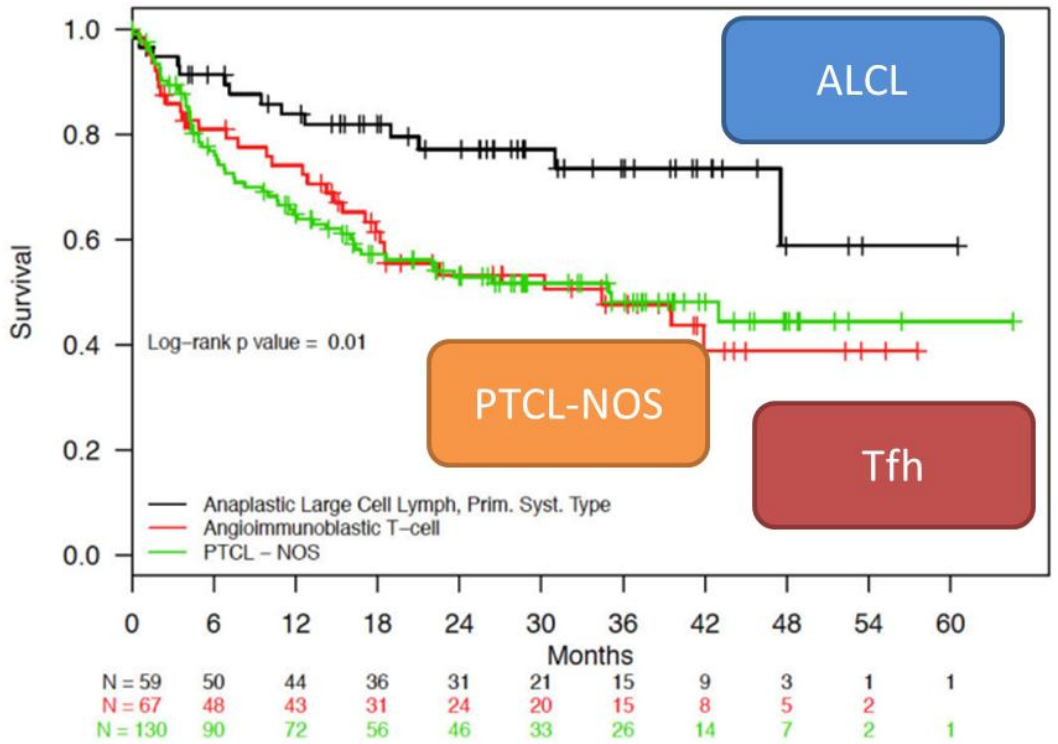
**Brentuximab – CHP***

Brentuximab – CHP**
CHOP
CHOEP/EPOCH




ALK positive

ALK negative



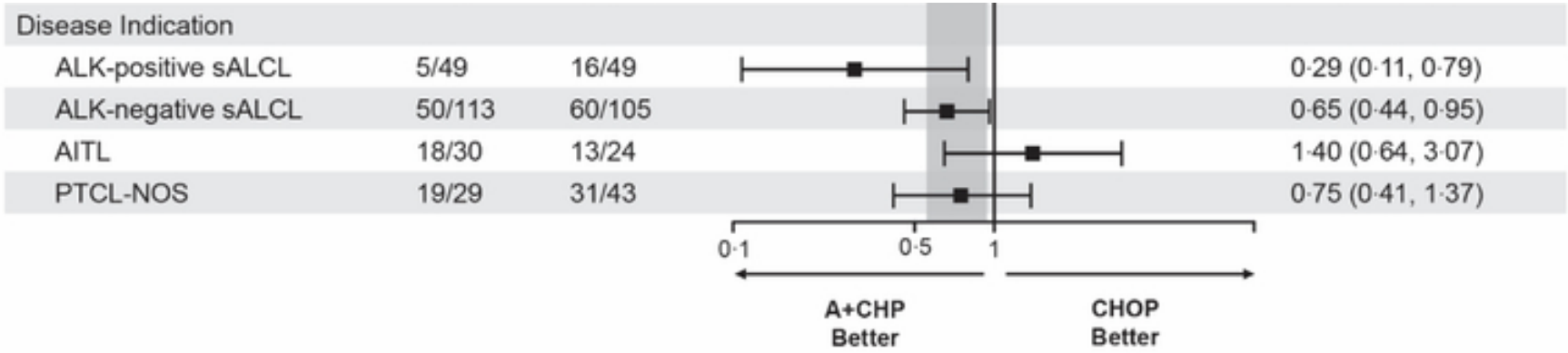

Parrila Castellar et al. Blood. 2014; Carson et al. Cancer 2017.

# Brentuximab and CD30

BV-CHP approved based on ECHELON-2

Required 10% CD30 expression – arbitrary selection

Almost all of the advantage for BV-CHP vs CHOP was derived from ALCL

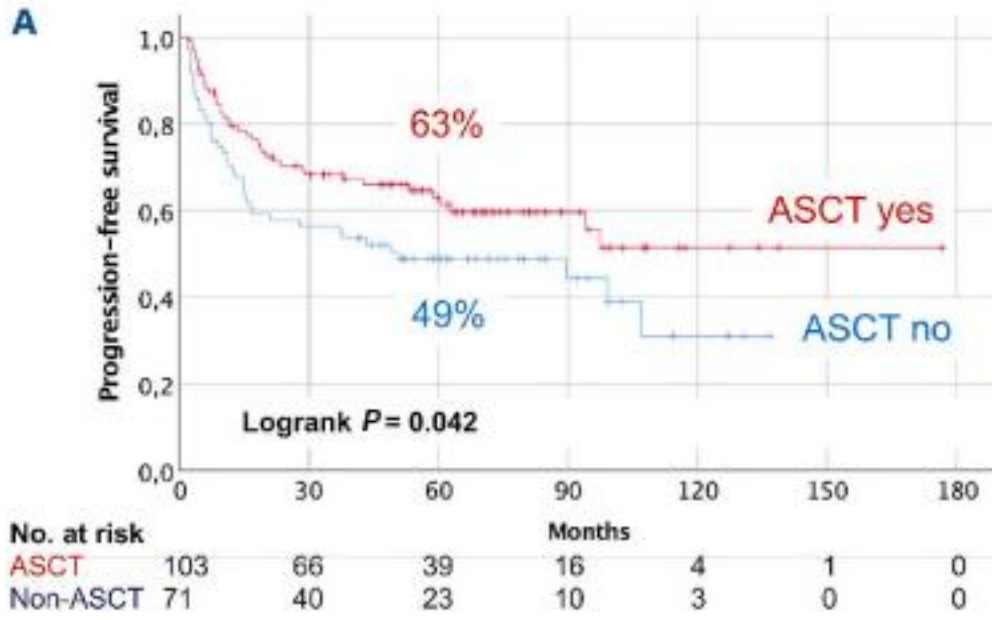


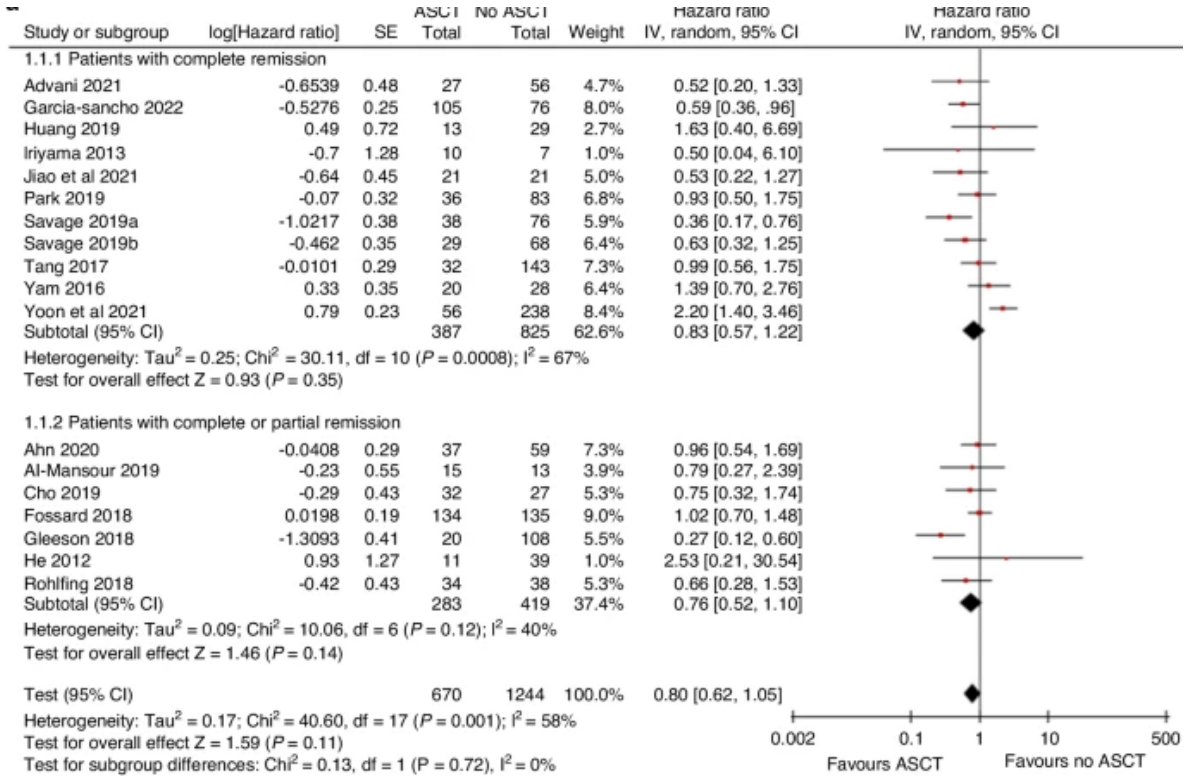

- Studies across PTCL, cutaneous T-cell lymphoma, and DLBCL all agree: CD30 expression does NOT correlate with clinical outcomes with brentuximab
- Do NOT base your decision to give/not give brentuximab on CD30 expression
- I personally only use BV-CHP for ALCL. In other types, I save brentuximab for the relapsed/refractory setting. Even “CD30 negative” lymphomas can have remarkable responses to brentuximab

# To transplant or not to transplant

Benefit of transplant is unclear in consolidation

- Patients receiving autoSCT do better than those not consolidation
- Not randomized; the small benefit may be
  Selection bias
- Most offer autoSCT in fit patients




Garcia-Sancho et al. Haematologica. 2022; Girard et al. Bone Marrow Transp 2024.

# Other T-cell lymphoma types

1. NK/T cell lymphoma
2. Adult T-cell leukemia/lymphoma
3. T-large granular lymphocytic leukemia
4. T-prolymphocytic leukemia
5. Hepatosplenic gamma delta T-cell lymphoma
6. Intestinal lymphomas
7. Cutaneous T-cell lymphomas

# Extranodal NK/T cell lymphoma

Most commonly **nasal**/sinus location

**EBV** positive

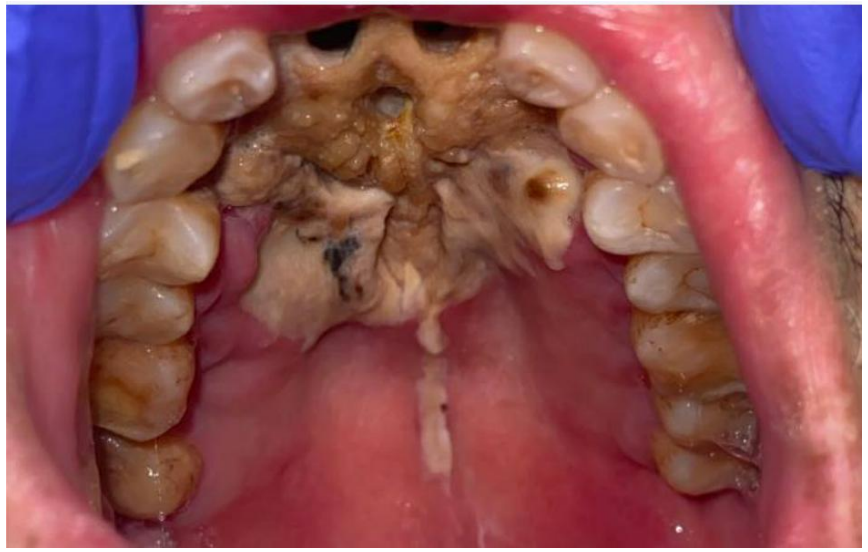
Early stage has excellent cure rate 90+%

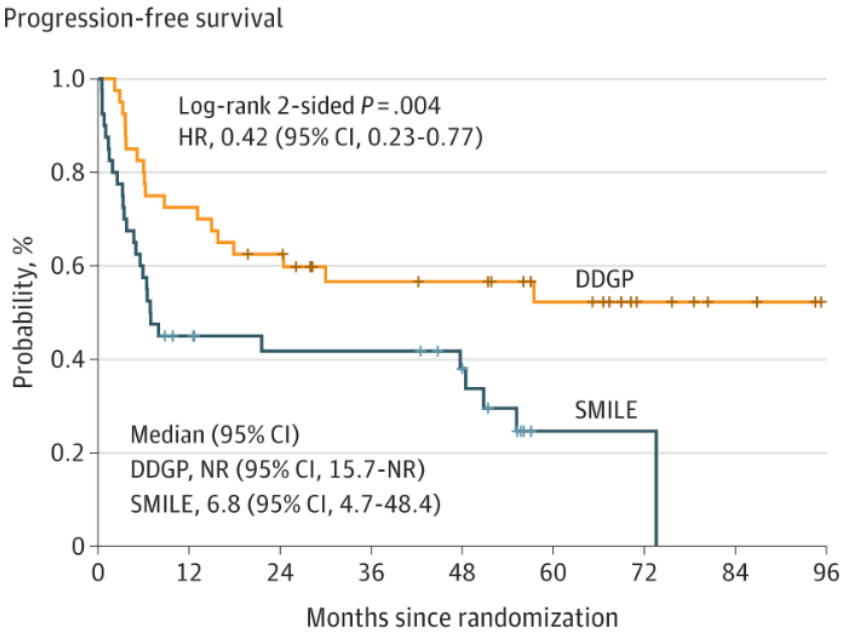
For early stage chemotherapy **plus radiation**

For advanced stage the key is **asparaginase**

- SMI**L**E
- DDG**P** (beat SMILE in phase 3)
- **P**-GemOX

Nivolumab or pembrolizumab useful in relapsed disease






Wang et al. JAMA Onc. 2022

# Adult T-cell Leukemia / Lymphoma

- HTLV-1 associated
  - Endemic in Japan, S. America, W. Africa, Iran

- Subtypes
  - Acute
  - Lymphoma
  - Chronic
  - Smoldering

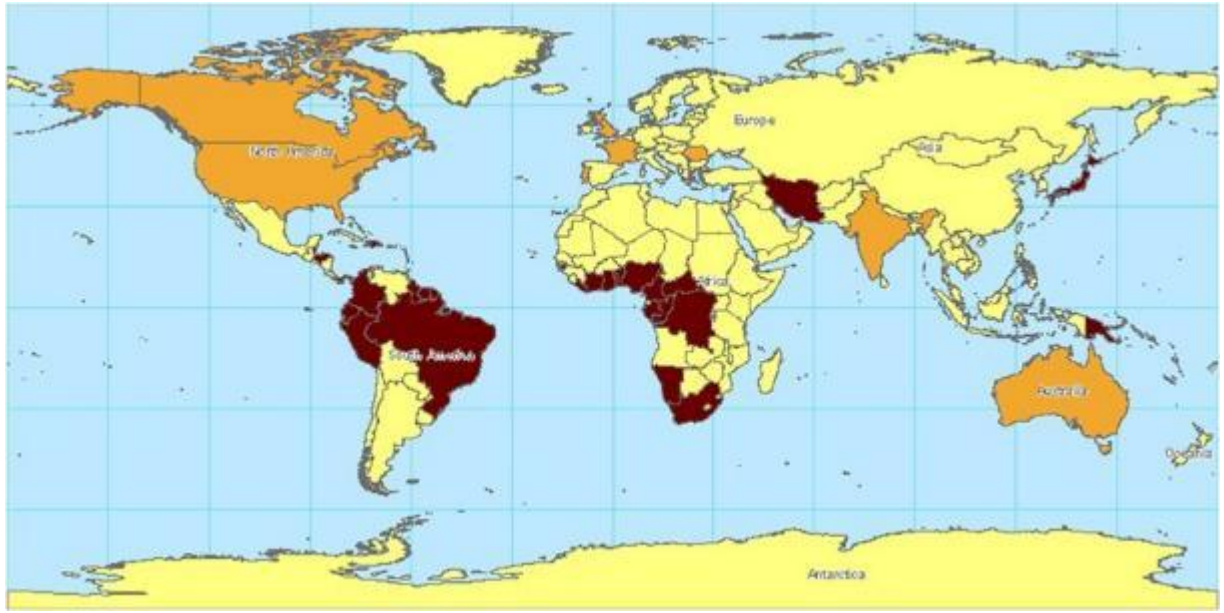
- Clinical presents as
  - **Hypercalcemia**
  - Adenopathy, splenomegaly
  - Skin involvement

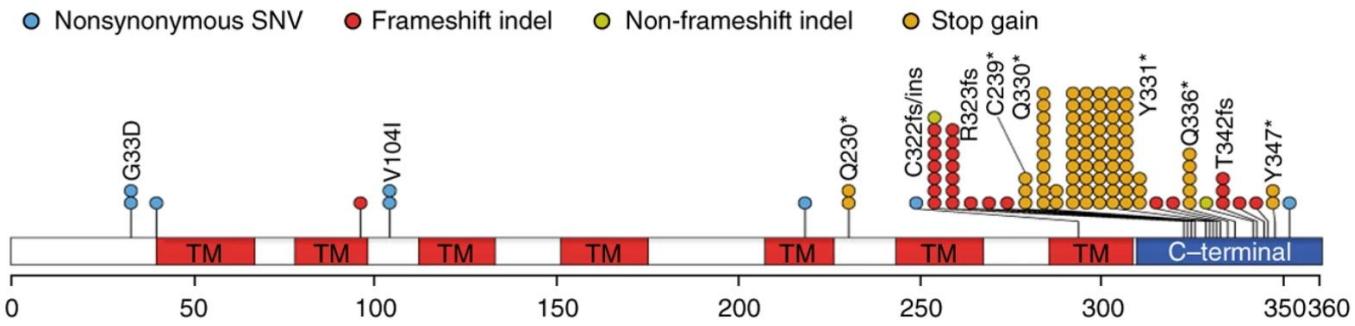
- CCR4 gain of function mutations (~33%)
  - May respond better to mogamulizumab

- Mogamulizumab is anti-CCR4 antibody

- Usually CHOP-like induction, but often consolidate with *allogeneic* SCT

ATLL endemic regions



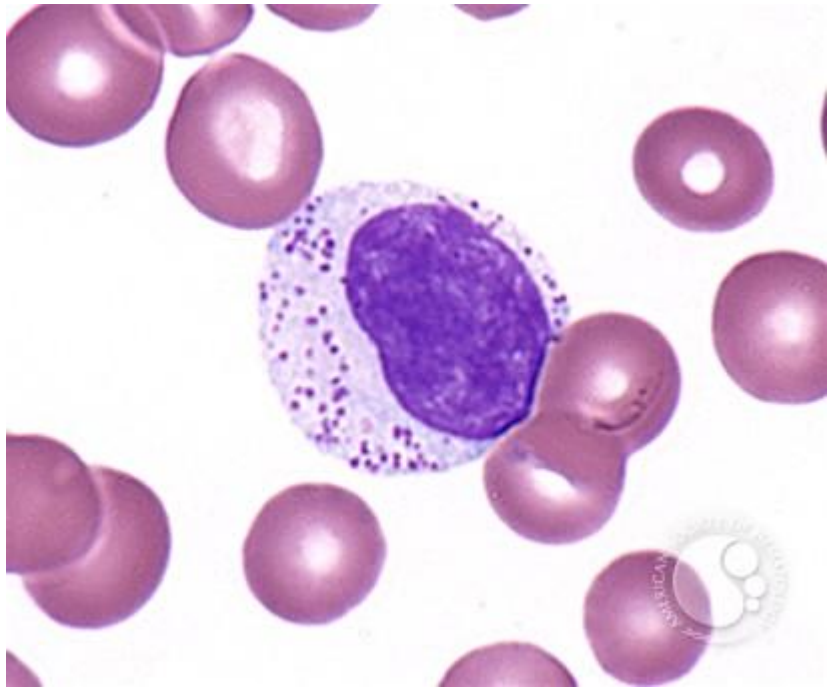



CCR4 mutations in ATLL

Kataoka et al. Nat Genet 2015.

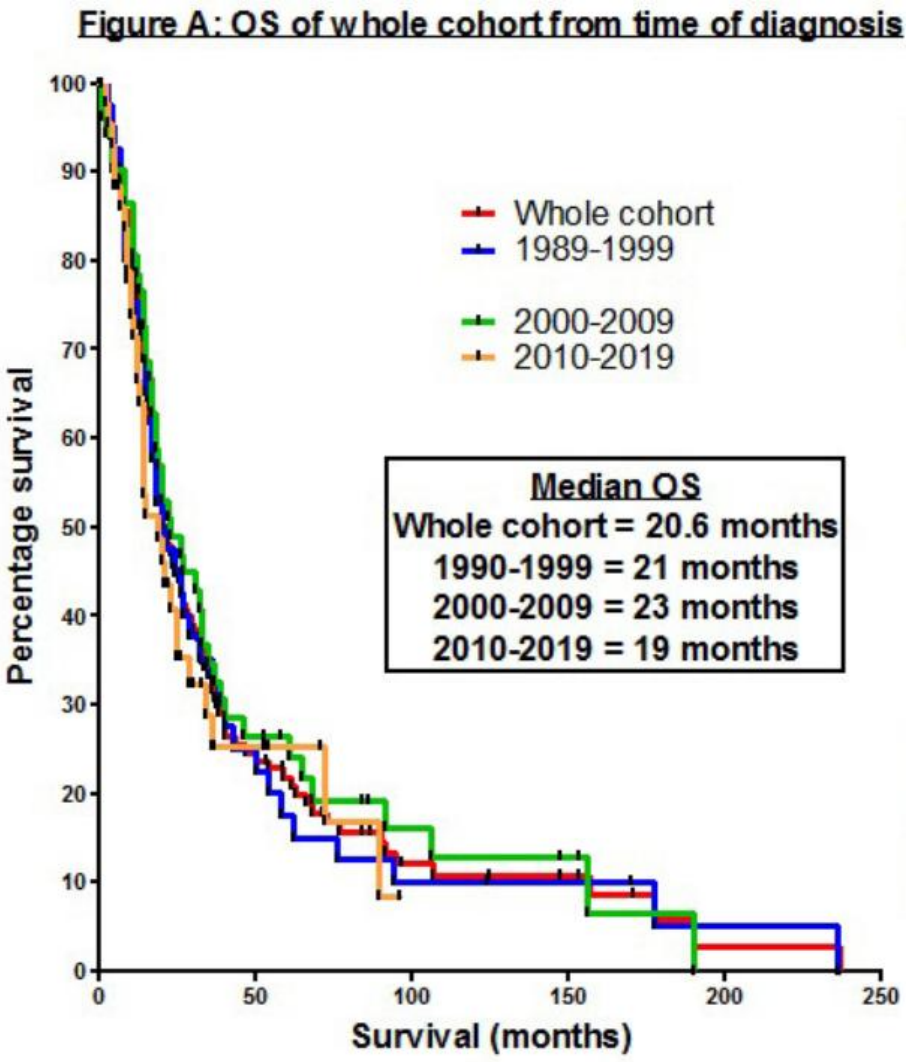
# T-cell large granular lymphocytic leukemia (T-LGL)

- Chronic and indolent
- Associated with **autoimmune diseases (rheumatoid arthritis)** and **cytopenias**; these are the most common indications for treatment
- CD3+, TCRαβ+, CD8+, CD16+, CD45RA+, and **CD57+**
- **STAT3** mutations in 40%
- Goal for treatment is typically to control neutropenia or anemia or autoimmune
  - Methotrexate
  - Cyclophosphamide (may soon become preferred 1st therapy)
  - Cyclosporine A
  - Ruxolitinib



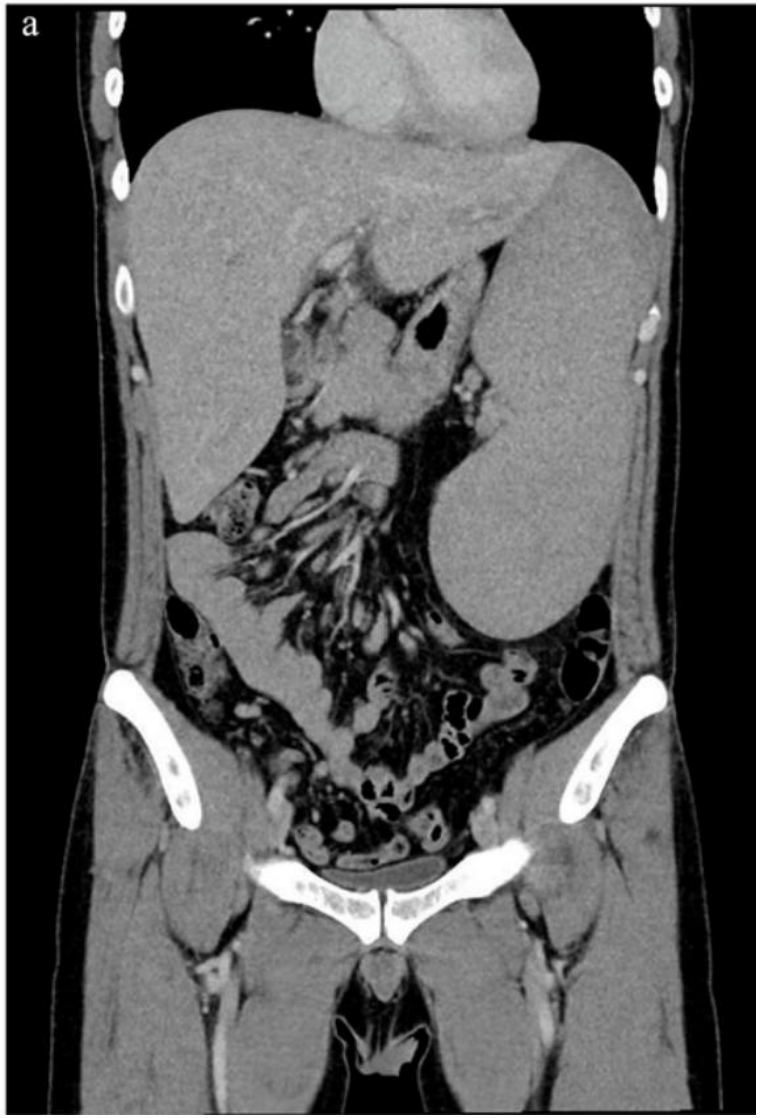
# T-cell prolymphocytic leukemia (T-PLL)

- Aggressive leukemia – often very high white count
  - May be preceded by an indolent phase
- Diagnostic confirmation by **TCL1** expression or FISH for **chromosome 14 (usually inversion)** TCL1 structural variants
- ATM mutations are common
- Initial treatment with **alemtuzumab (anti-CD52)**
- Allogeneic stem cell transplant improves survival but probably not curative




Cross et al. Blood 2019.

# Hepatosplenic gamma delta T-cell lymphoma



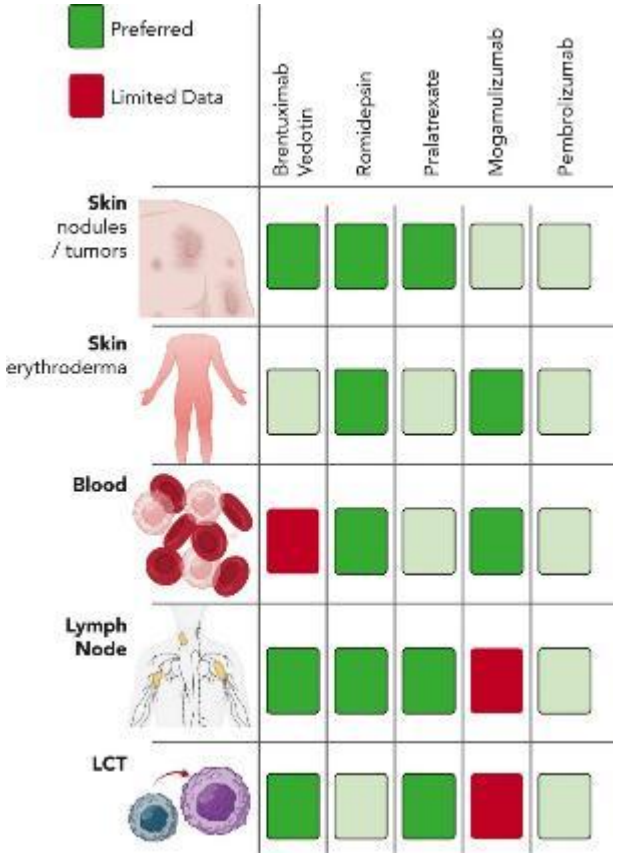

- Young male predominance
- Spleen, liver, bone marrow
  - Either CD4/CD8 double negative, or CD8+, positive for **CD56**
  - Risk of HLH
- Association with **inflammatory bowel disease** and immune suppression
- Iso7q, trisomy 8, SETD2 and STAT5B mutations
- For adults, often given ifosfamide, cisplatin, etoposide (ICE) followed by allogeneic transplant

# Intestinal T-cell lymphomas

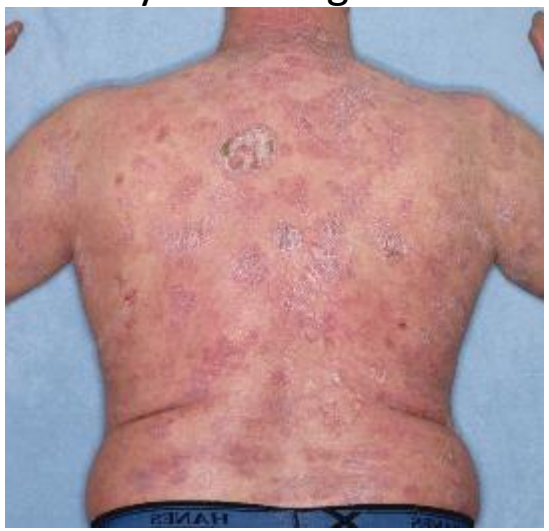
| Enteropathy associated T-cell (EATL) | Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma (MEITL) |
|---|---|
| Celiac disease, HLA-DQ2/DQ8 | Asian/Hispanic |
| Jejunum and ileum | Jejunum and ileum |
| Cytotoxic phenotype, usually CD4/CD8 double negative | Cytotoxic phenotype, usually CD4/CD8 double negative |
| CD30 often positive | CD30-negative |
| JAK/STAT alterations | JAK/STAT alterations |
| Aggressive / ~7 months prognosis | Aggressive / ~7 months prognosis |

# Cutaneous T-cell lymphomas

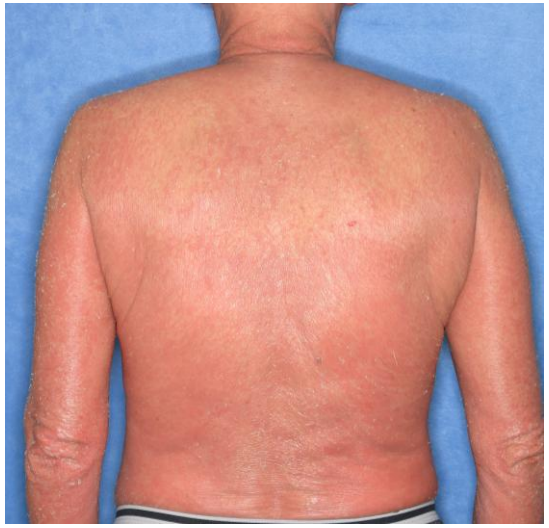
- Skin lymphoma
  - Sezary syndrome typically **erythrodermic**
  - Sezary syndrome has **leukemic** involvement
- **CD4+ clonal T-cells, negative for CD7 and CD26**
- Large cell transformation (>25% of infiltrate)
- Only curative treatment is allogeneic SCT
- **Mogamulizumab** and **Brentuximab** both approved based on phase 3 data




Mycosis fungoides



Sezary Syndrome



Khodadoust et al. Blood 2023.

# T-cell specific therapies

| Treatment | MoA | Key toxicities |
|---|---|---|
| Romidepsin | Histone deacetylase inhibitor | Nausea, thrombocytopenia, QT prolongation |
| Belinostat | Histone deacetylase inhibitor | Nausea, fever, anemia |
| Pralatrexate | DHFR inhibitor, targets uptake by RFC-1 | Mucositis |
| Brentuximab | Anti-CD30 antibody drug conjugate | Neuropathy; Black box for PML |
| Mogamulizumab | Anti-CCR4 “naked” antibody | Rash, Black box for autoimmune (e.g. myositis) |
| Alemtuzumab | Anti-CD52 “naked” antibody | Many; Black box for infection, infusion reaction. stroke and cervicocephalic arterial dissection |
| Duvelisib | PI3K delta inhibitor | Hepatitis; Black box for infections, diarrhea, or colitis, cutaneous reactions, and pneumonitis |

# Thank you!