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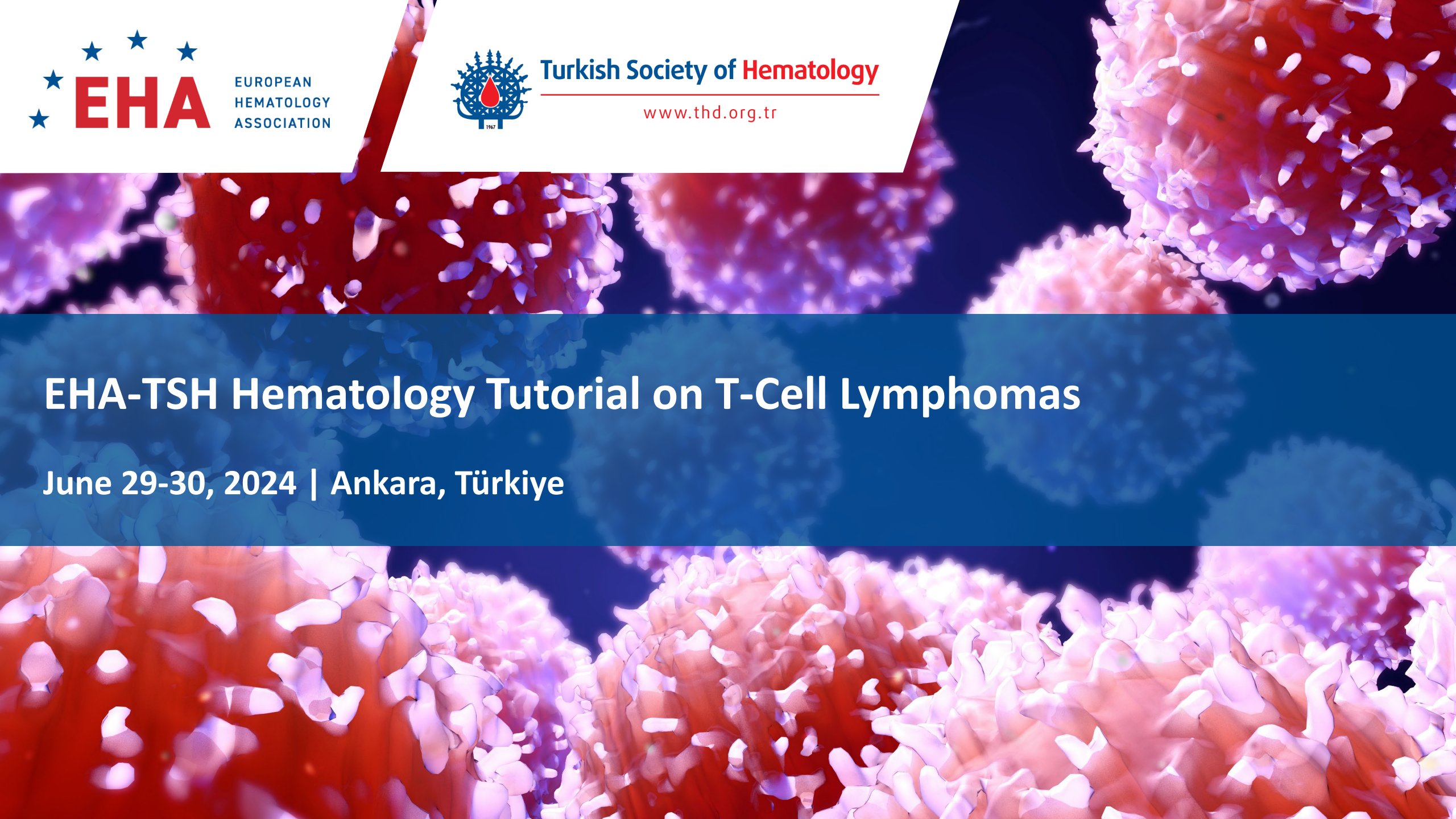


EHA-TSH Hematology Tutorial on T-Cell Lymphomas

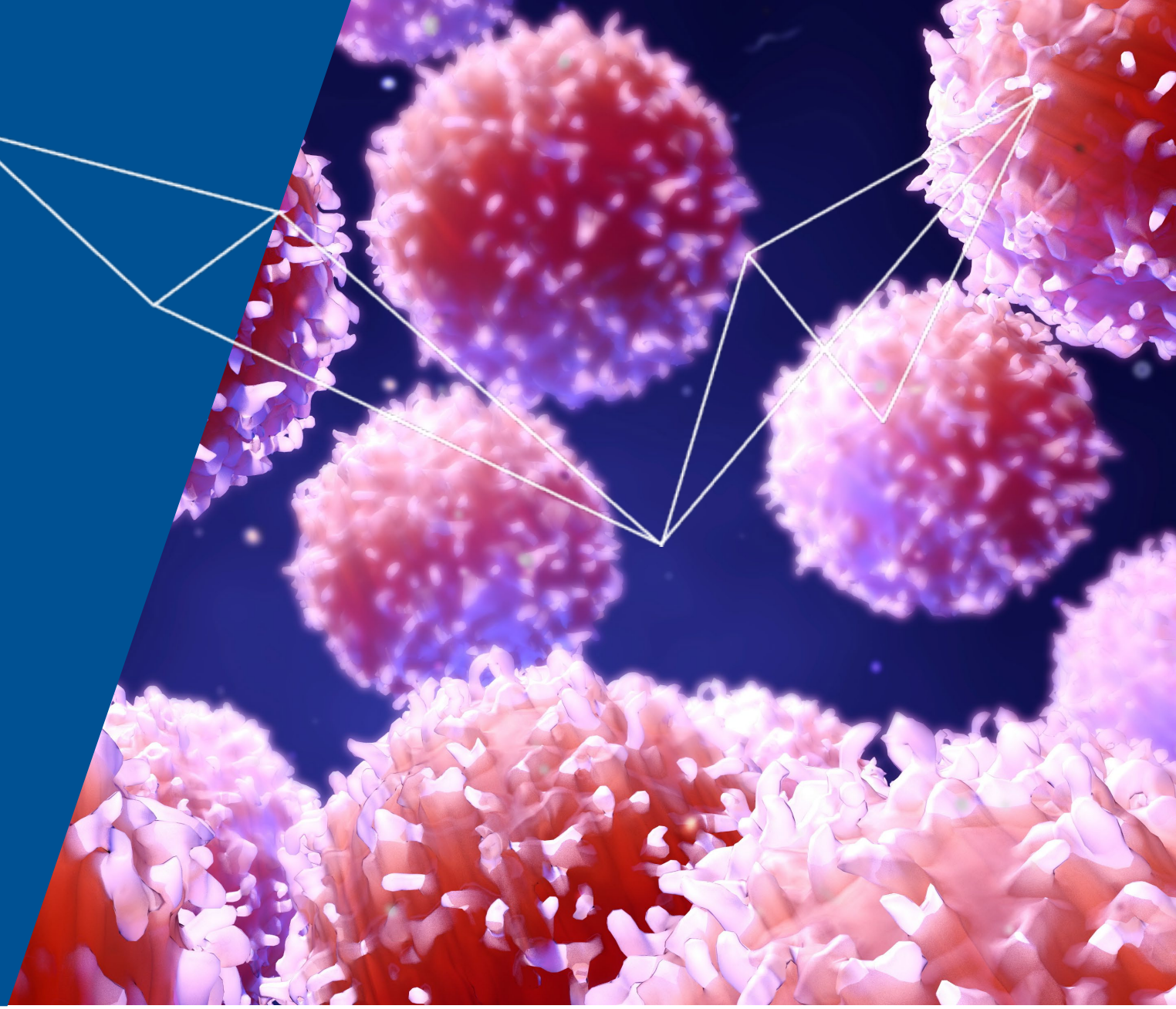
June 29-30, 2024 | Ankara, Türkiye

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Session 1

New classification and epidemiology of T cell diseases

June 29, 2024



Updated classification and molecular evaluation of nodal T-cell lymphomas

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IEO European Institute of Oncology IRCCS, Milano, Italy

June 29, 2024

DISCLOSURE

- Sandoz (Consultancy, non-financial)

Learning objectives

After attending this presentation, you will be able to:

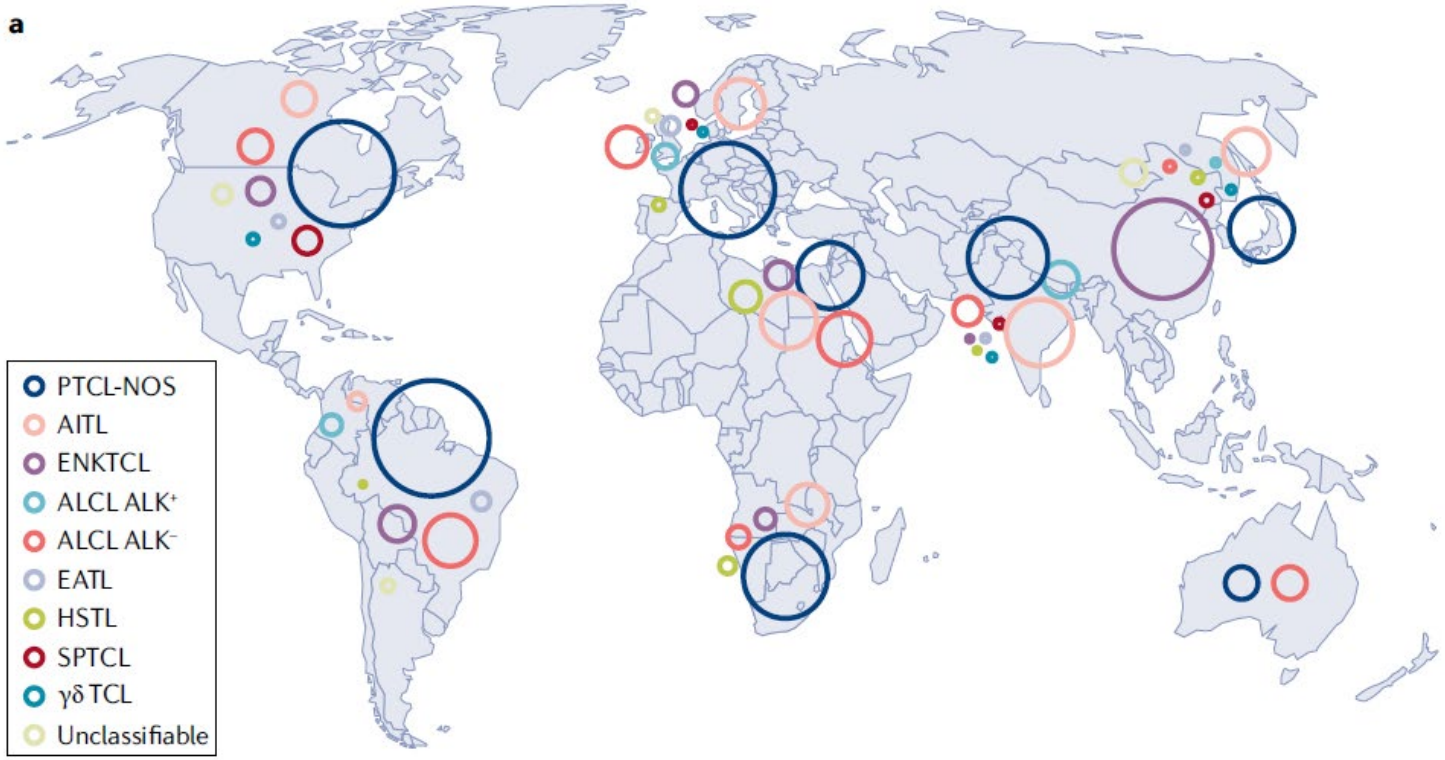
1. Understand the updates in the classification of nodal T-cell lymphomas based on the latest WHO and ICC guidelines

2. Recognize the molecular characteristics of these lymphomas

3. Explore potential prognostic and therapeutic implications based on specific genetic alterations

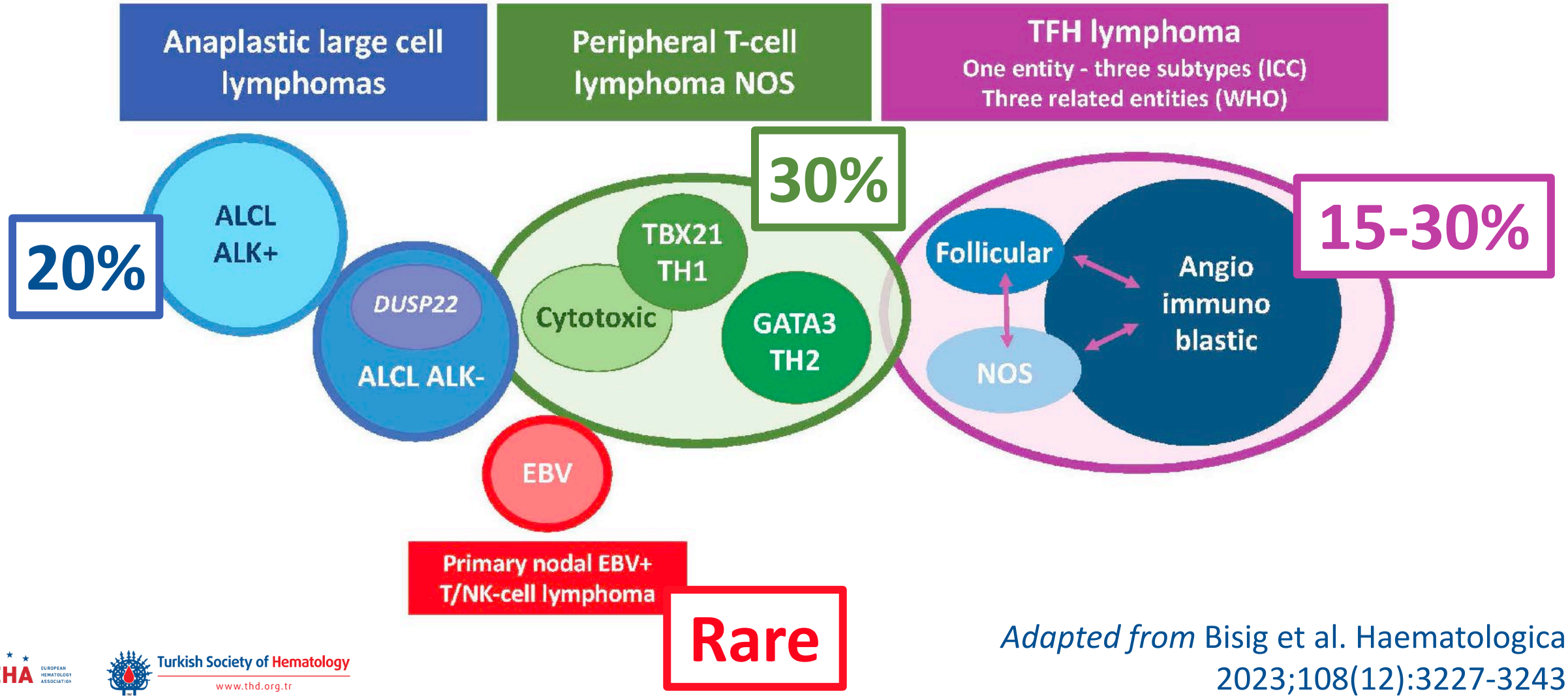
Peripheral T-cell lymphomas

- Diverse group of neoplasms (> 30 entities) that arise from mature NK or T cells
- 10% of all lymphomas in Western countries – up to 20% in Asia



From Fiore D et al. Nat Rev Cancer 2020;20(6):323-342

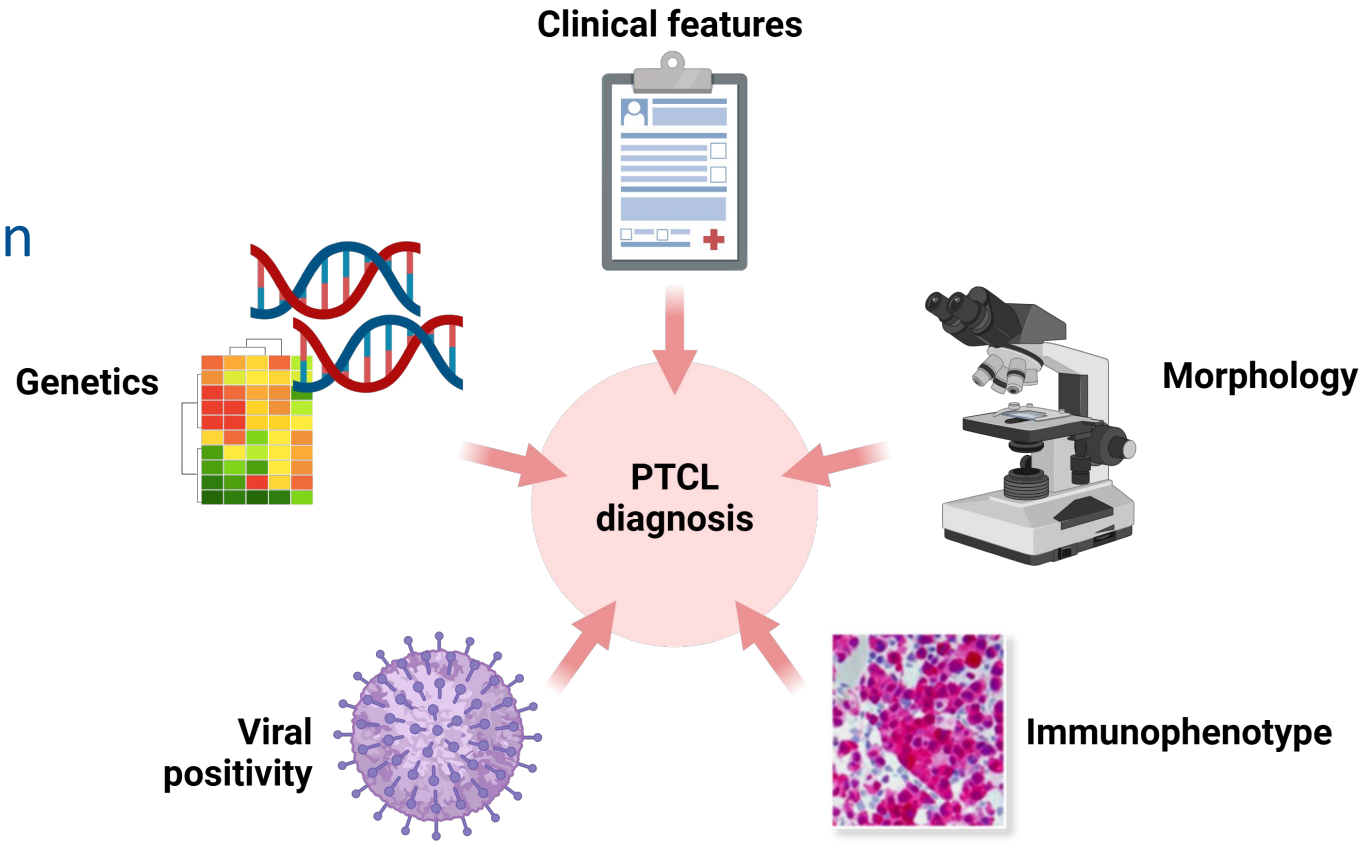
Nodal T-cell lymphomas



Adapted from Bisig et al. Haematologica 2023;108(12):3227-3243

New classifications: ICC and WHO-HAEM5

- Updates of the former WHO-HAEM4R
- Multiparametric definition

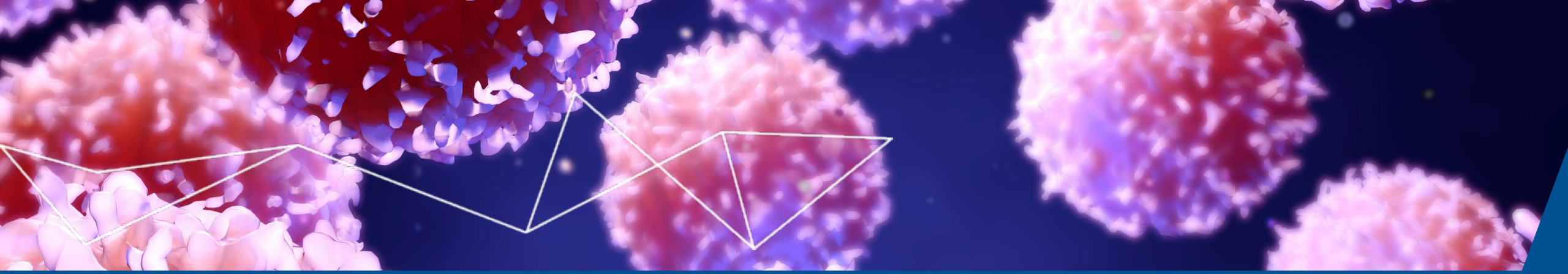


International Consensus Classification (ICC) → Campo et al. Blood. 2022;140(11):1229-1253

5th World Health Organization classification of hematological malignancy → Alaggio et al. Leukemia 2022;36:1720–1748

New classifications: ICC and WHO-HAEM5

WHO-HAEM4R	ICC 2022	WHO-HAEM5
Anaplastic large cell lymphoma, ALK-positive	Anaplastic large cell lymphoma, ALK-positive	Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative	Anaplastic large cell lymphoma, ALK-negative	Anaplastic large cell lymphoma, ALK-negative
Nodal lymphomas of T follicular helper origin ❑ Angioimmunoblastic T-cell lymphoma ❑ Follicular T-cell lymphoma ❑ Nodal peripheral T-cell lymphoma with TFH phenotype	Follicular helper T-cell lymphoma ❑ TFH lymphoma, angioimmunoblastic type ❑ TFH lymphoma, follicular type ❑ TFH cell lymphoma, NOS	Nodal T-follicular helper (TFH) cell lymphoma ❑ Nodal TFH lymphoma, angioimmunoblastic type ❑ Nodal TFH cell lymphoma, follicular type ❑ Nodal TFH cell lymphoma, NOS
Not listed as an entity (PTCL, NOS)	Primary nodal EBV+ T-cell/NK-cell lymphoma	EBV+ nodal T- and NK-cell lymphoma
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS



ANAPLASTIC LARGE CELL LYMPHOMA

- Heterogeneous group
- Distinct morphology
- Uniform CD30 expression

ANAPLASTIC LARGE CELL LYMPHOMA

WHO-HAEM5 and 2022 ICC define 4 forms of ALCL:

- ❑ Anaplastic lymphoma kinase (ALK)-positive
- ❑ ALK-negative
- ❑ Primary cutaneous
- ❑ Breast implant–associated

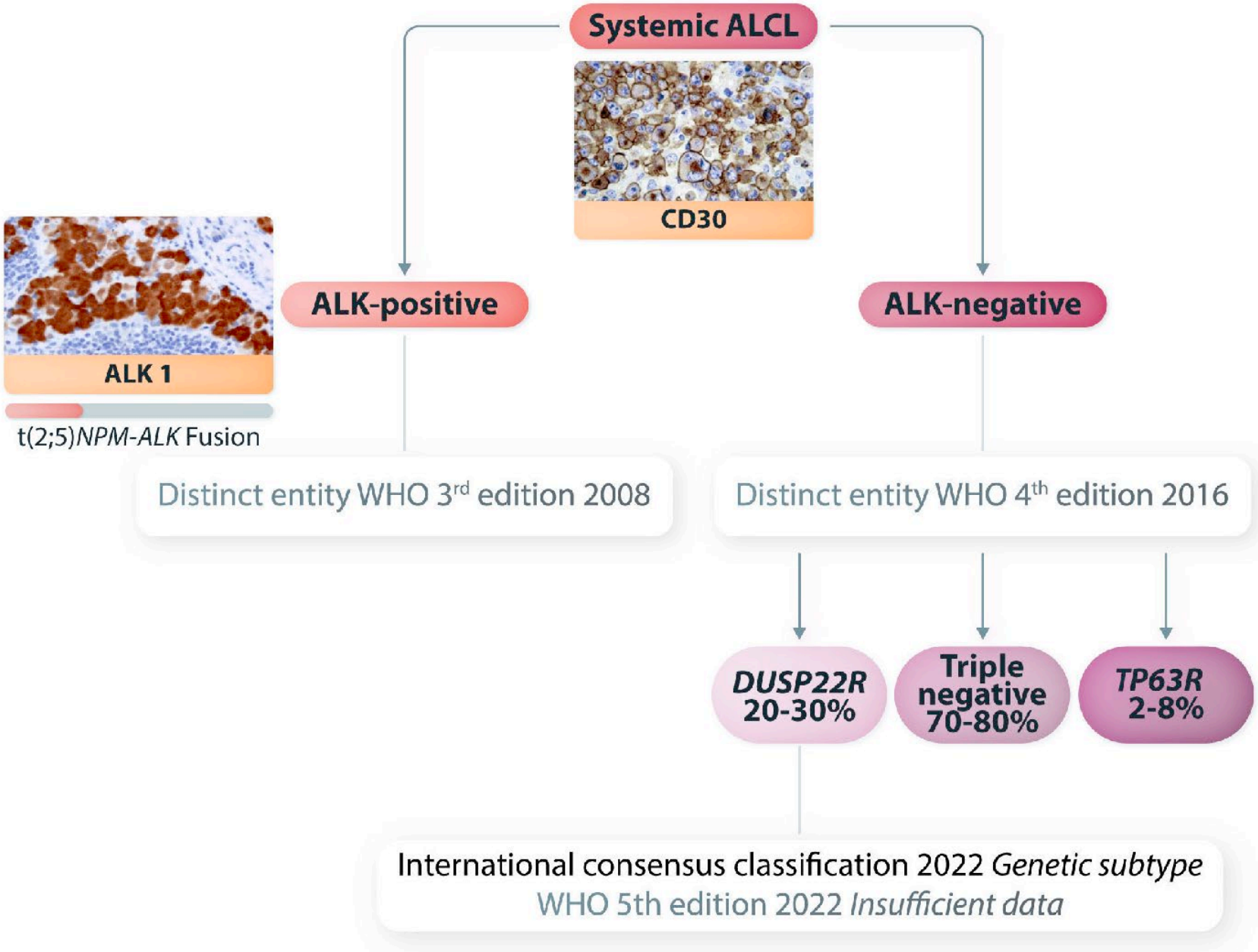
ANAPLASTIC LARGE CELL LYMPHOMA

- Anaplastic lymphoma kinase (ALK)-positive
- ALK-negative

Systemic

Localized

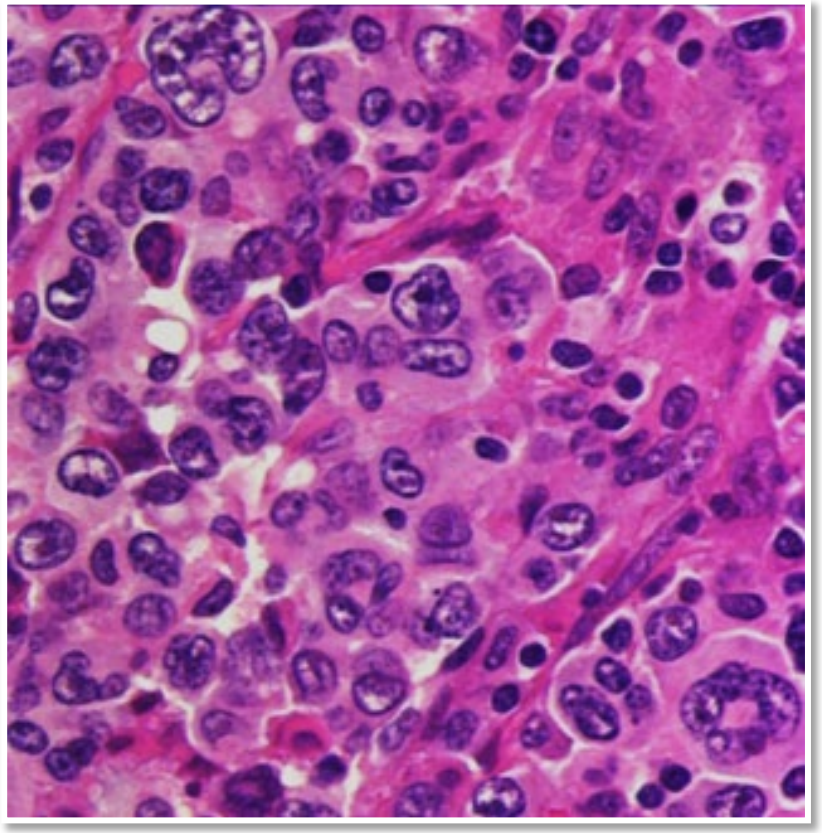
- Primary cutaneous
- Breast implant–associated



Adapted from Savage et al. Haematologica 2023;108(6):1463-1467

MICROSCOPIC FEATURES

- Lymph node architecture is usually effaced
- Sinusoidal infiltration
- Hallmark cells: large kidney- or horseshoe-shaped nuclei
- Other cells may have immunoblastic features
- Histological patterns of ALK+ ALCL:
  - ❑ Common 60%
  - ❑ Lymphohistiocytic 10%
  - ❑ Small cell 10%
  - ❑ Hodgkin-like <5%

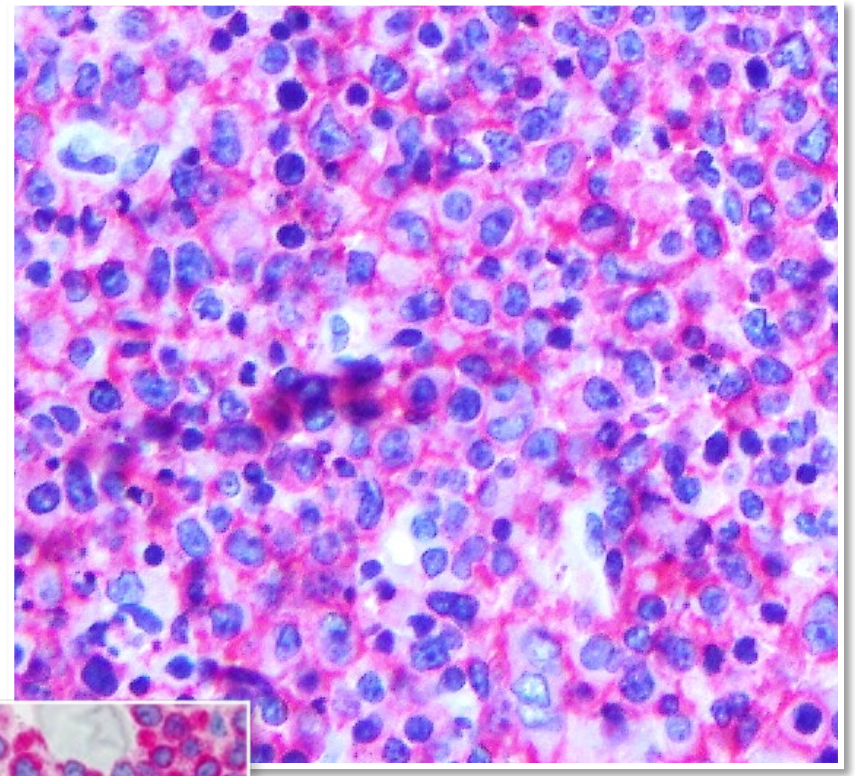


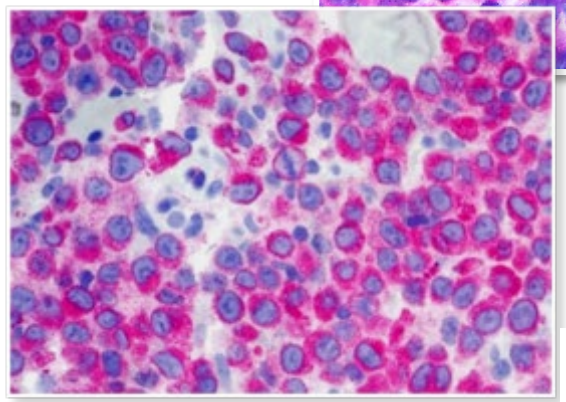
Hallmark cells

IMMUNOPHENOTYPE

- Diffuse and uniform CD30 expression
- Most ALCLs are CD4+ and express cytotoxic markers (perforin, TIA1 and granzyme B)
- Frequent loss of pan-T-cell markers (“null” phenotype”)

CD30





Perforin

ALK-positive ALCL

Young males (median age, 30-35 years)

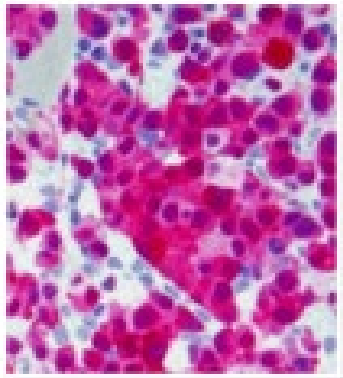
Rare leukemic presentation

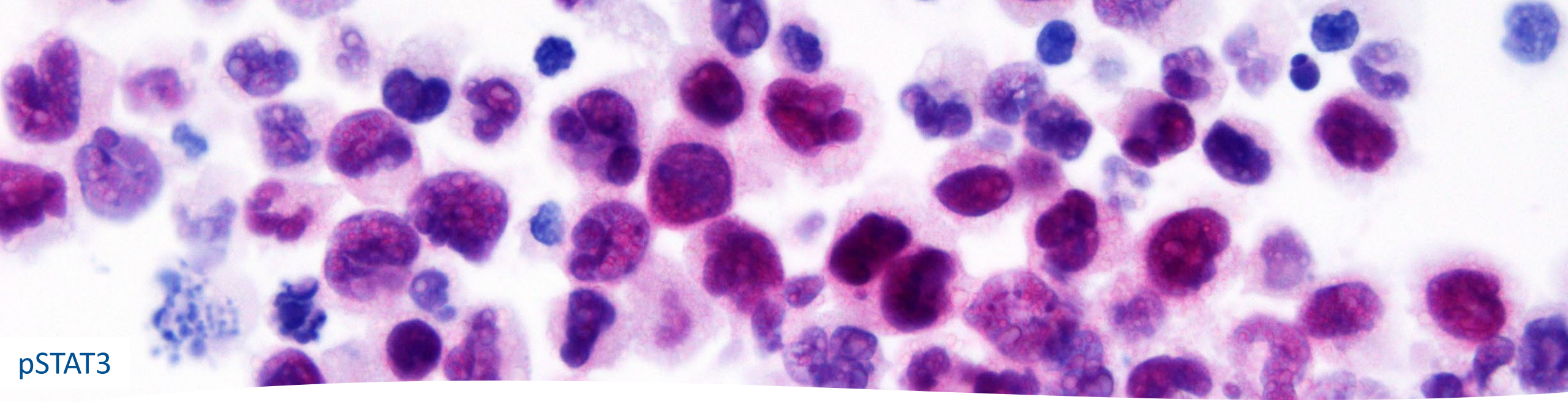
ALK translocation on 2p23: → Nuclear + cytoplasmatic

- ❑ *NPM*1 t(2;5)(p23;q35) [80%]
- ❑ *TPM3* t(1;2)(q25;p23) [20%]
- ❑ *CLTC* t(2;17)(p23;q23) [2%]
- ❑ Others (*ATIC, MSN*, …)

Cytoplasmatic ± membranous

ALK



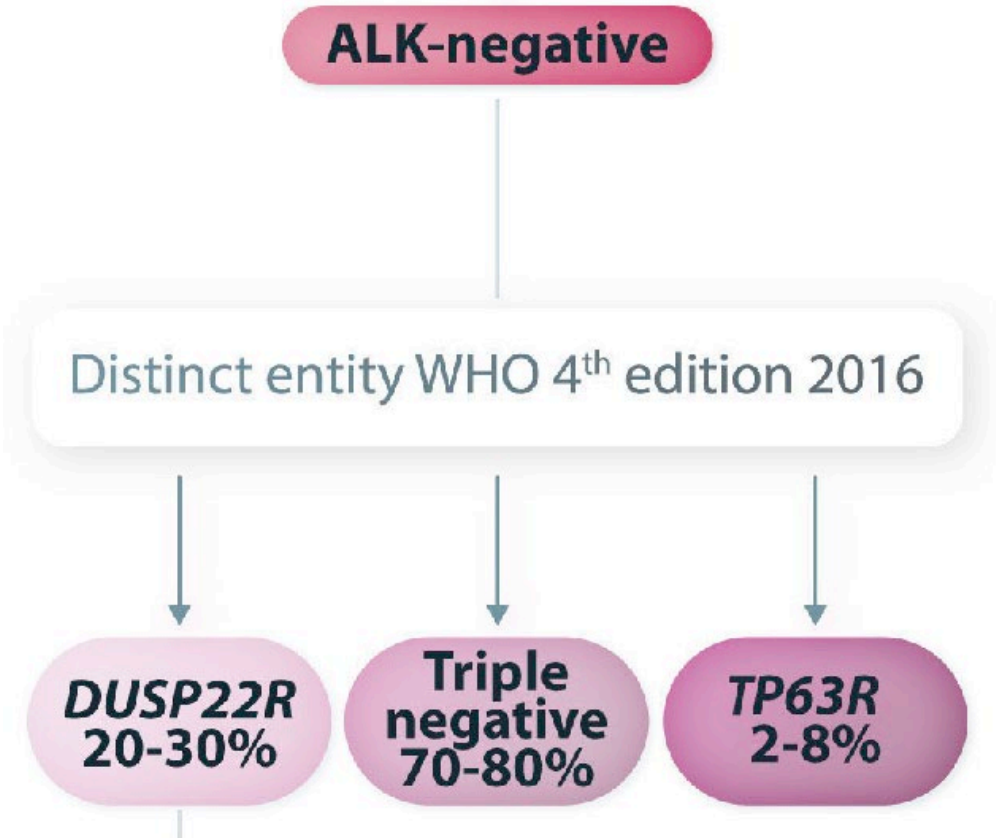


MOLECULAR FEATURES ALK+ ALCL

- ALK fusion proteins have constitutive tyrosine kinase activity
- ↑ MAPK and JAK/STAT pathways
- Nuclear phospho-STAT3 (pSTAT3) is detected in nearly all cases
- Recurrent mutation in *NOTCH1* (20%) and *TP53* (11%)

ALK-negative ALCL

- Older patients
- More aggressive than ALK+ ALCL
- Rare cases harboring both TP63-R and DUSP22-R



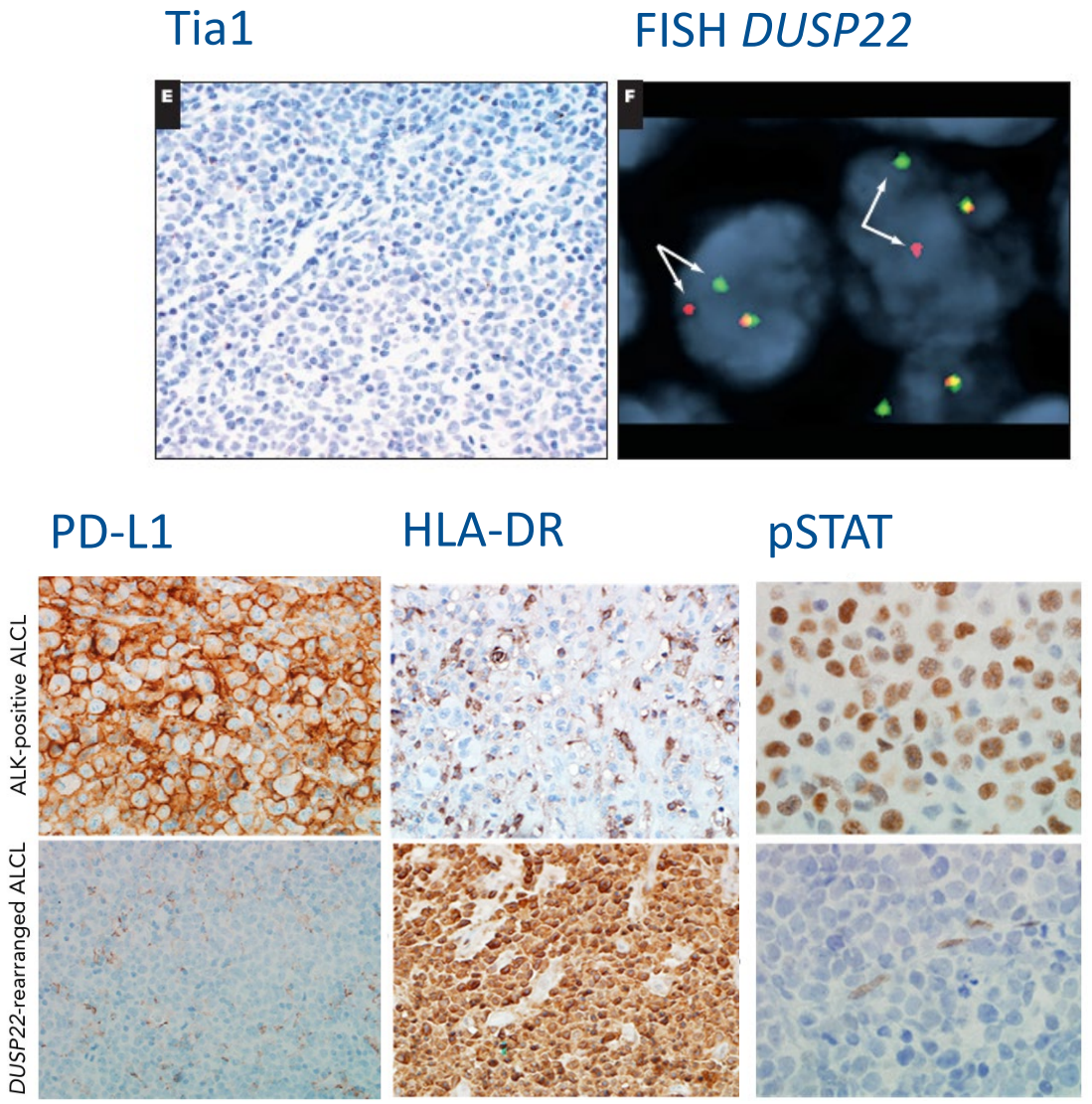
«Triple negative» ALCL

JAK/STAT pathway activation

- Activating mutations in *JAK1*, *JAK3*, and *STAT3*
- Tyrosine kinase gene fusions (STAT3::JAK2, NFKB2::TYK2, and NCOR2::ROS1)
- ROS1 → receptor tyrosine kinase (RTK) with structural homology to ALK
- Granzyme B and PD-L1/CD274, transcriptional targets of STAT3, are highly expressed

DUSP22-R ALCL

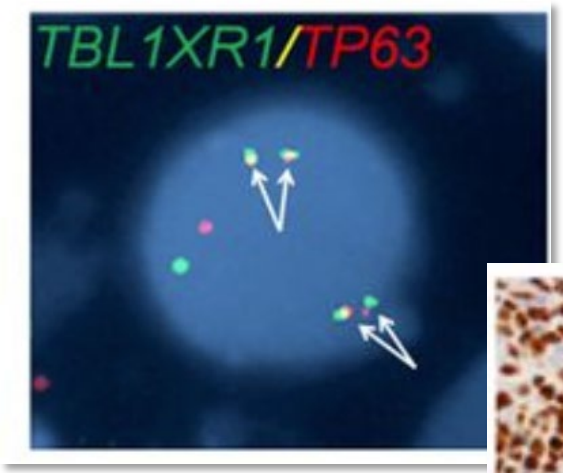
- Absence of JAK/STAT3 pathway activation
- Absent expression of PD-L1 and high expression of CD58 and HLA class II
- DNA hypomethylation
- Absent expression of cytotoxic molecules
- LEF1+
- *MSC* E116K mutation (30%)

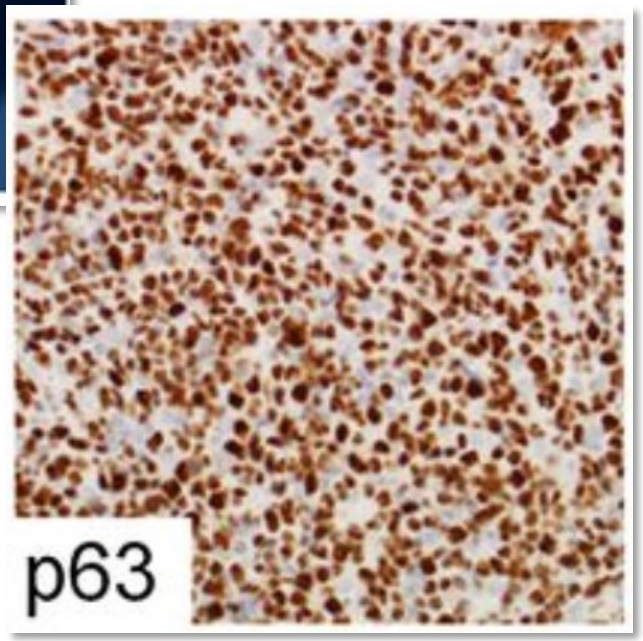


Adapted from Luchtel et al. Blood 2018; 132(13):1386-1398
Adapted from Parrilla Castellar et al. Blood 2014; 124(9):1473-1480

TP63-R ALCL

- TP63-R ⟶ fusion transcripts
- The most common is TBL1XR1::TP63, corresponding to inv(3)(q26q28)

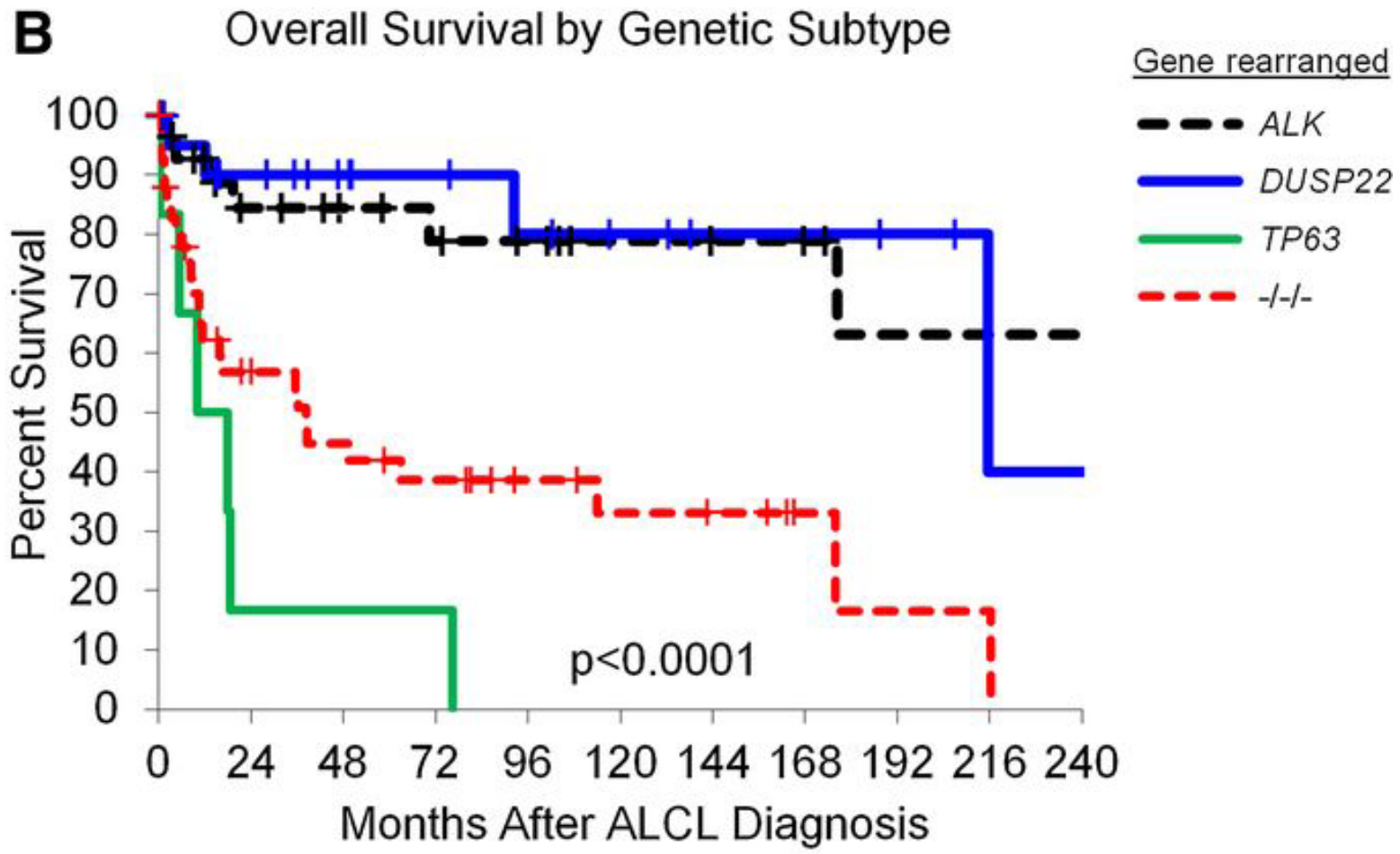




- Immunohistochemistry for p63 is highly sensitive although not specific
- Useful to select cases for TP63 FISH

Adapted from Parrilla Castellar et al. Blood 2014; 124(9):1473-1480

PROGNOSIS

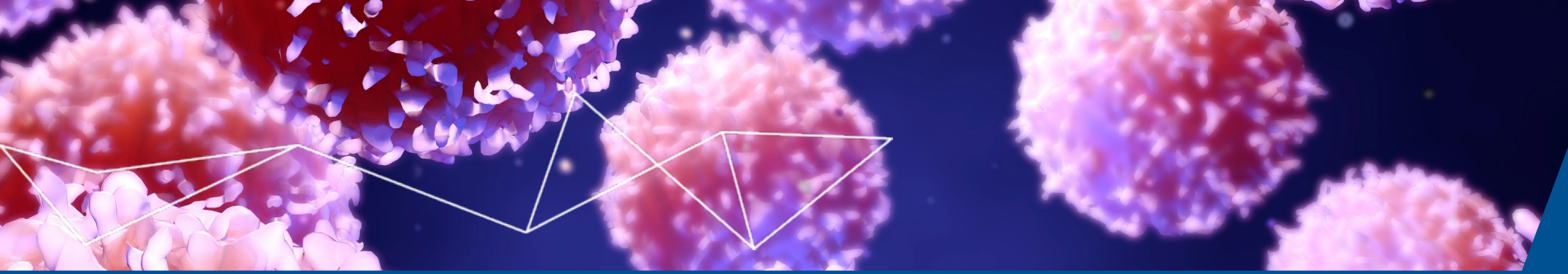


Adapted from Parrilla Castellar et al. Blood 2014; 124(9):1473-1480

PROGNOSIS – DUSP22-R

Feature	First author (Study location/group)					
	Parilla-Castellar (Mayo)[6]	Pedersen (Denmark)[10]	Hapgood (BC Cancer)[12]	Onaindia (Spain)[11]	Sibon (LYSA)[13]	Qiu (MDACC)[14]
DUSP22-R cases, N	22	5	12	4	47	22
DUSP22-R among ALK-negative cases, %	30	19	19	18	45	28
Treatment, %						
CHOP(like)	90	100	92	50[b]	94[c]	90
Consolidative auto-SCT	5	50[d]	8	0	19	27
Missing treatment data	36			25		
5-year PFS, %	nr	nr	40	nr	57	40[d]
5-year OS, %	90	80	40	100	65	40

Adapted from Savage et al. Haematologica 2023;108(6):1463-1467



T-FOLLICULAR HELPER CELL LYMPHOMA

- TFH phenotype
- GEP similar to normal Tfh cells
- Similar molecular landscape

T-FOLLICULAR HELPER CELL LYMPHOMA

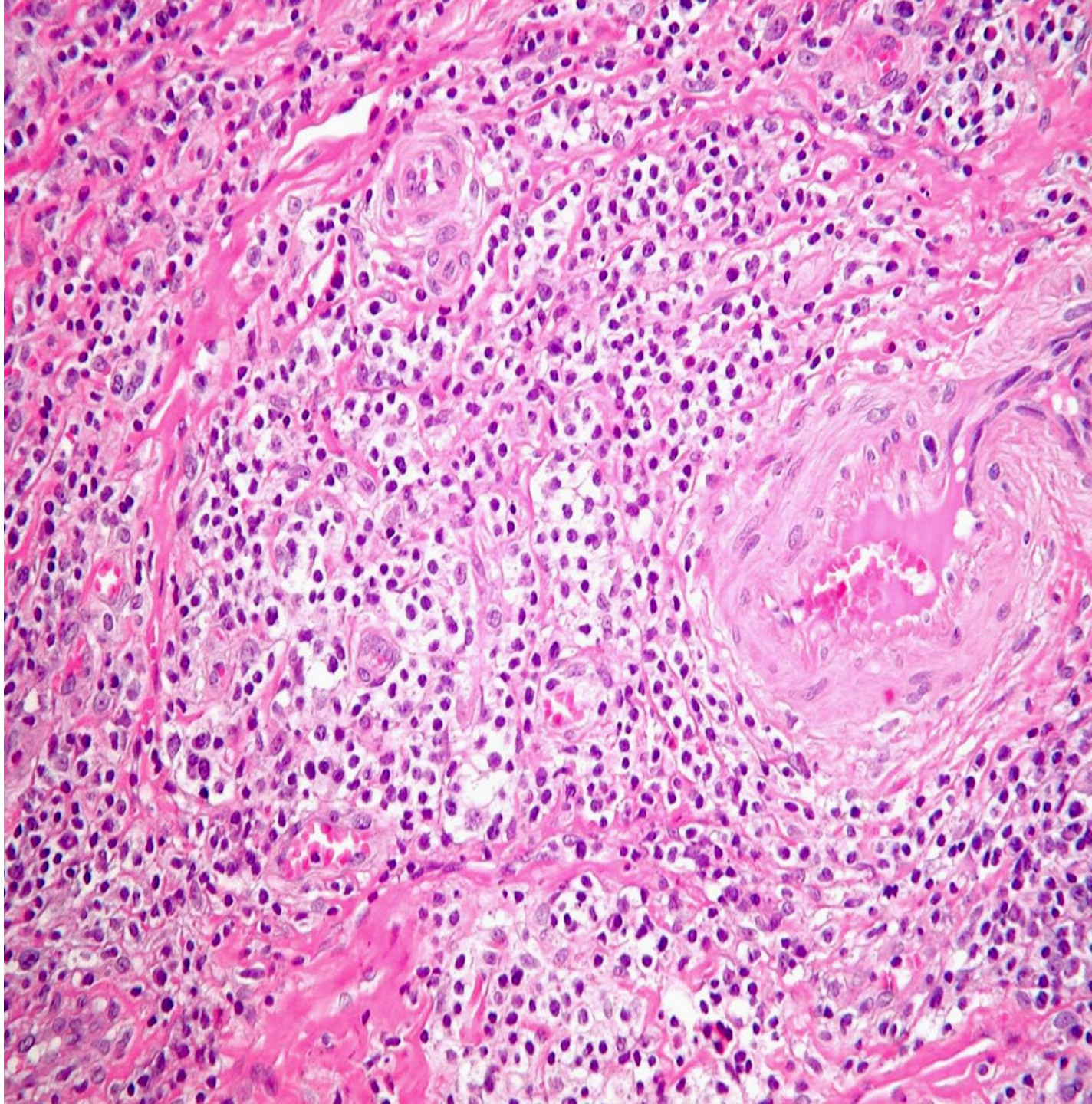
WHO-HAEM4R (2017) → «umbrella category» that included AITL, follicular T-cell lymphoma, and nodal PTCL with TFH phenotype

ICC and WHO-HAEM5 → TFHL is a single entity with 3 subtypes:

- ❑ Angioimmunoblastic-type
- ❑ Follicular-type
- ❑ TFHL, NOS

AITL-type
MICROSCOPIC FEATURES

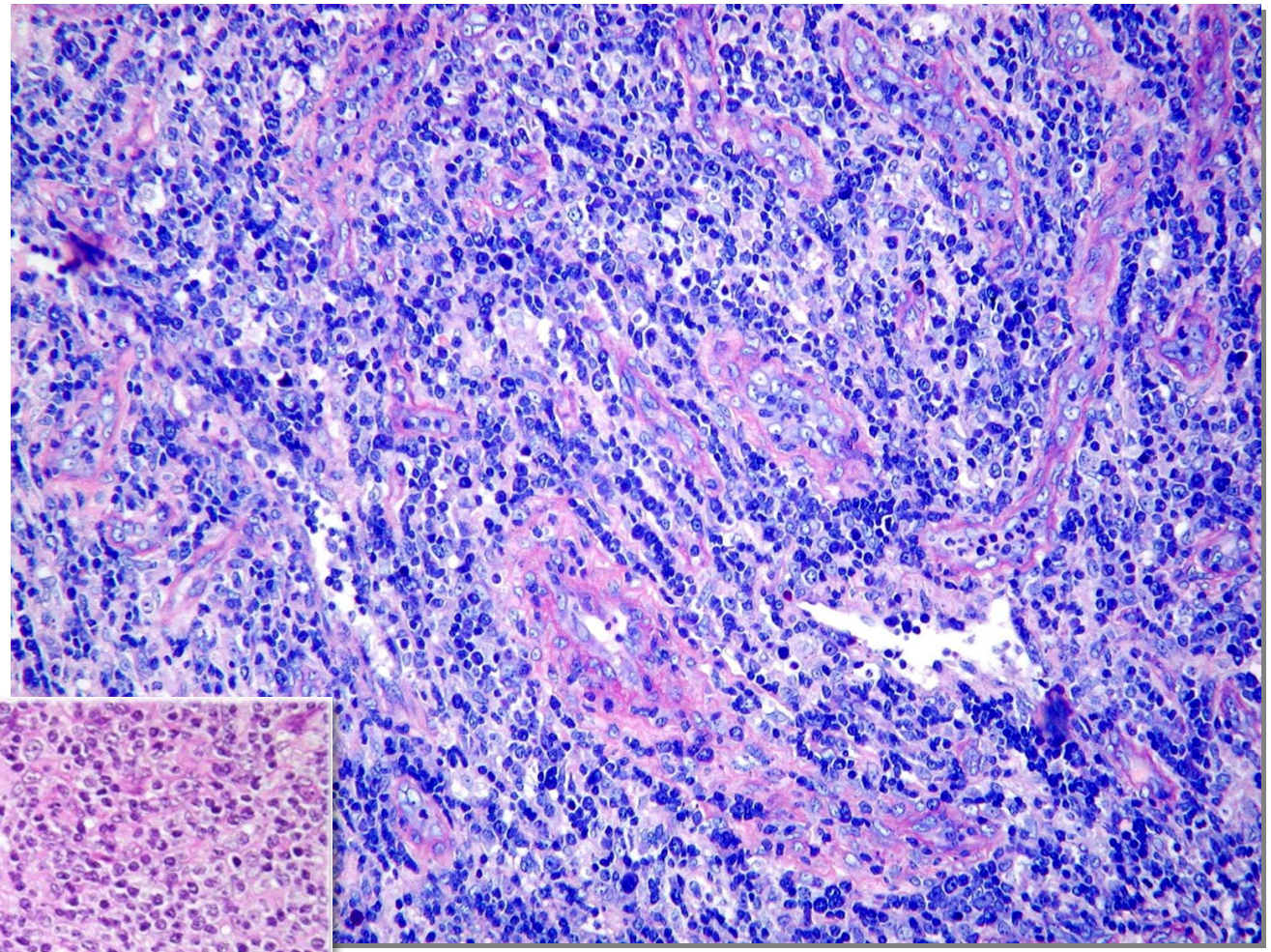
- Perifollicular (Patterns 1-2) or Diffuse (Pattern 3)
- Small- to medium-sized lymphocytes, often with pale, clear cytoplasm
- Inflammatory background:
  - ❑ Small lymphocytes
  - ❑ Immunoblasts (HRS-like)
  - ❑ Histiocytes
  - ❑ Eosinophils

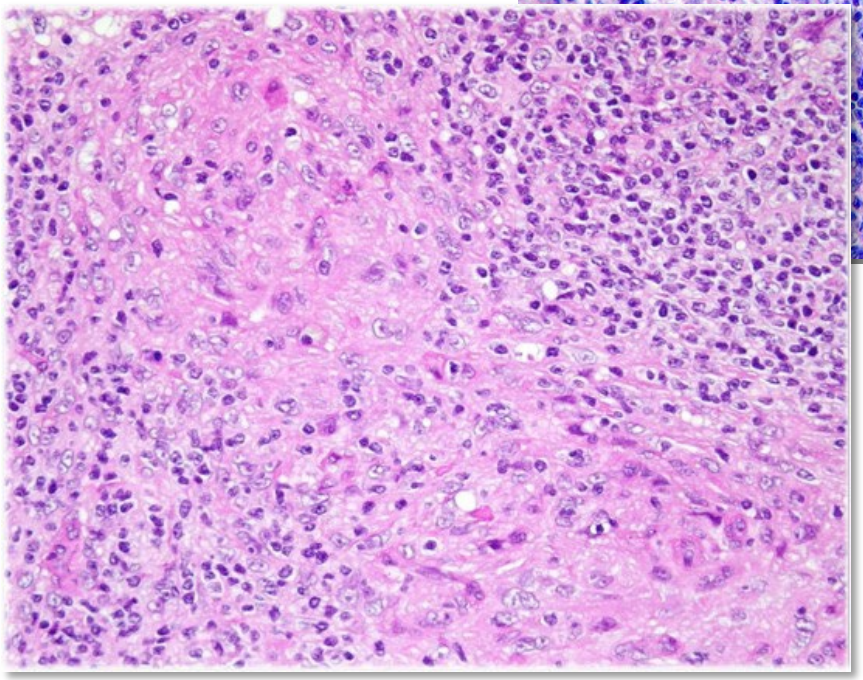


AITL-type
MICROSCOPIC FEATURES

- Prominent, branching high endothelial venules

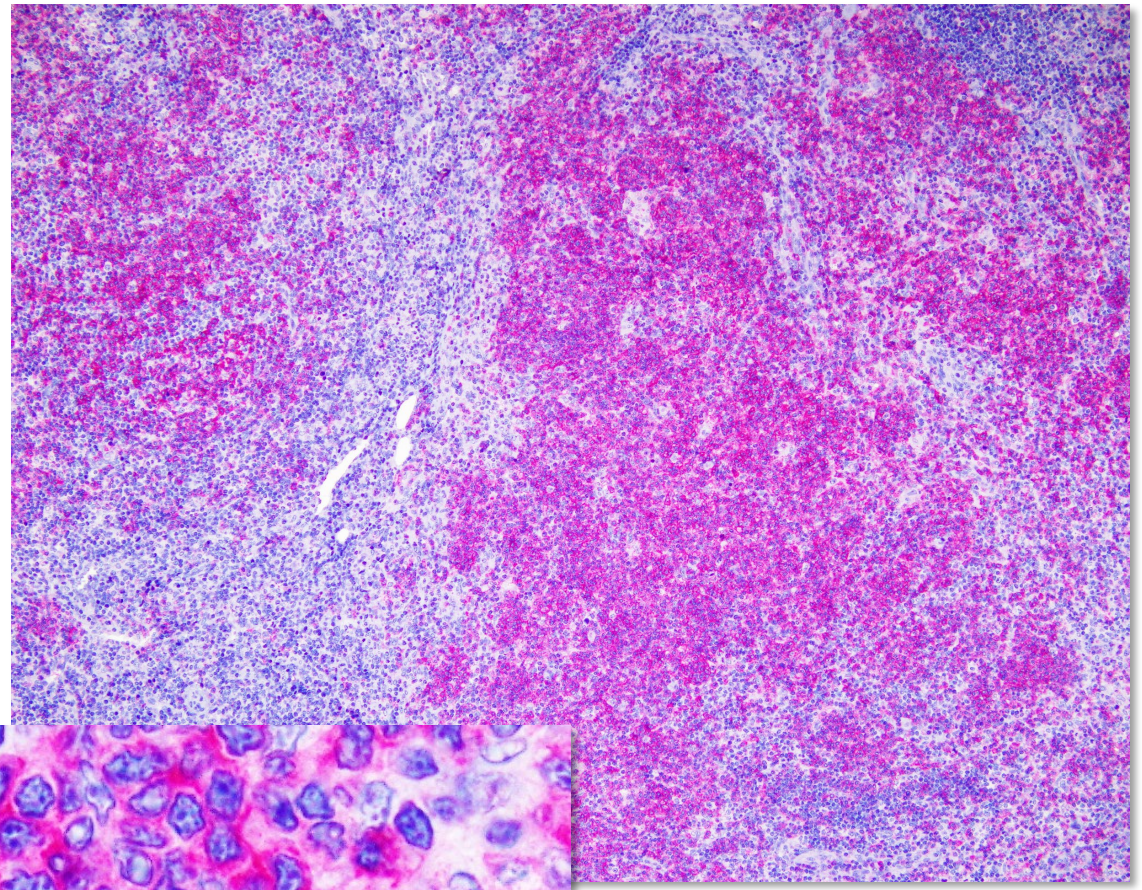
- Proliferation follicular dendritic cells (FDCs)

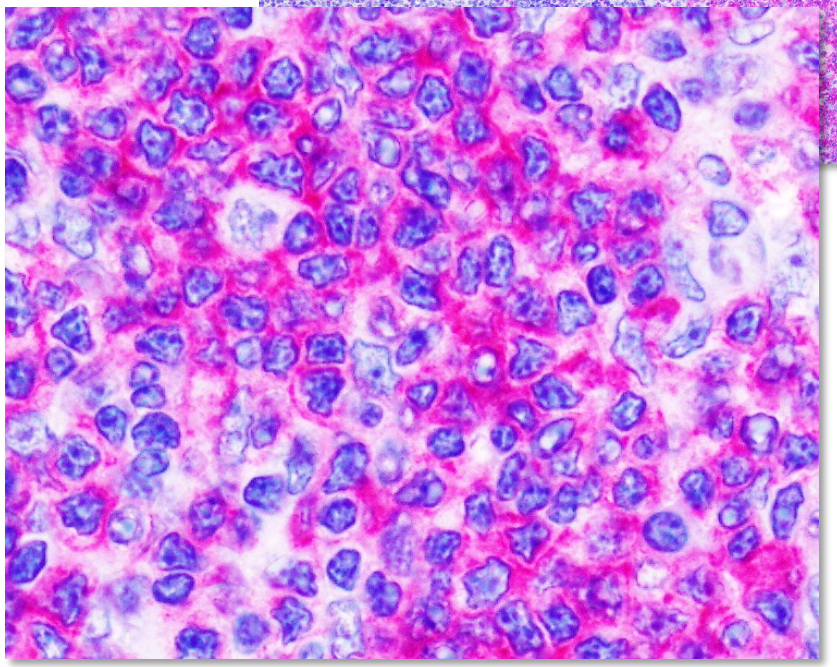




FOLLICULAR-type
MICROSCOPIC FEATURES

- Lacks characteristic features of AITL
- Two distinct patterns:
  - ❑ FL-like pattern: resembling follicular lymphoma
  - ❑ PTGC-like pattern: large nodules reminiscent of progressive transformation of germinal centers
- Absent/minimal HEVs and FDCs proliferation of

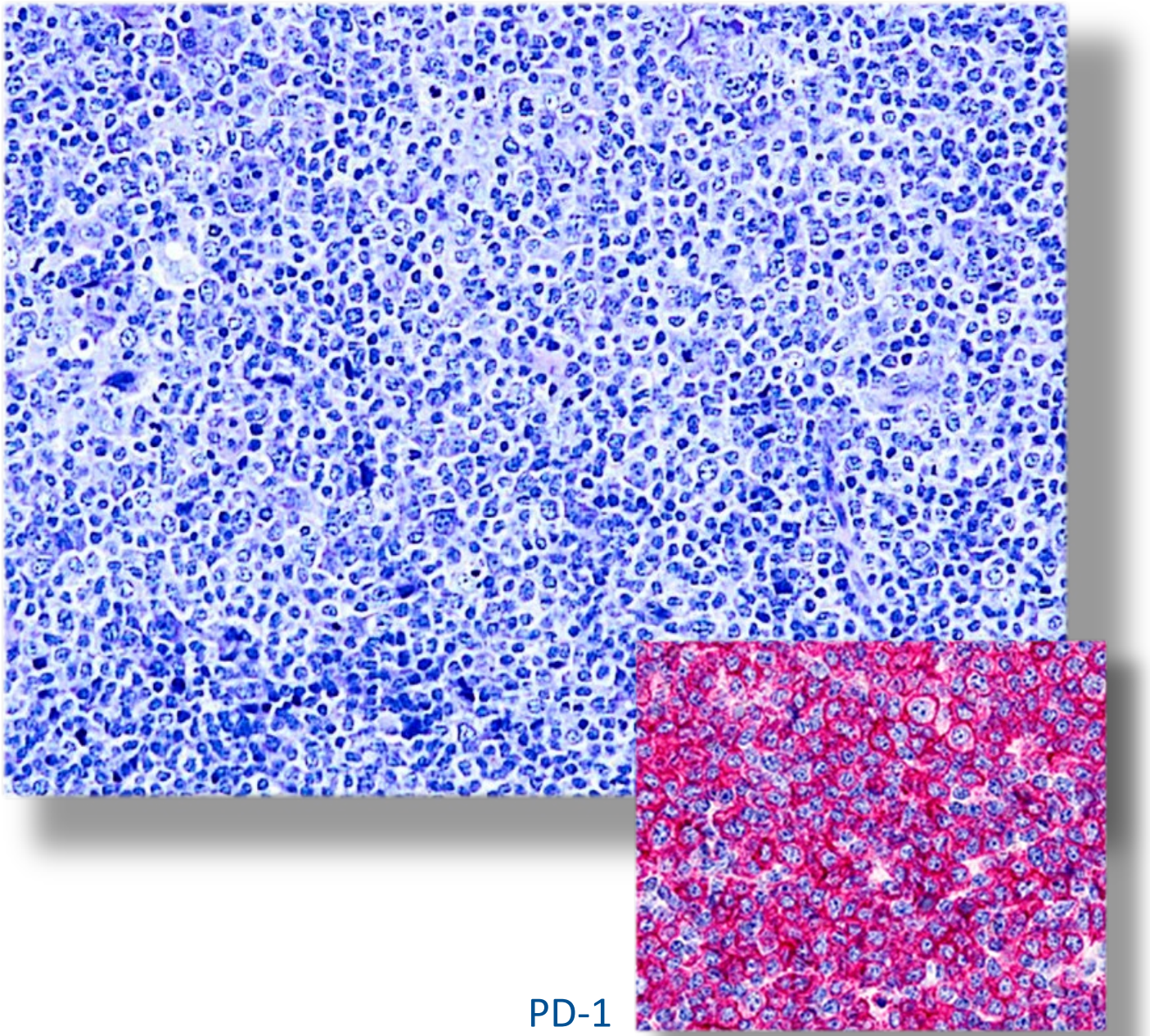




PD-1

TFHL, NOS
MICROSCOPIC FEATURES

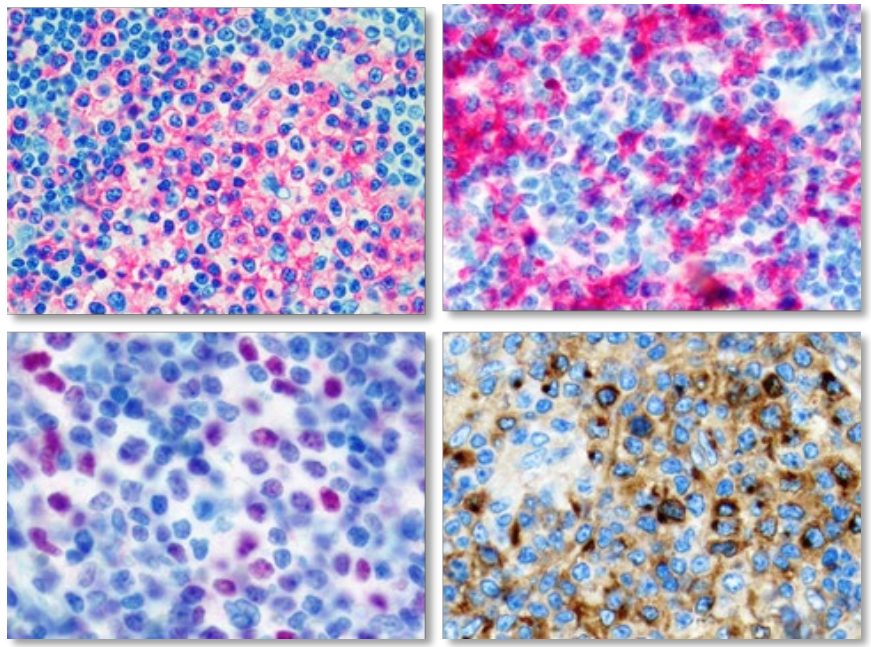
- TFHL-NOS lack features of AITL and TFHL-F
- The lymph node architecture is usually effaced
- Medium- to large-sized CD4+ cells expressing at least 2 TFH markers

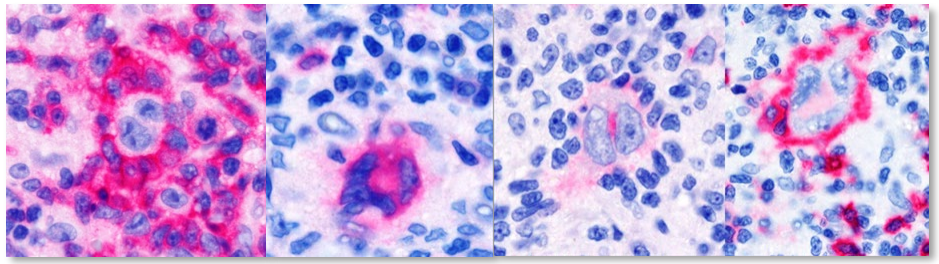


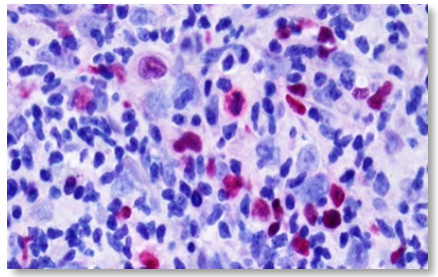
PD-1

IMMUNOPHENOTYPE

- Neoplastic cells
  - ❑ CD4+
  - ❑ Preserved expression of CD2, CD3, and CD5 with loss/diminished expression of CD7
  - ❑ At least 2 TFH markers (CD10, BCL6, CXCL13, ICOS, and PD1) are positive
- Intermingled B-immunoblasts (CD20+/CD30+), often associated with Epstein-Barr virus (EBV) infection



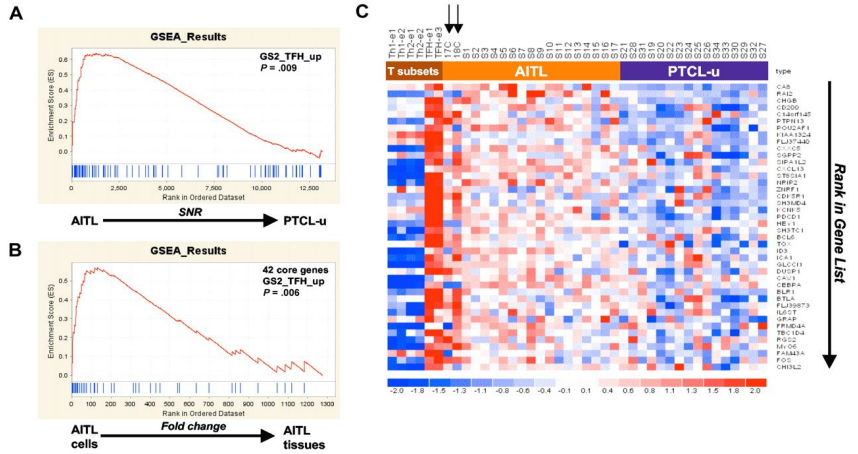


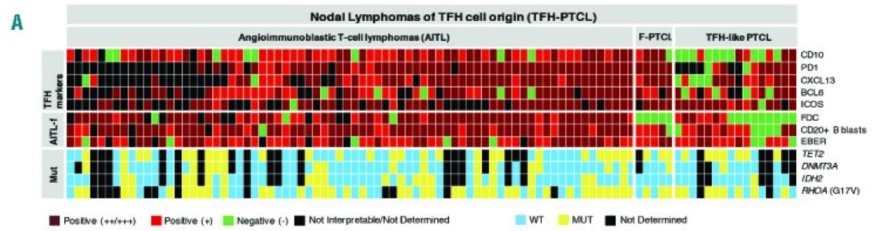


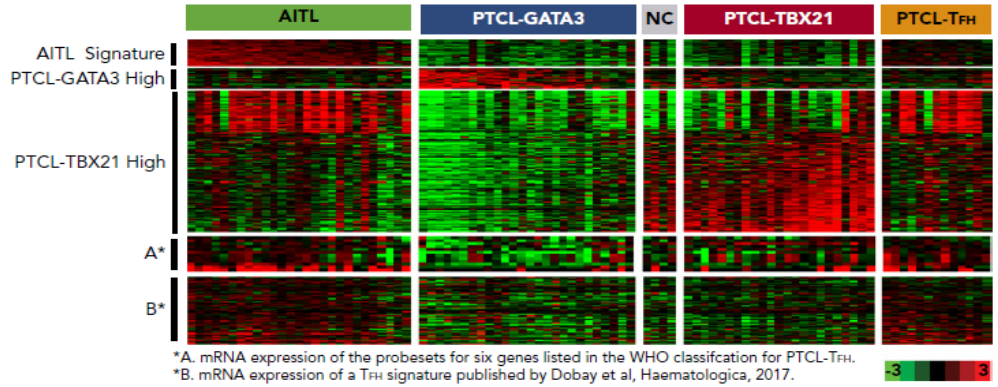
EBV (EBER-ISH)

MOLECULAR FEATURES

- The 3 subtypes share gene expression signatures and mutational profiles
- In 2007, GEP analyses identified the TFH cell as the cell of origin of AITL
- Further analysis identified additional nodal PTCLs with GEP features of TFH derivation







de Leval et al. Blood 2007;109(11):4952-4963
Dobay et al. Haematologica 2017;102(4):e148-e151
Heavican et al. Blood 2019;133(15):1664-1676

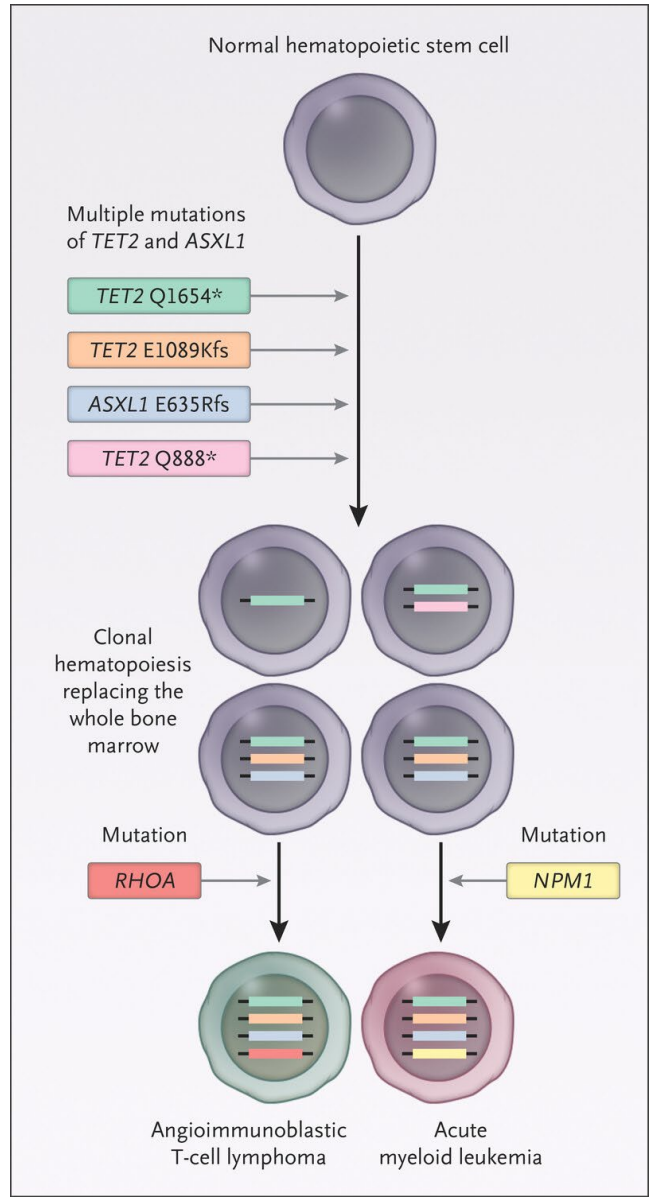
MOLECULAR FEATURES

- Frequently mutated genes include *RHOA, TET2, DNMT3A*, and *IDH2*
- *RHOA* G17V [50%-70%] binds to VAV1 → accelerating T-cell receptor (TCR) signaling
- *RHOA* G17V expression in CD4 T cells led to TFH differentiation

Lemonnier F et al. Blood 2012;120(7):1462-1469
Palomero et al. Nat Genet 2014;46(2):166-170
Sakata-Yanagimoto et al. Nat Genet 2014;46(2):171-175
Vallois et al. Blood 2016;128(11):1490-1502
Lemonnier F et al. PNAS 2016;113(52):15084-15089

MOLECULAR FEATURES

- Recurrent mutations in epigenetic modifier genes (*TET2, IDH2*^{R17}, and *DNMT3A*)
- Also found in healthy individuals with clonal hematopoiesis
- Possible multistep pathogenesis of TFHL:
  - ❑ «first hit»: *TET2* +/- *DNMT3A*
  - ❑ "second hit": *RHOA* G17V, other genes

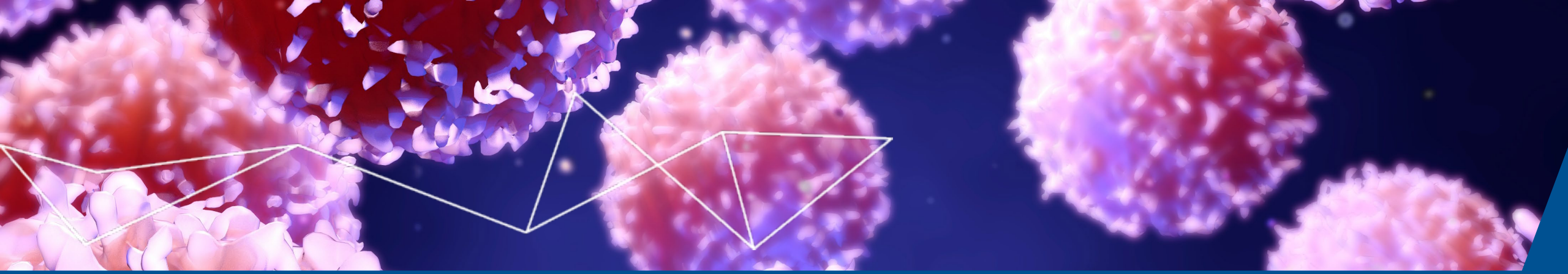


Tiacci et al. NEJM 2018;379(10):981–4
Lewis et al. Blood Adv 2020;4:2261–2271

PROGNOSIS

- The overall prognosis of patients with TFHL is poor (3-year OS ~ 50%)
- Lenalidomide + CHOP: *DNMT3A* mutations are associated with shorter response rate to chemotherapy and adverse PFS
- Co-occurrence of *TET2/IDH/DNMT3A* mutation was associated with shorter PFS and OS

Lemonnier et al. Blood Adv 2021;5(2):539-548



PRIMARY NODAL EBV–POSITIVE T/NK-CELL LYMPHOMA

PRIMARY NODAL EBV–POSITIVE T/NK-CELL LYMPHOMA

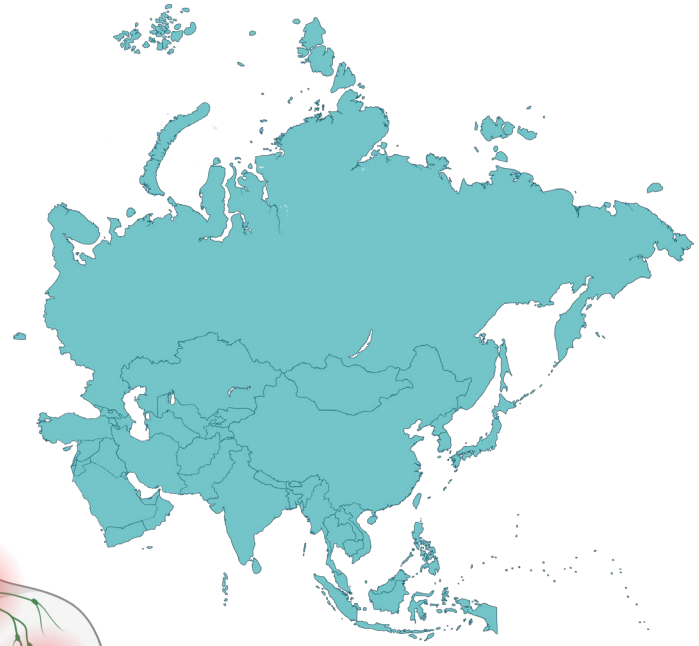
- Most EBV+ T/NK-cell lymphomas arise in extranodal sites (e.g ENKTL)
- **Primary nodal** EBV+ nTNKLs are much rarer

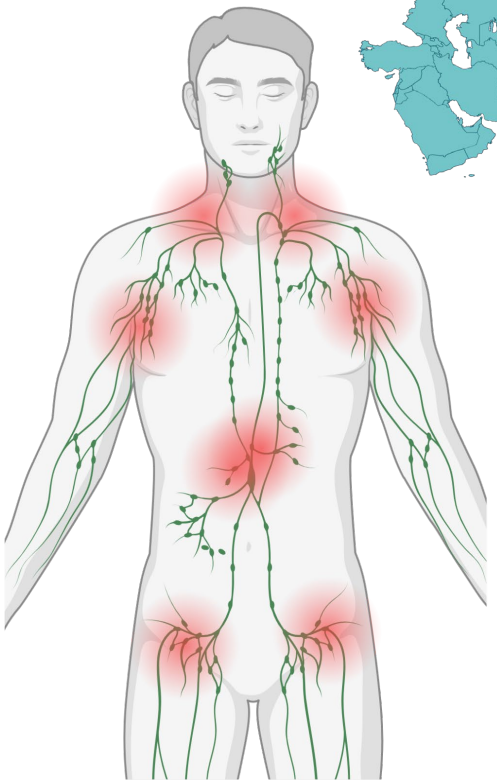
- Classified as a variant of PTCL-NOS in WHO-HAEM4R
- **New distinct entity** in ICC and WHO-HAEM5

WHO-HAEM4R	ICC 2022	WHO-HAEM5
Not listed as an entity (PTCL, NOS)	Primary nodal EBV+ T-cell/NK-cell lymphoma	EBV+ nodal T- and NK-cell lymphoma

CLINICAL FEATURES

- East Asia (≈ ENKTL)
- Usually affecting the elderly, advanced stage disease
- Often associated with immunodeficiency
- Lymphadenopathy with or without extranodal involvement
- No nasal involvement
- Advanced-stage disease and B symptoms

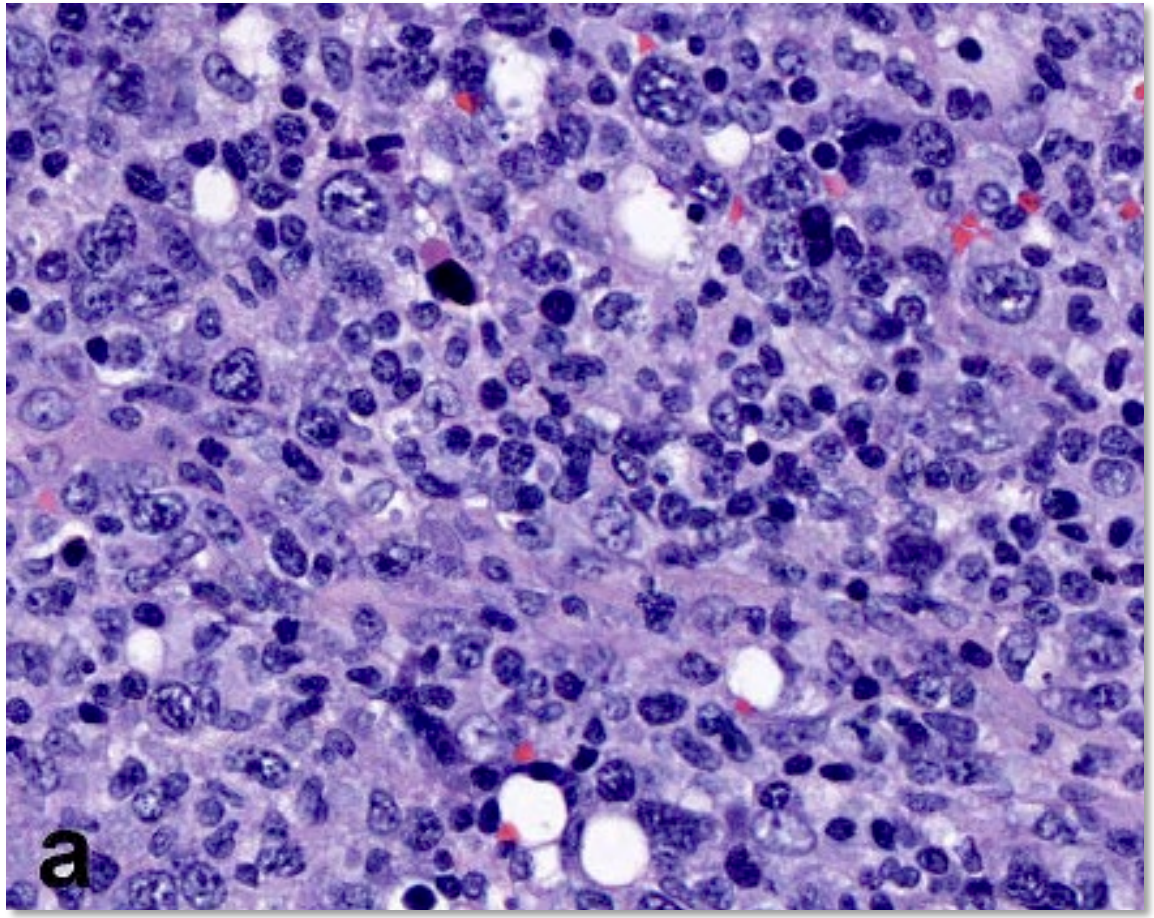




Ng et al. Haematologica 2018;103:278–287

MICROSCOPIC FEATURES

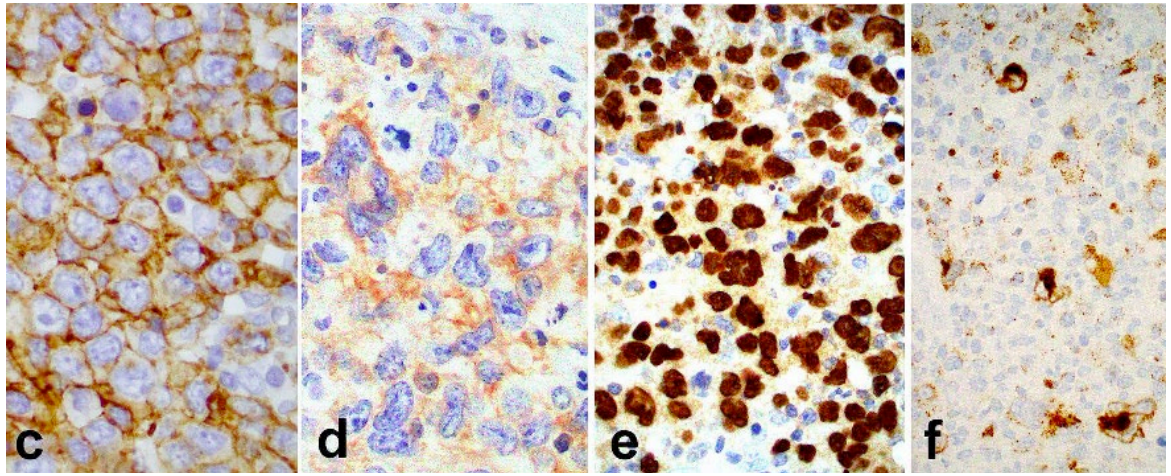
- Medium- to large-sized lymphocytes (mimicking DLBCL)
- Angiocentric infiltration and necrosis are uncommon (≠ ENKTL)



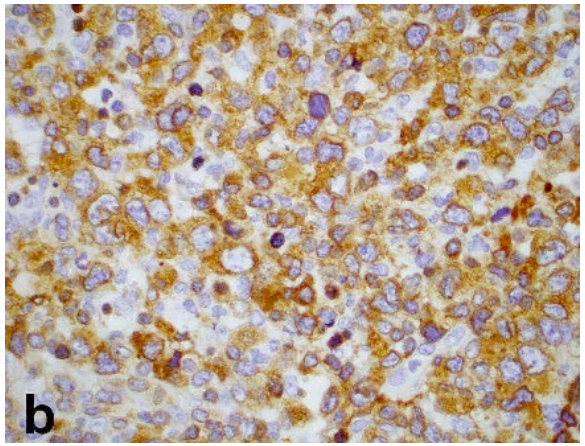
Adapted from Wai et al. Haematologica 2022;107(8):1864-1879

IMMUNOPHENOTYPE

- Positive for pan-T-cell markers and cytotoxic molecules
- Usually CD8+/CD56-
- Frequent loss of CD5
- In situ hybridization for EBV-encoded small RNAs (EBER ISH) is positive by definition
- Type 2 EBV latency pattern



CD8 TCRβ EBER-ISH GyzB

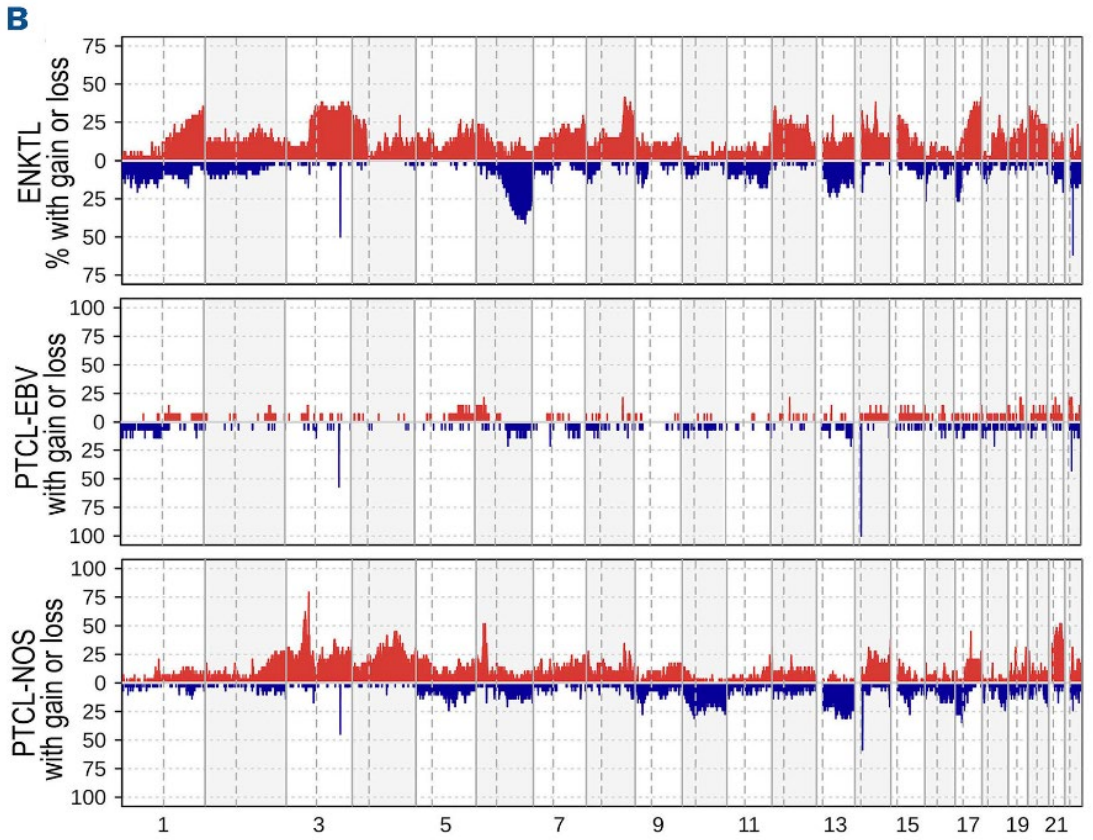


CD3

Adapted from Wai et al. Haematologica 2022;107(8):1864-1879

MOLECULAR FEATURES

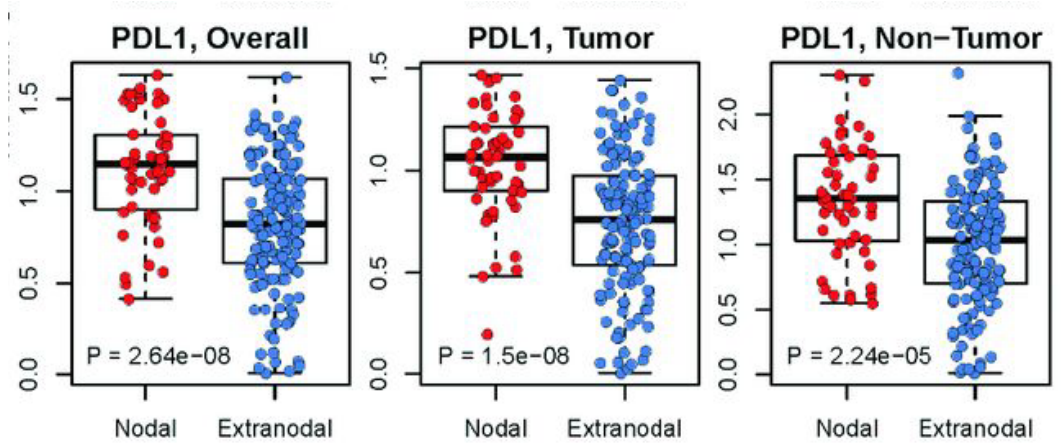
- Predominantly of **T-cell origin** (80% clonal rearrangement of TCR genes)
- Mutations in *TET2* (64%), *PIK3CD* (33%), *DDX3X* (20%), and *STAT3* (19%)
- Lower genomic instability than ENKTL or PTCL-NOS



Adapted from Wai et al. Haematologica 2022;107(8):1864-1879

MOLECULAR FEATURES

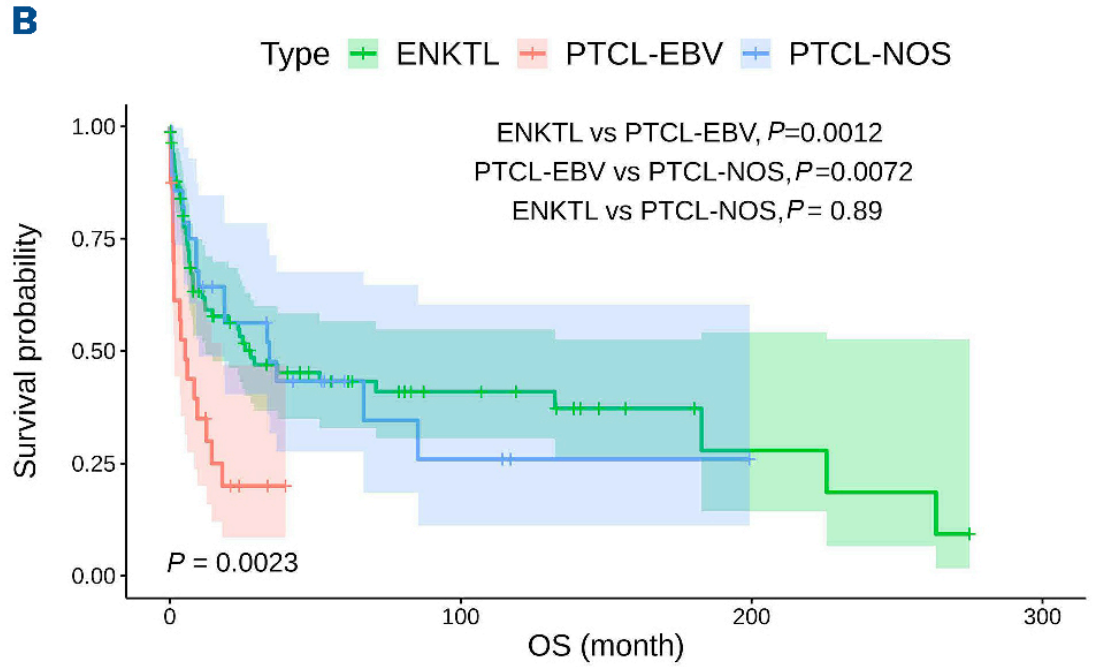
- Upregulation of genes related to
  - ❑ Cytotoxic activation
  - ❑ JAK/STAT signaling
  - ❑ Immune-related pathways (CD274/PD-L1)



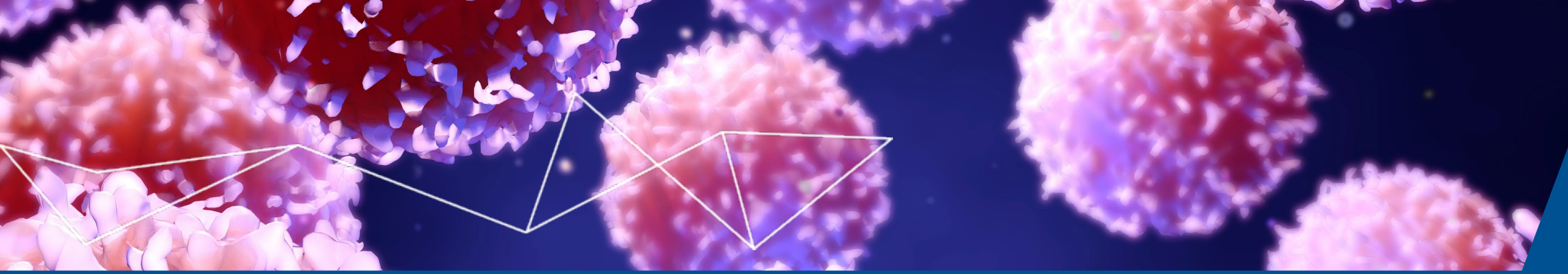
Adapted from Ng et al. Haematologica 2018;103:278–287

PROGNOSIS

- Poor outcomes compared with ENKTL or PTCL-NOS
- Median OS is 2.5 to 8.9 months



Adapted from Wai et al. Haematologica 2022;107(8):1864-1879

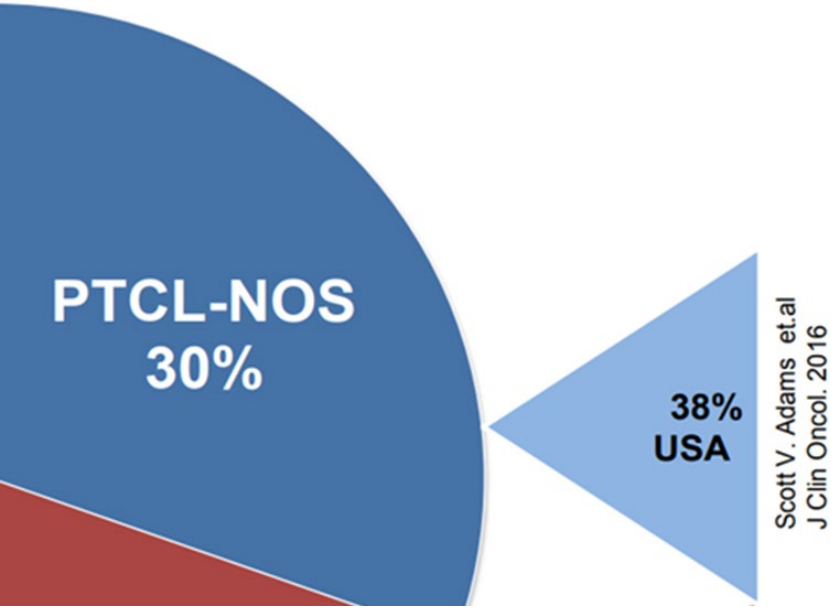


PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED

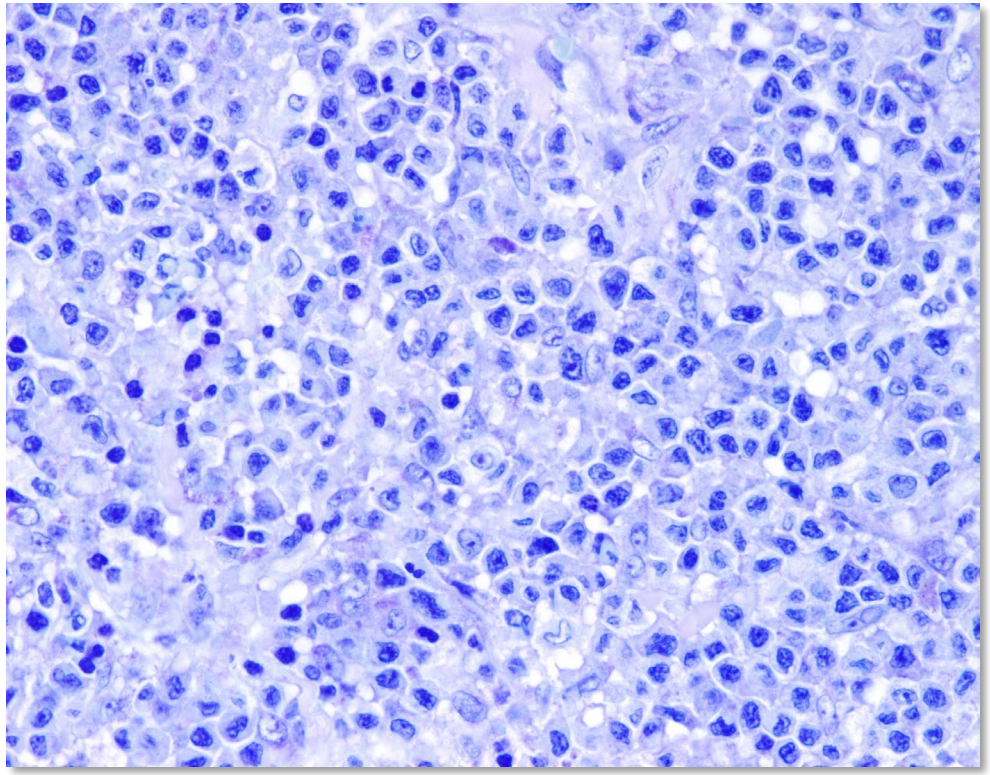
PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED

- Heterogeneous category

- Diagnosis of exclusion: nodal mature T-cell lymphomas that cannot be assigned to a specific entity



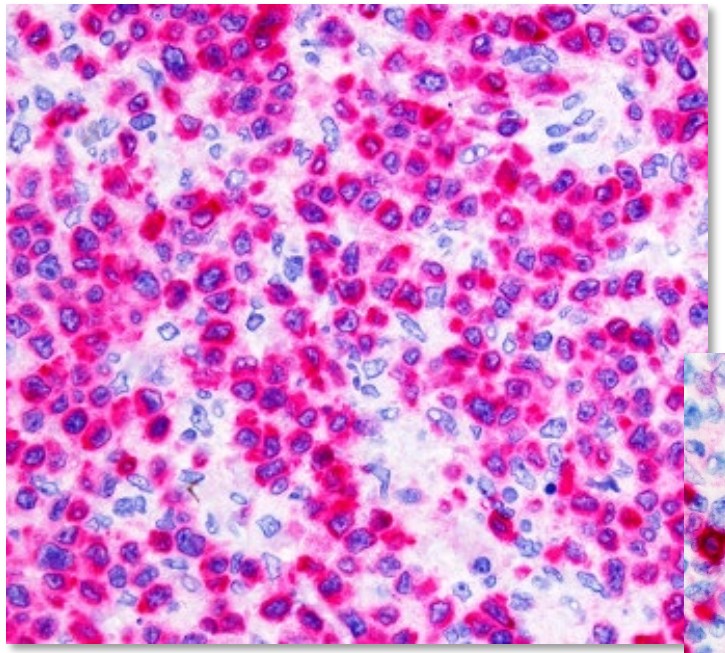
MICROSCOPIC FEATURES



- Paracortical or diffuse pattern
- Wide spectrum of cytologic features
  - ❑ medium-sized cells with irregular nucleai (most often)
  - ❑ small or large-sized T cells
- Inflammatory background
- Epithelioid histiocytes can be numerous in so-called Lennert lymphoma
- Scattered HRS-like and/or EBV-positive B-immunoblasts

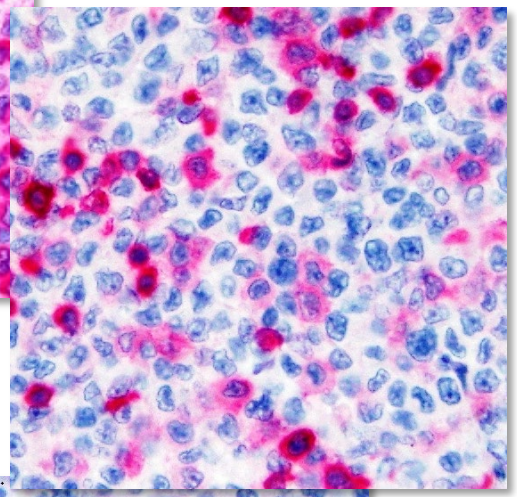
IMMUNOPHENOTYPE

- Mature T-cell phenotype
- Aberrant loss or diminished expression of one or more pan-T-cell markers (CD2, CD3, CD5, CD7, and TCR)

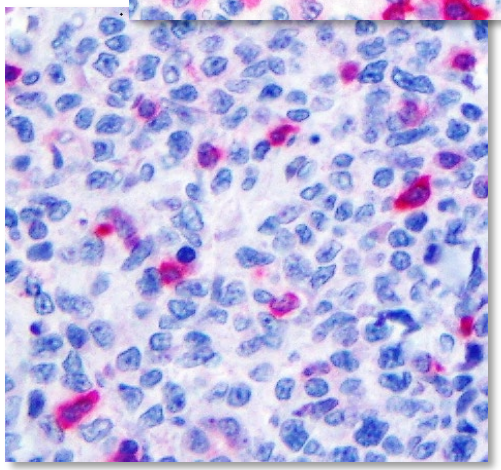


CD3

CD5



CD7



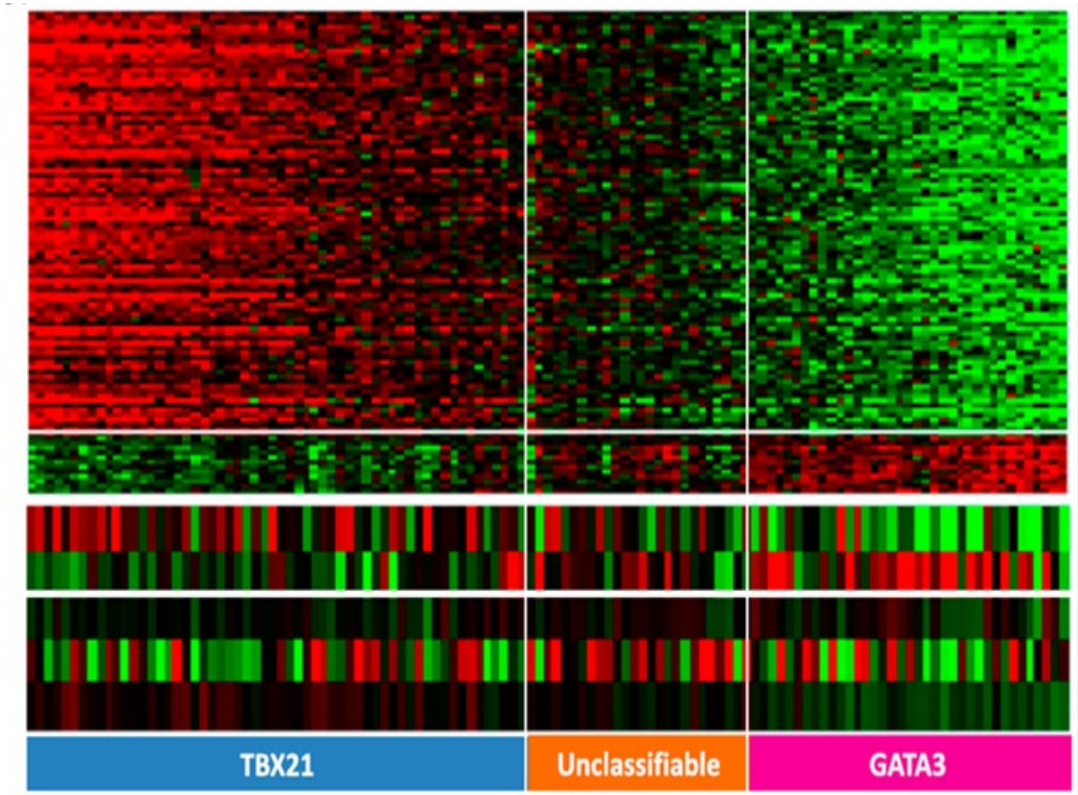
- Mostly CD4+/CD8- → exclude TFH phenotype
- Cytotoxic molecules are positive in a subset of cases → exclude EBV+

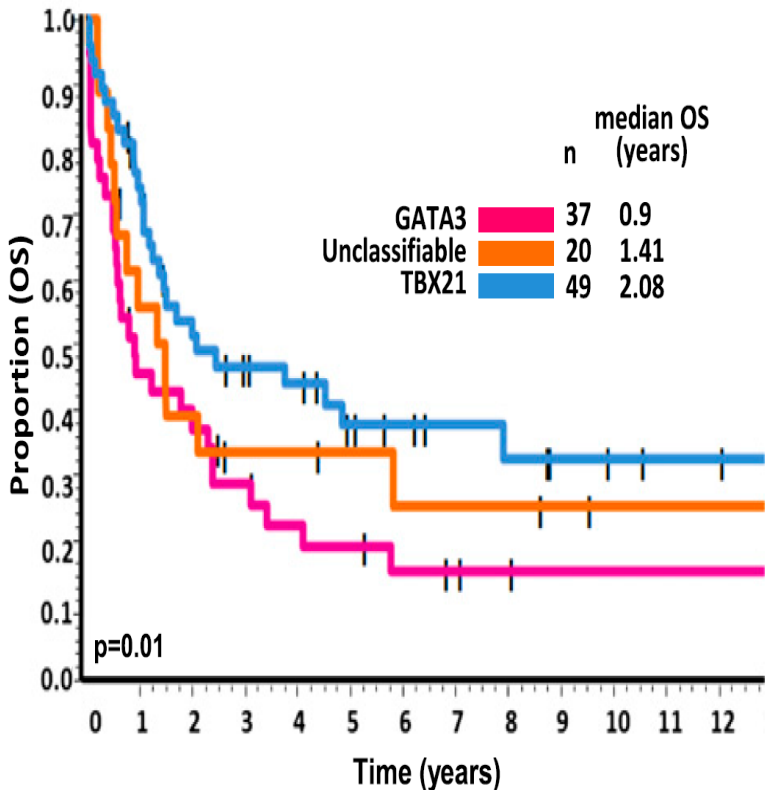
MOLECULAR FEATURES

- Highly heterogeneous and complex genomic landscape
- Recurrent mutations in genes associated with:
  - ❑ TCR pathway (*PLCG1* and *CARD11*)
  - ❑ JAK/STAT pathway (*JAK3, STAT3*, and *SOCS1*)
  - ❑ Cell cycle (*TP53, CDKN2A*, and *ATM*)
  - ❑ DNA methylation (*TET2* and *DNMT3A*)
- *TP53* and *CDKN2A* mutations and/or deletions
- Fusion genes involving *FER* and *VAV1*

MOLECULAR FEATURES – TBX21 and GATA3

Two distinct molecular subtypes have been recognized by GEP





Adapted from Iqbal et al. Blood 2014;123:2915–2923

MOLECULAR FEATURES – TBX21 and GATA3

PTCL-TBX21

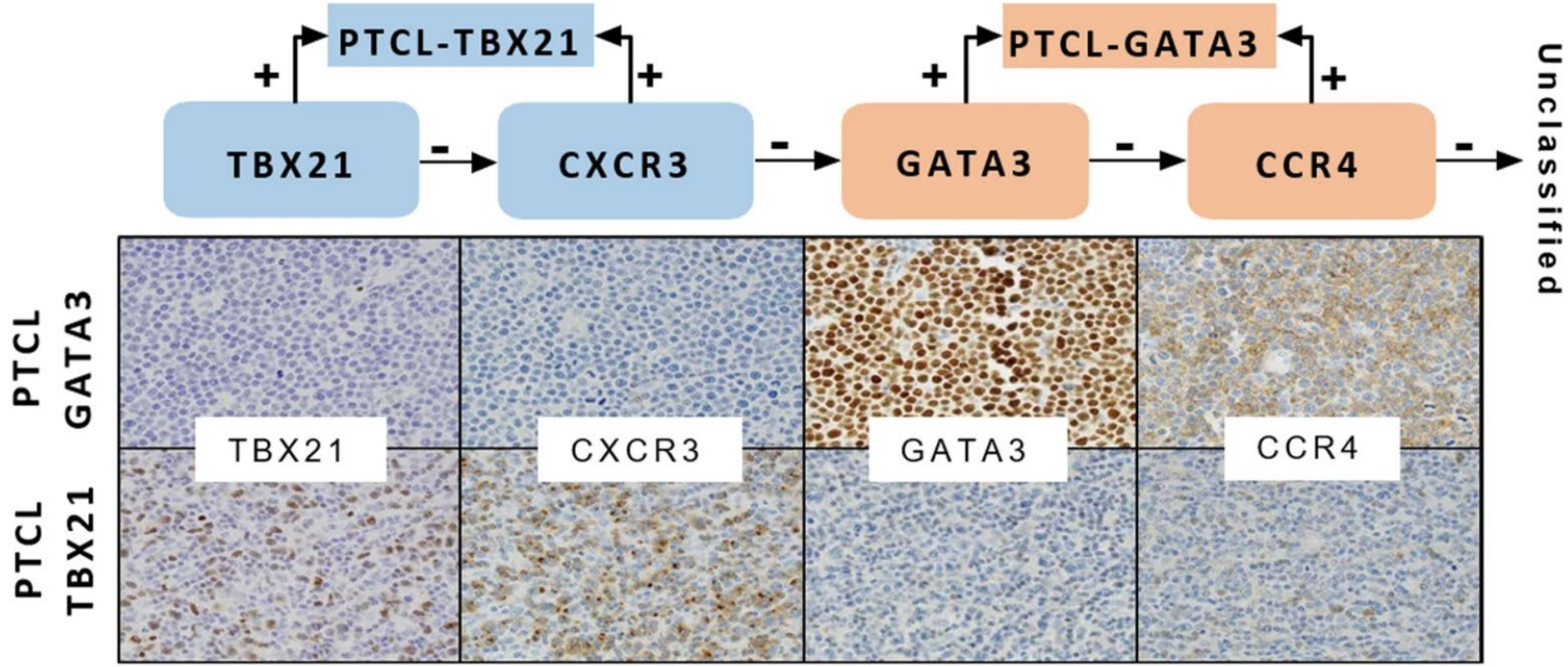
- ❑ Th1-like signature
- ❑ High expression of TBX21 and EOMES and their target genes (CXCR3, IL2RB, CCL3, and IFNG)
- ❑ Fewer of copy number alterations (CNAs)
- ❑ Frequent mutations in genes associated with DNA methylation
- ❑ More favorable prognosis

PTCL-GATA3

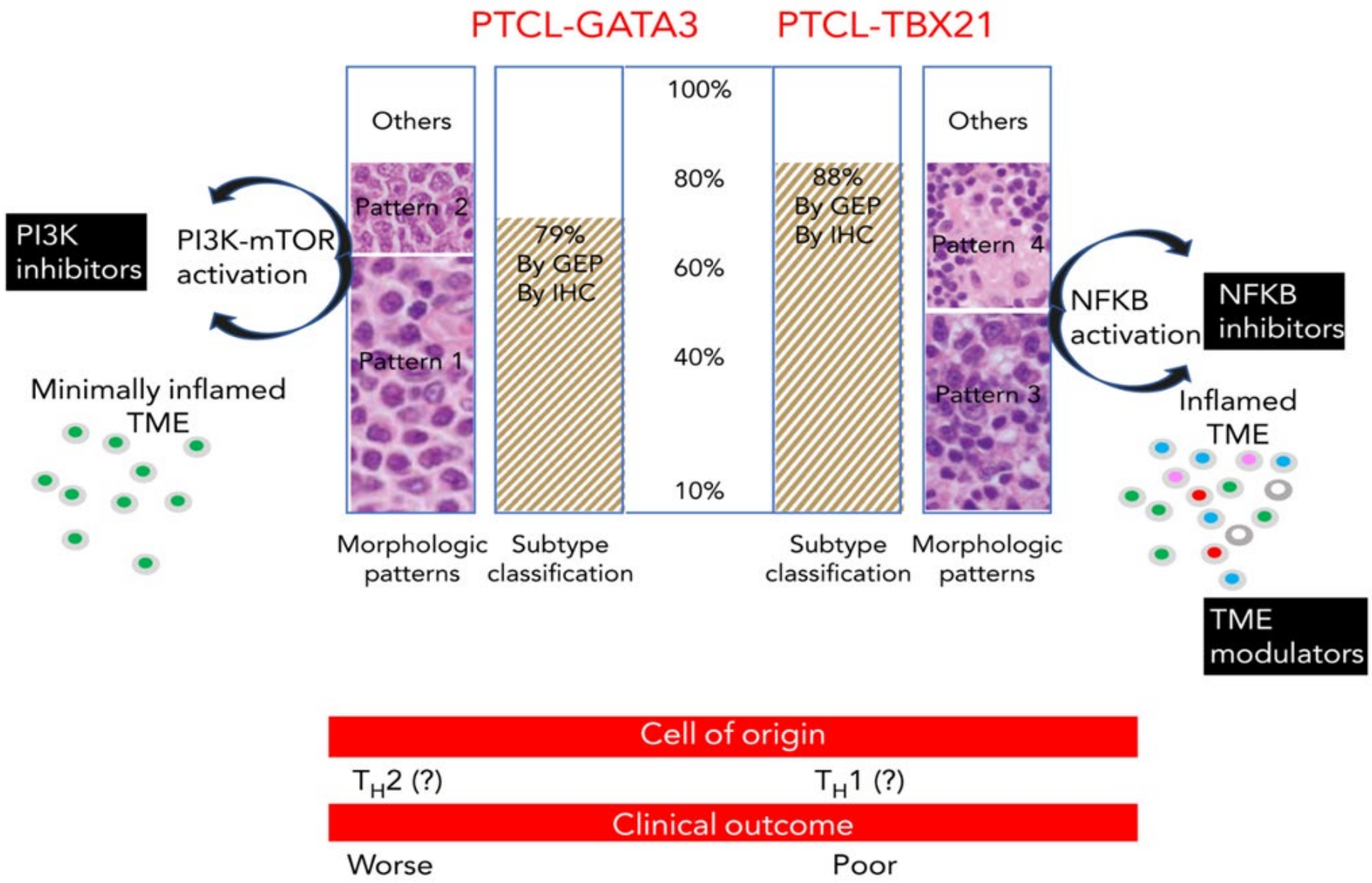
- ❑ Th2-like signature
- ❑ High expression of GATA3 and its target genes (CCR4, IL17RA, CXCR7)
- ❑ Higher level of CNAs
- ❑ Loss/ mutation of tumor suppressor genes (CDKN2A/B-TP53 & PTEN-PI3K)
- ❑ Poorer prognosis

Heavican et al. Blood 2019;133:1664–1676

How to diagnose in daily practice?



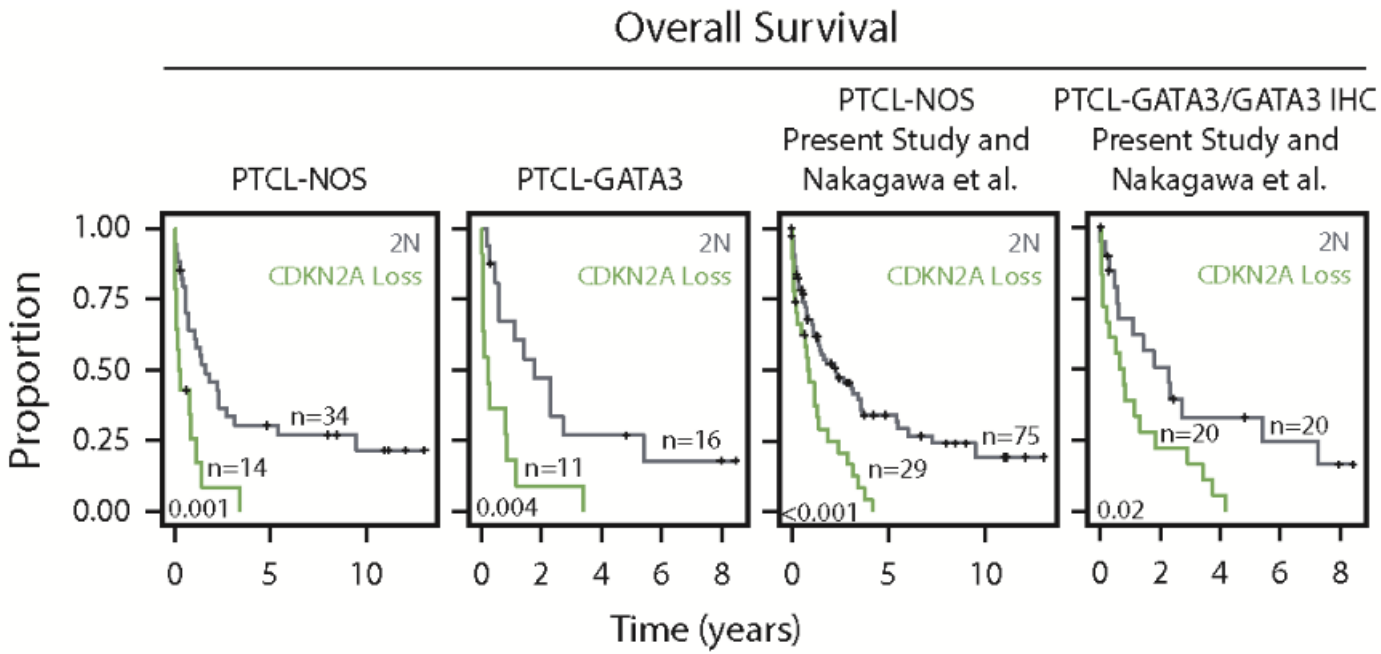
Amador et al. Blood 2019;134:2159–2170



Adapted from Carbone A, Gloghini A. Blood 2019;134(24):2120-2121

PROGNOSIS

- Poor response to therapy, frequent relapses, and short OS
- Molecular features associated with inferior OS:
  - ❑ PTCL-GATA3 subtype
  - ❑ Cytotoxic phenotype
  - ❑ *TP53* and/or *CDKN2A* alterations



Heavican et al. Blood 2019;133:1664–1676

EUROPEAN HEMATOLOGY ASSOCIATION

Thank you

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