T-Cell NHL: Novel Approaches & Challenges

17th Annual New Orleans
Summer Cancer Meeting
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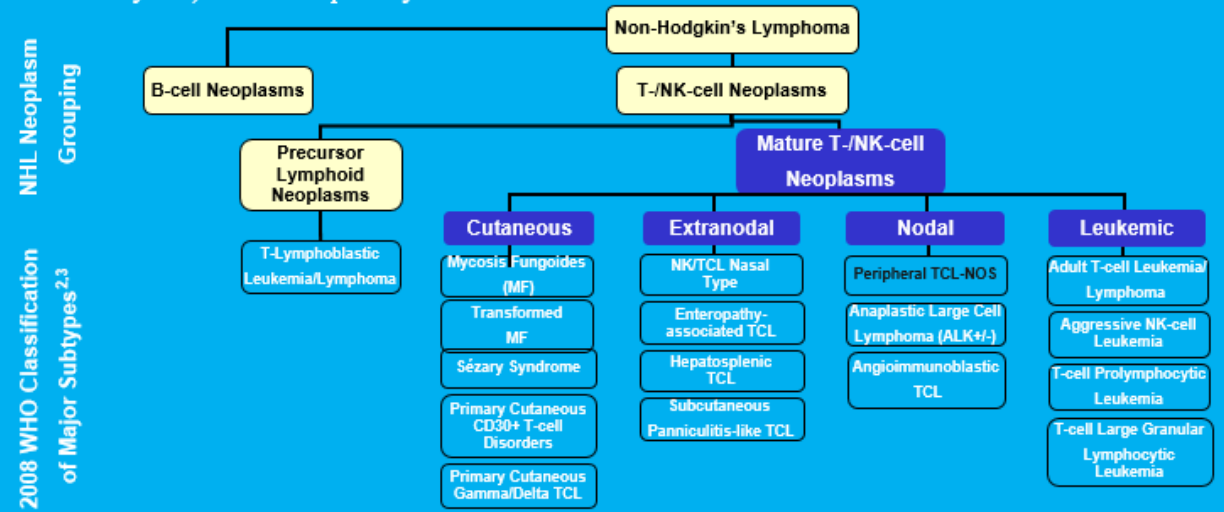
Classification of Peripheral T-cell Lymphoma (PTCL)

- PTCL is a heterogeneous group of aggressive, mature T-/NK-cell lymphomas[1]
  - PTCL does not refer to anatomic sites, but rather to the involvement of more mature (post-thymic) T cells vs pre-thymic or immature T cells[1]



1. Armitage JO, et al. *Ann Oncol*. 2004;15:1447-1449.
2. Adapted from Rodriguez J, et al. *Crit Rev Oncol Hematol*. 2008.
3. Adapted from Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2008

Mycosis fungoides

- Prototype of CTCL
- Low-grade lymphoma
- Post-thymic T-cell malignancy ($CD4^+$/$CD45RO^+$)
- Features of T-regulatory (CD25+ FOX P3+), Th2-and Th17 - Cell Phenotype
- Th_2 cytokine profile: secretion of IL-4, IL-5, IL-6, IL-10, IL-17, IL-18
- Patch, plaque and tumor lesions
- Characteristic histology:
  - Upper-dermal band-like atypical lymphocytic infiltrate
  - Epidermotropism
  - Pautrier's microabscesses

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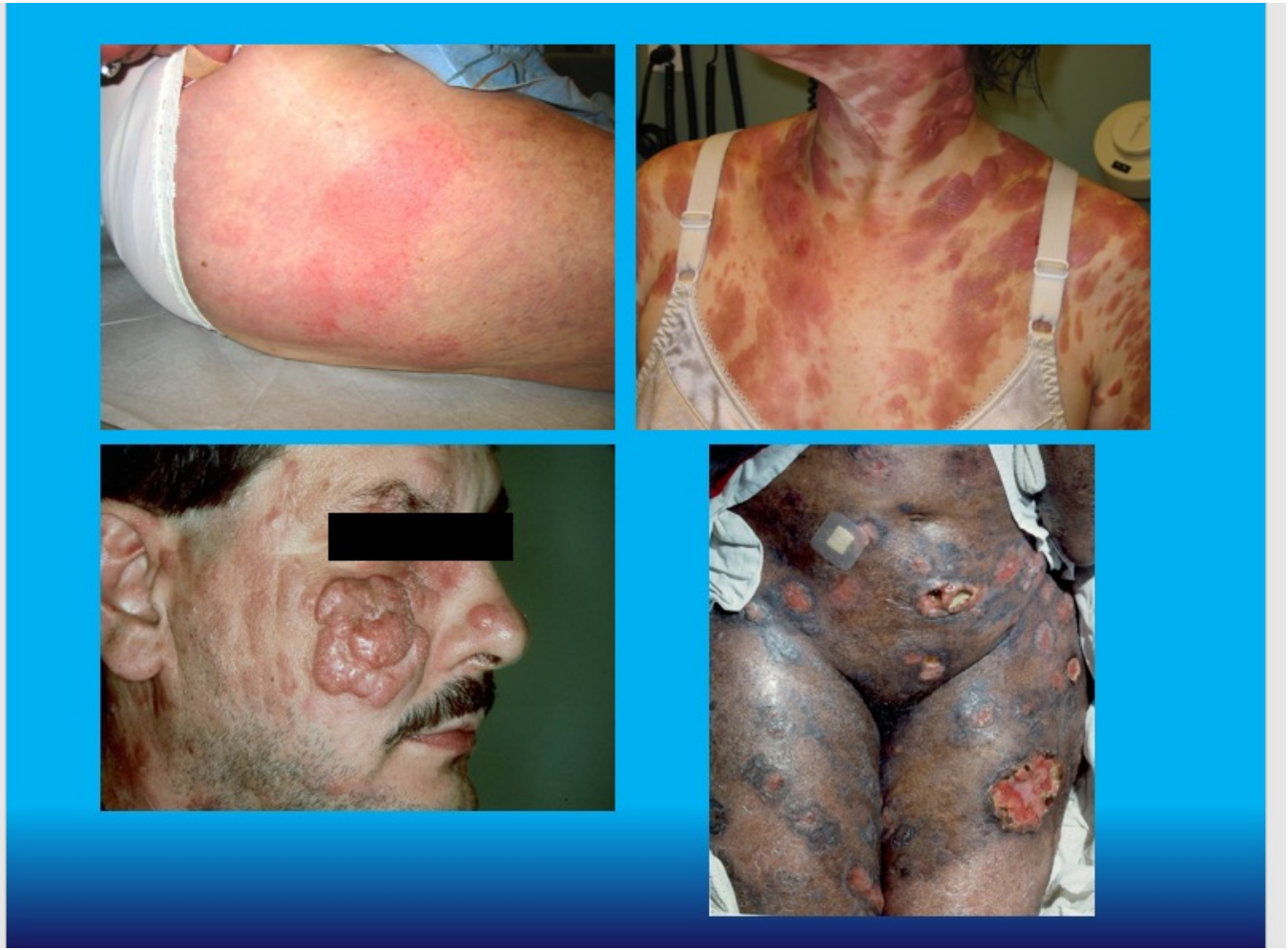
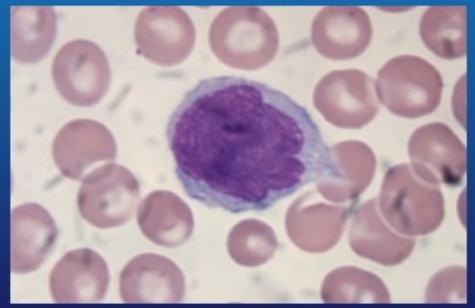
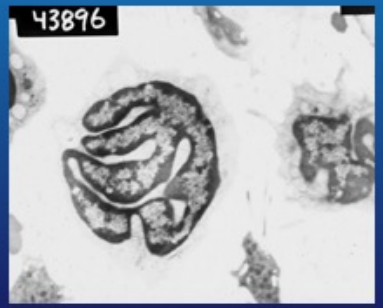


Sézary syndrome

- Systemic and aggressive variant
- Exfoliative erythroderma, Ectropion, alopecia, palmoplantar keratoderma
- Severe pruritus
- Circulating, atypical, malignant T-lymphocytes (Sézary cells – $CD3^{+}$, $CD4^{+}$, $CD5^{+}$, $CD7^{+/-}$, $CD8^{-}$, $CD25^{+/-}$, $CD26^{-}$, $CD30^{-}$, $CD45RO^{+}$, $CD52^{+}$, $CD158^{+}$)





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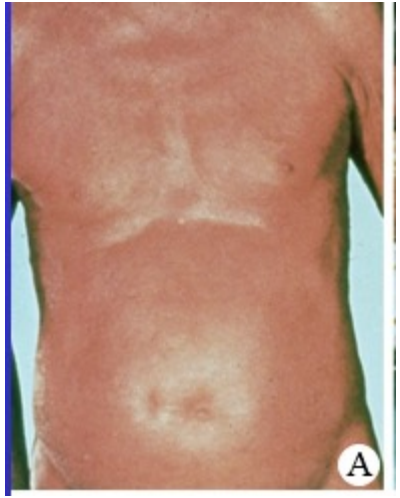
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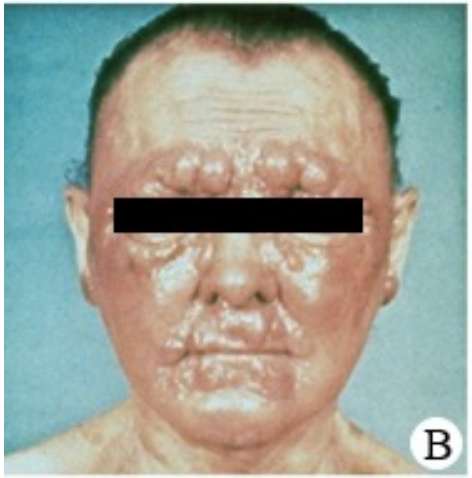
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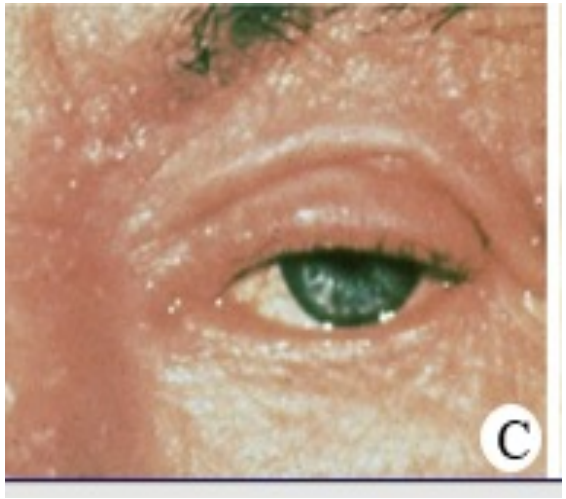
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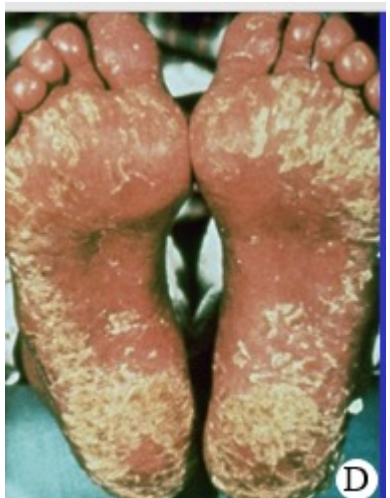
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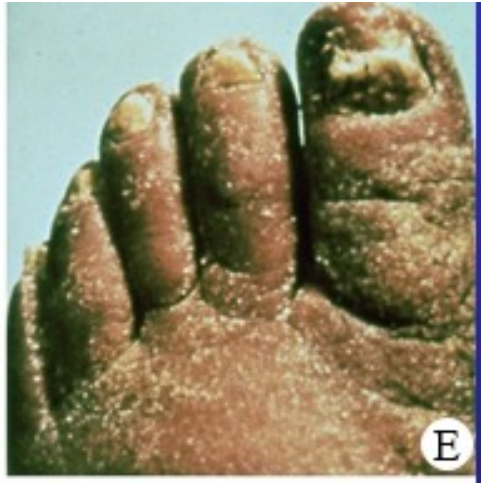
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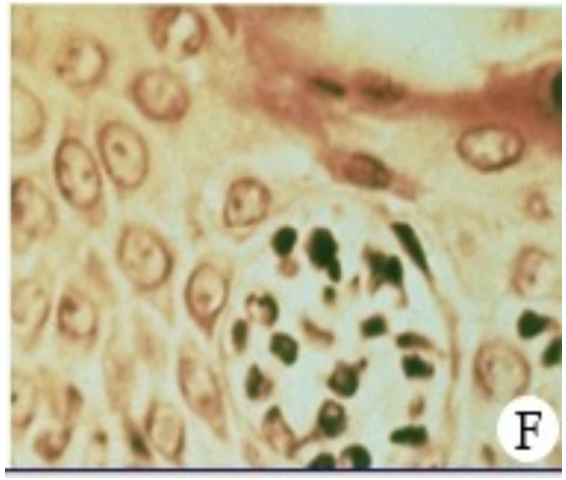
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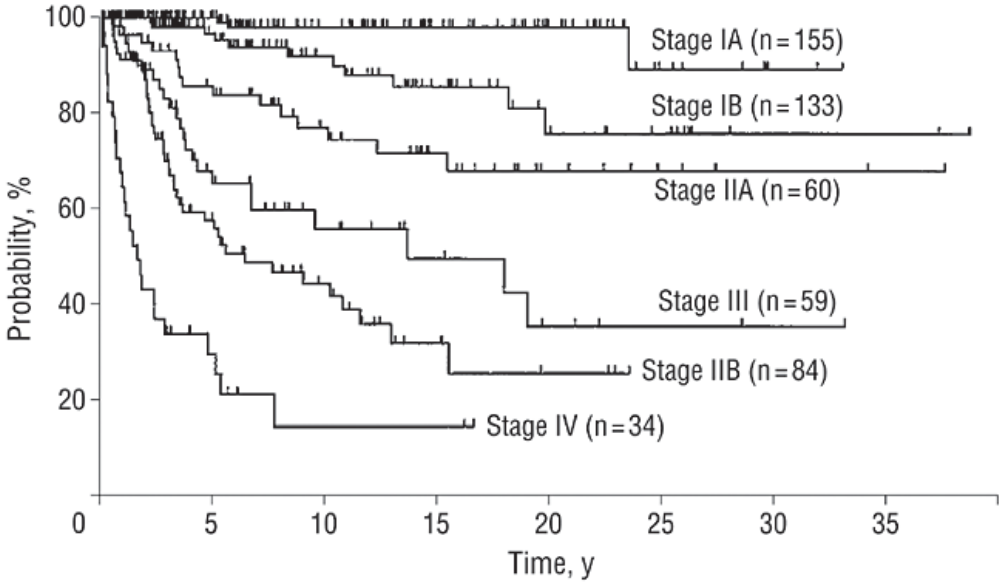
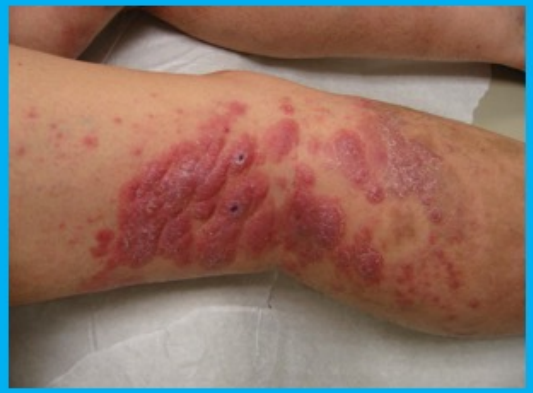
Actuarial disease-specific survival of 525 patients with mycosis fungoides and Sezary syndrome according to their clinical stage at diagnosis (stages IA-IV)

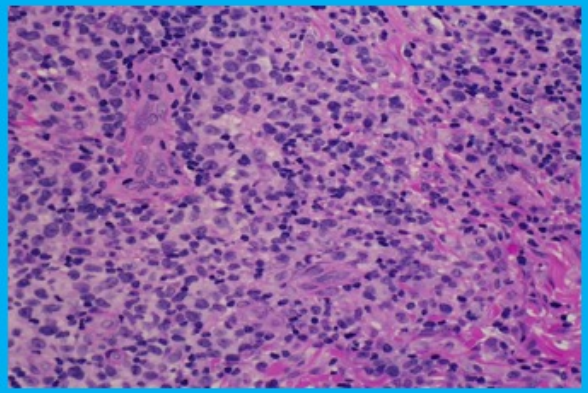


Kim, Y. H. et al. Arch Dermatol 2003;139:857-866.

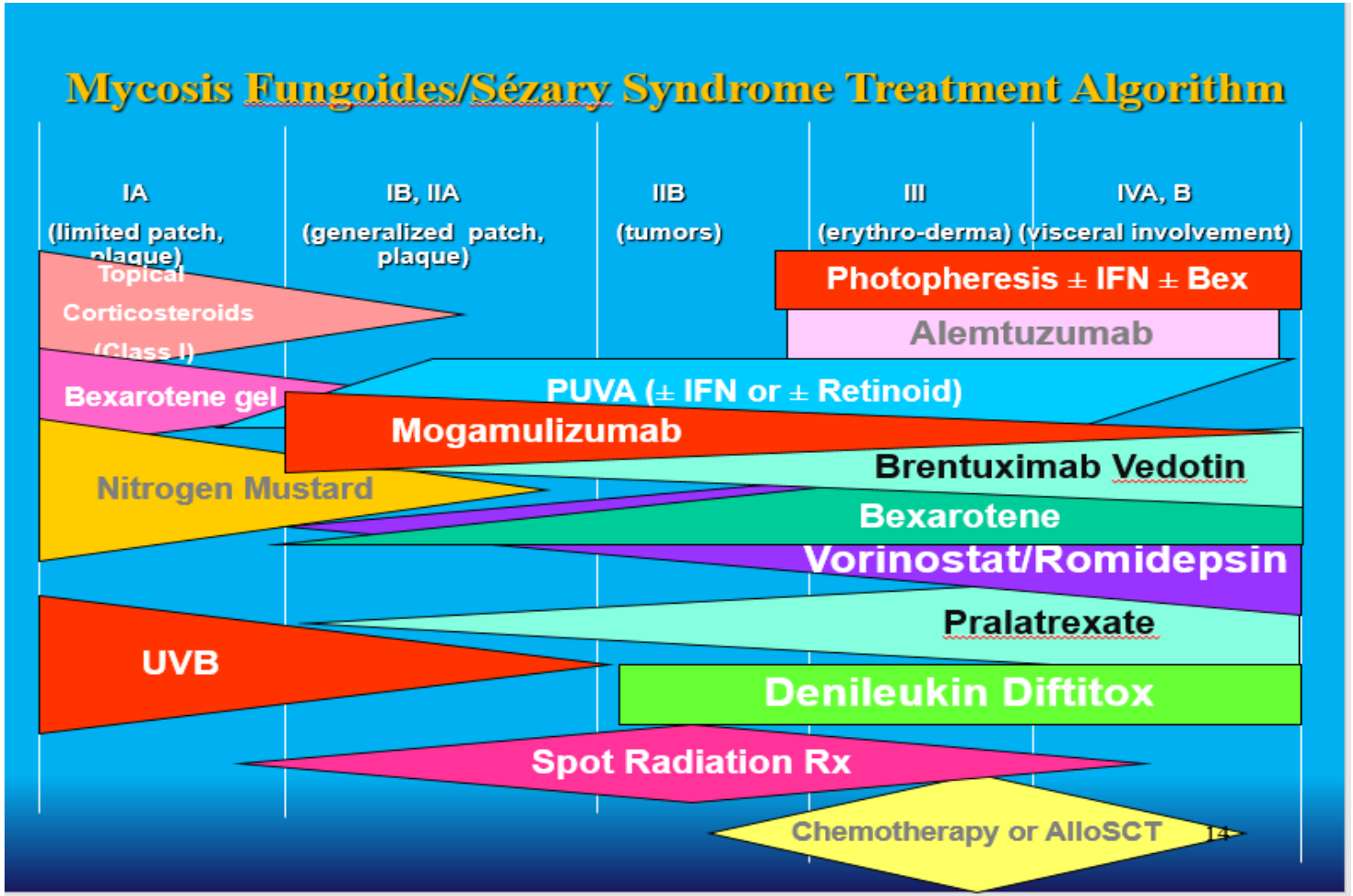
ARCHIVES OF DERMATOLOGY

MF/SS large cell transformation

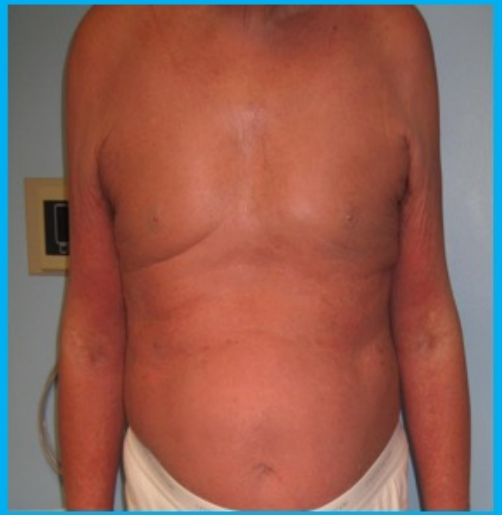




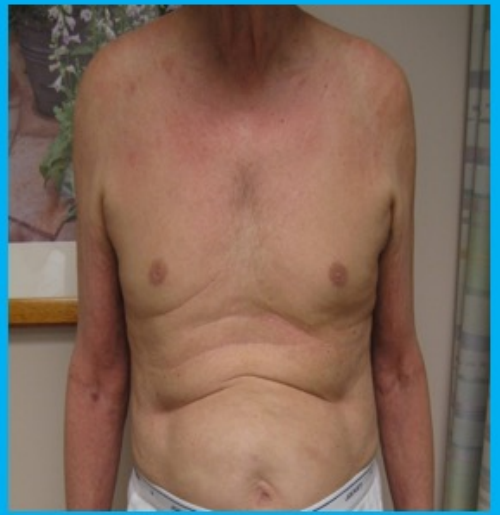
- $CD30^- > CD30^+$
- Increase LDH
- Systemic symptoms
- Poor Prognosis
- ? Transformation Rate


Mycosis Fungoides/Sézary Syndrome Treatment Algorithm
IA
(limited patch, plaque)
IB, IIA
(generalized patch, plaque)
IIB
(tumors)
III
(erythro-derma)
IVA, B
(visceral involvement)
Topical Corticosteroids (Class I)
Photopheresis ± IFN ± Bex
Alemtuzumab
Bexarotene gel
PUVA (± IFN or ± Retinoid)
Mogamulizumab
Brentuximab Vedotin
Nitrogen Mustard
Bexarotene
Vorinostat/Romidepsin
Pralatrexate
UVB
Denileukin Diftitox
Spot Radiation Rx
Chemotherapy or AlloSCT

Anti – CCR 4 Antibody
Case Study: Patient 05-MDACC
(MF; Stage IVA ; 4 Prior Therapies)



Pretreatment
Course 1 Day 1

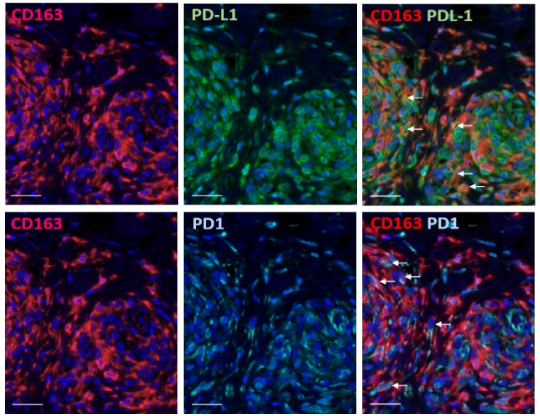


Post treatment
Post Course 6

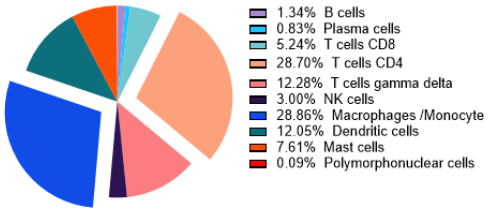
50

Dissecting the Tumor Microenvironment in Cutaneous T Cell Lymphoma

Multispectral Imaging



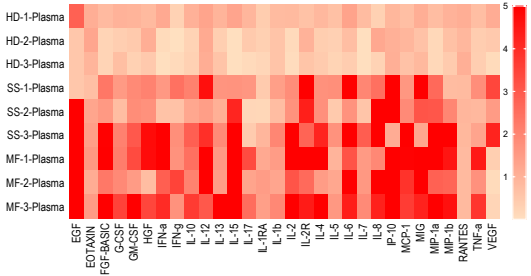
N= 50



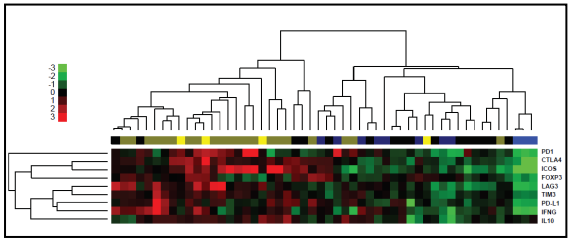
MicroRNA Profiling

miRNAs	logFC	PValue	FDR	PDCD1_cor	PDCD1L1_cor	CTLA4_cor	LAG3_cor	TIM3_cor	ICOS_cor
hsa-miR-155-5p	1.56	8.79E-06	0.000106841	0.43	0.42	0.58	0.55	0.63	0.74
hsa-miR-625-3p	1.95	1.62E-15	5.19E-13	0.43	0.40	0.58	0.60	0.59	0.69
hsa-miR-130b-3p	1.28	1.76E-14	2.70E-12	0.26	0.55	0.50	0.48	0.70	0.69
hsa-miR-146a-5p	1.57	1.95E-09	7.19E-08	0.53	0.24	0.68	0.39	0.38	0.76
hsa-miR-625-5p	1.34	4.69E-10	2.25E-08	0.49	0.25	0.46	0.58	0.54	0.63
hsa-miR-142-5p	1.68	1.91E-12	1.67E-10	0.40	0.41	0.48	0.46	0.54	0.61
hsa-miR-146a-3p	1.82	4.31E-10	2.12E-08	0.45	0.30	0.64	0.33	0.46	0.66
hsa-miR-181a-3p	2.44	8.68E-24	1.67E-20	0.37	0.36	0.49	0.40	0.53	0.60
hsa-miR-142-3p	2.34	7.53E-23	7.24E-20	0.30	0.47	0.38	0.41	0.53	0.54
hsa-miR-181b-5p	1.52	2.65E-13	3.18E-11	0.41	0.27	0.49	0.39	0.43	0.65
hsa-miR-150-3p	1.29	3.18E-05	0.000341234	0.68	0.00	0.55	0.47	0.28	0.60
hsa-miR-181a-5p	1.42	5.87E-13	5.93E-11	0.40	0.25	0.44	0.33	0.43	0.61
hsa-miR-766-3p	1.02	3.85E-08	9.47E-07	0.13	0.41	0.37	0.51	0.45	0.54
hsa-miR-21-5p	1.44	6.70E-15	1.29E-12	0.24	0.52	0.26	0.34	0.60	0.33
hsa-miR-363-3p	1.19	3.69E-06	4.98E-05	0.41	0.13	0.35	0.53	0.49	0.33
hsa-miR-21-3p	2.14	3.35E-18	1.61E-15	0.24	0.46	0.27	0.27	0.53	0.39
hsa-miR-20b-5p	1.34	5.57E-06	7.18E-05	0.33	0.16	0.35	0.50	0.44	0.32
hsa-miR-9-5p	2.14	6.31E-16	2.42E-13	0.41	0.21	0.38	0.37	0.36	0.36
hsa-miR-1246	2.10	2.25E-11	1.66E-09	0.30	0.40	0.27	0.45	0.47	0.13

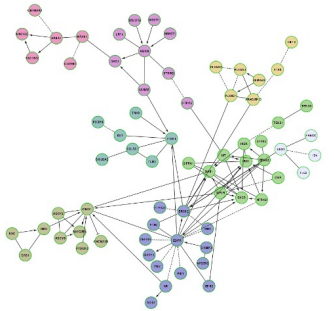
Multiplex Cytokine Analysis



Gene Sequencing Analysis

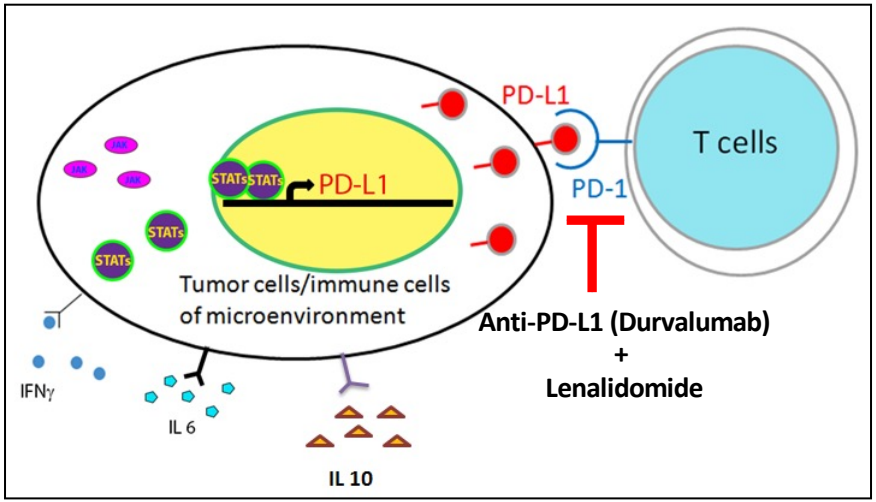


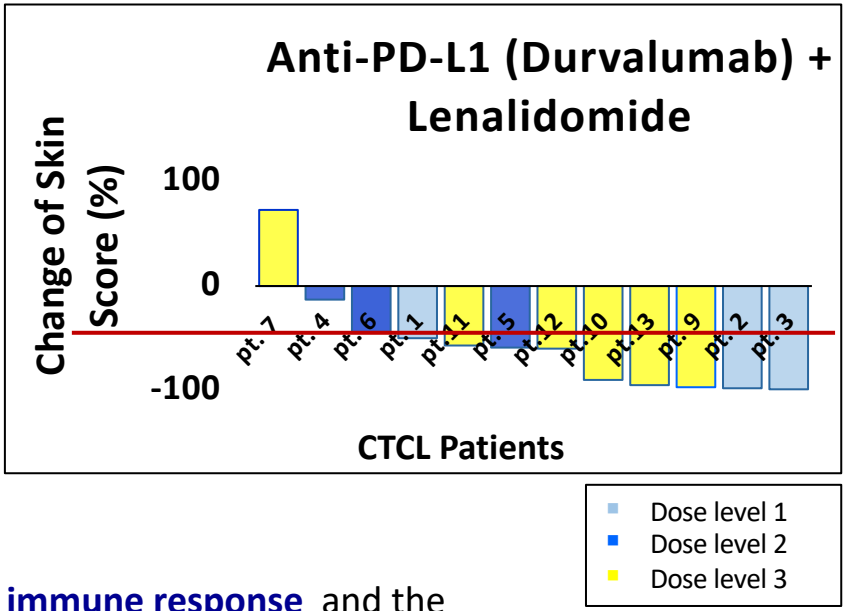
Network-based analysis of mRNAs connected with regulated miRNAs



Module	Pathway
0	EGFR pathway
1	PI3K-AKT Pathway
2	ECM-receptor interaction
3	cAMP signaling pathway
4	Focal Adhesion
5	Axon Guidance
6	None
7	None

Targeting PD-Ligand 1 (PD-L1) receptor and “T cell exhaustion”

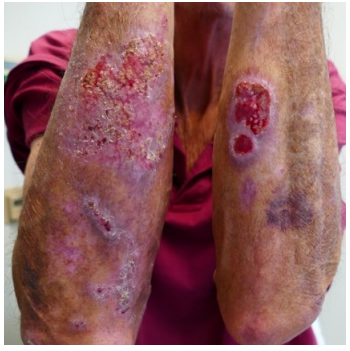




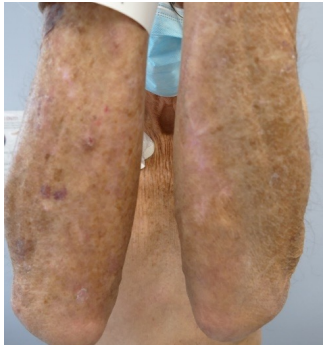
- **Anti-PD-L1** (Durvalumab) may restore an **anti-tumor immune response** and the combination of **durvalumab** and **lenalidomide** may enhance immune checkpoint blockade-induced immune responses

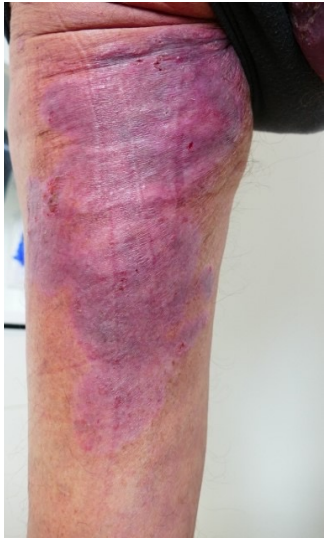
Responses to Anti-PD-L1 (Durvalumab) and Lenalidomide

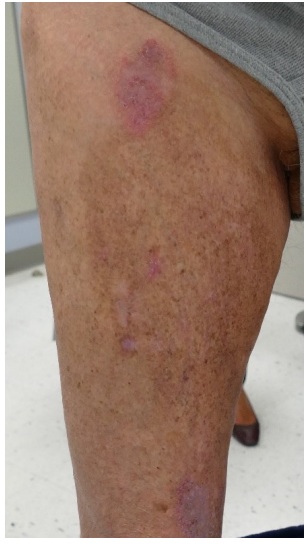
COH 009 Baseline



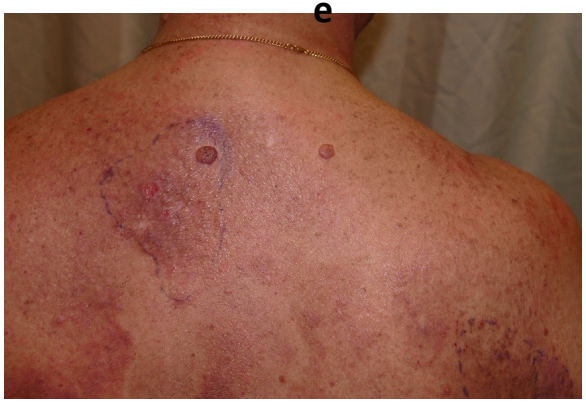
Cycle 8

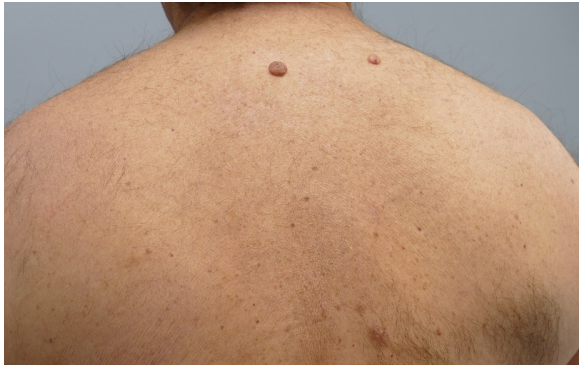




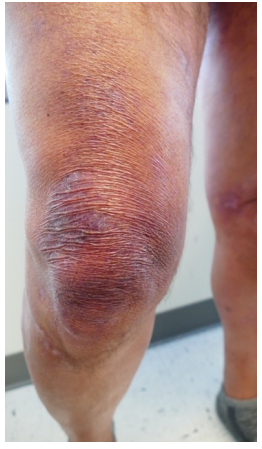


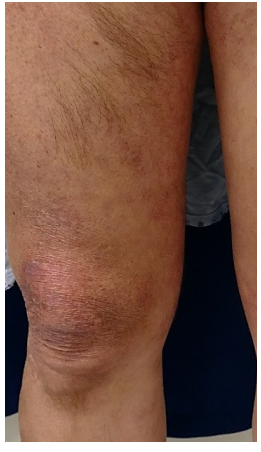
COH 003 Baseline



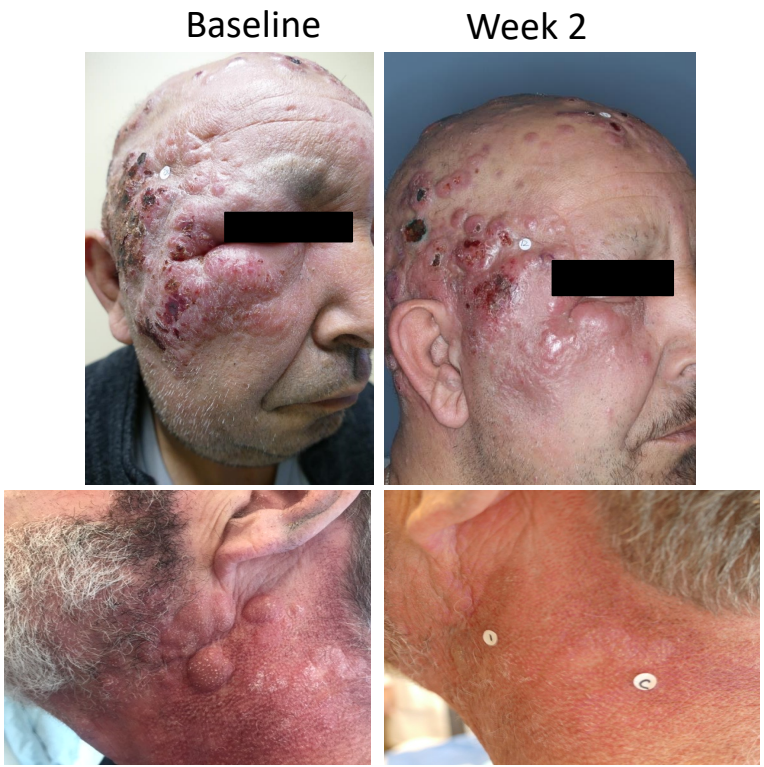


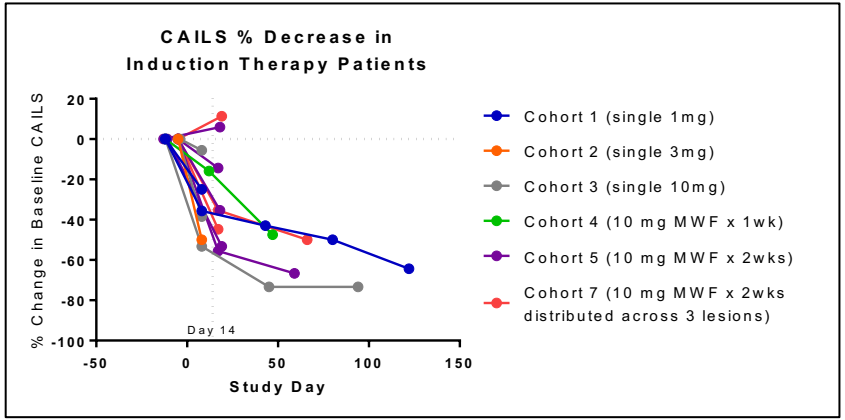
Cycle 13

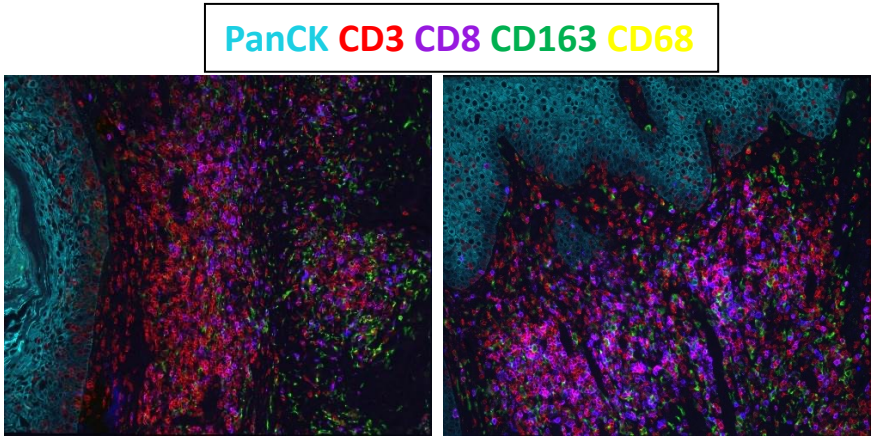




Intralesional Delivery of TTI-621, a Novel Biologic Targeting the Innate Immune Checkpoint CD47, in Patients with Relapsed or Refractory Mycosis Fungoides or Sézary Syndrome: a Multicenter Phase 1 Study



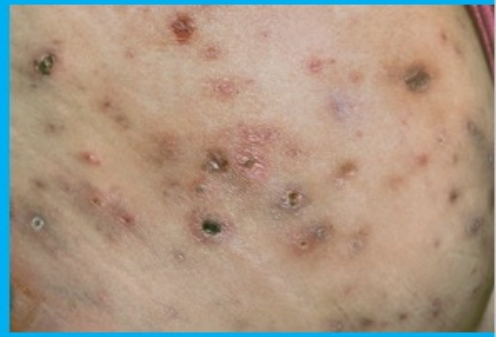


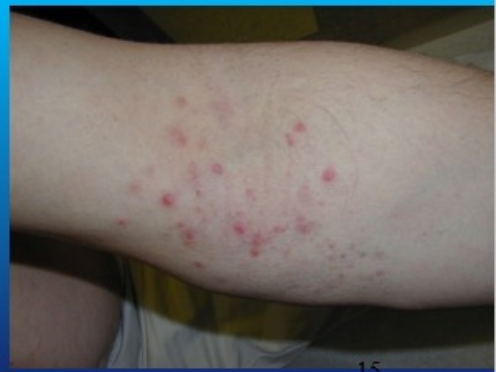


Querfeld C et al. The Lancet Haematology 2021

CD30+ Lymphoproliferative Disease
Lymphomatoid Papulosis

- **Recurrent papulonodular lesions**
  - Frequent ulceration
  - Spontaneous involution
- **Indolent course**
  - 10-20% progress to lymphoid malignancy
- **Observation vs palliative treatment**
  - PUVA, MTX, steroid, topical bexarotene





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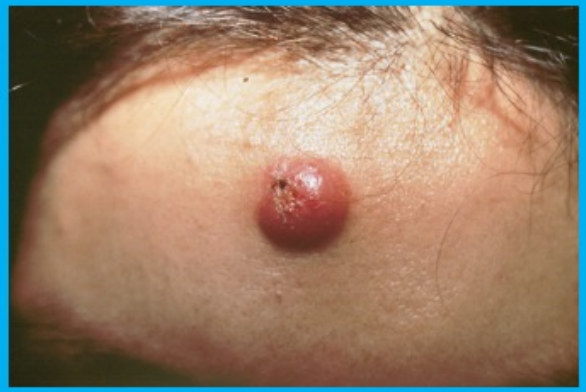

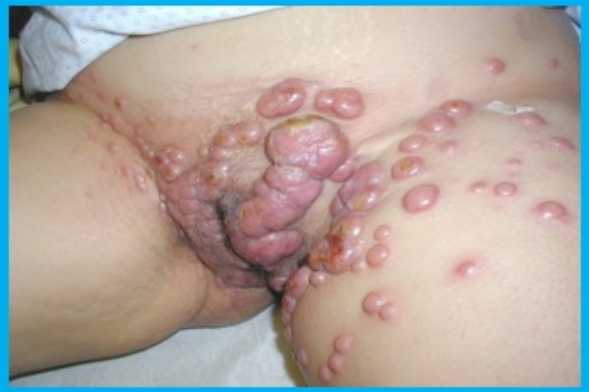

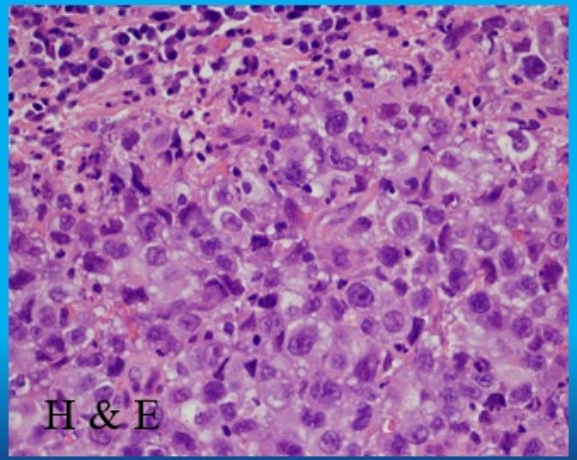

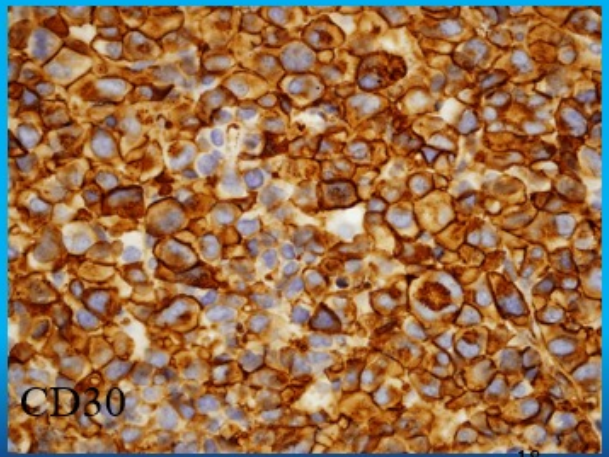

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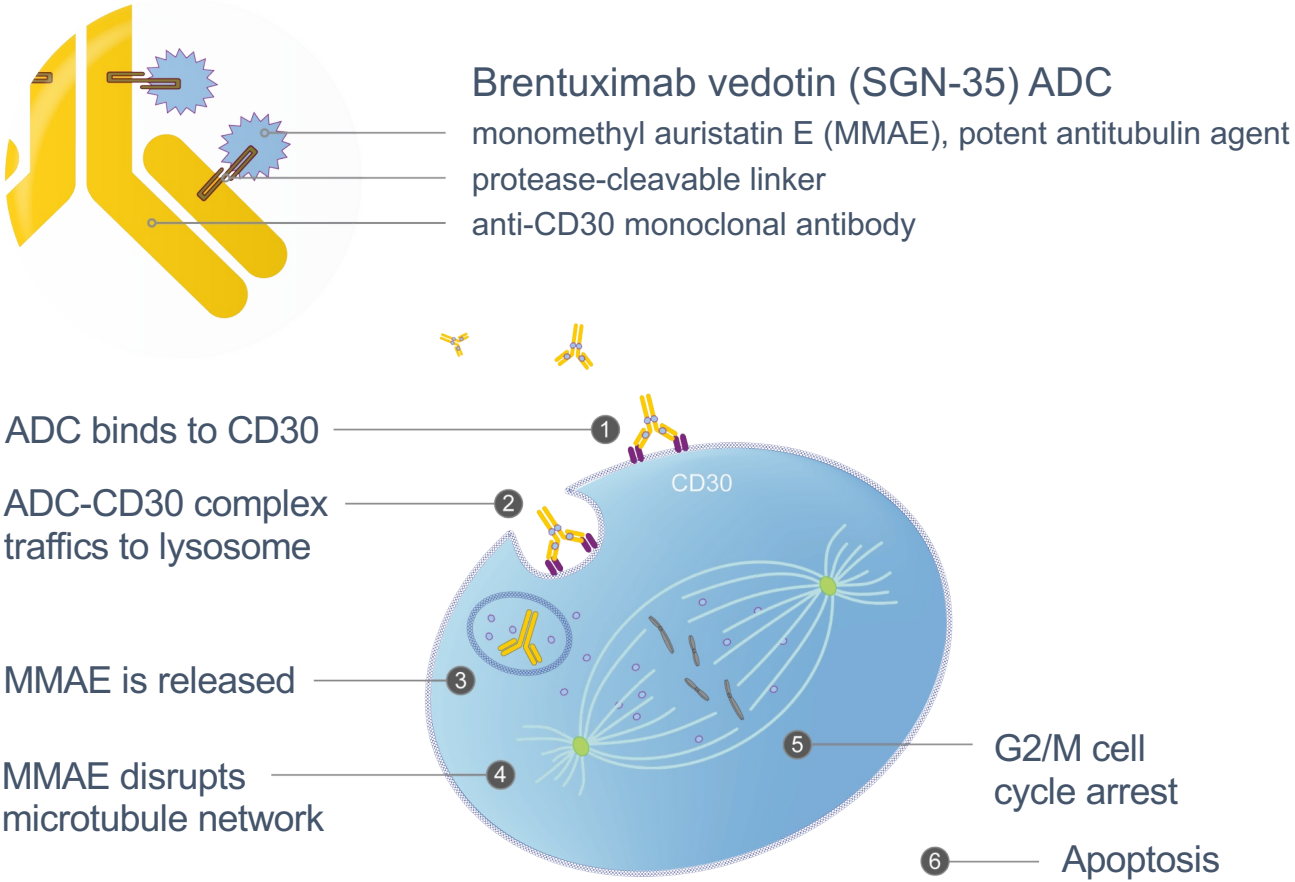
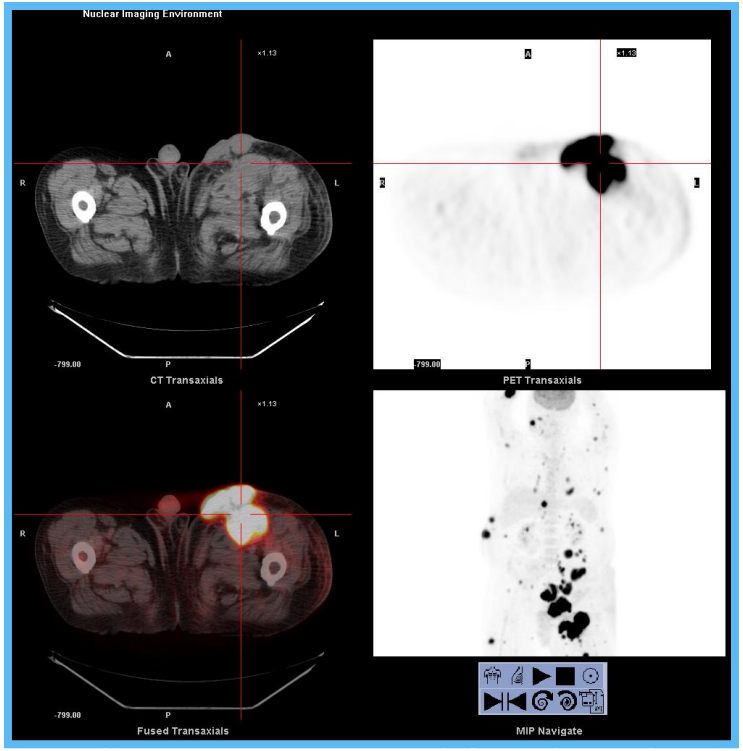
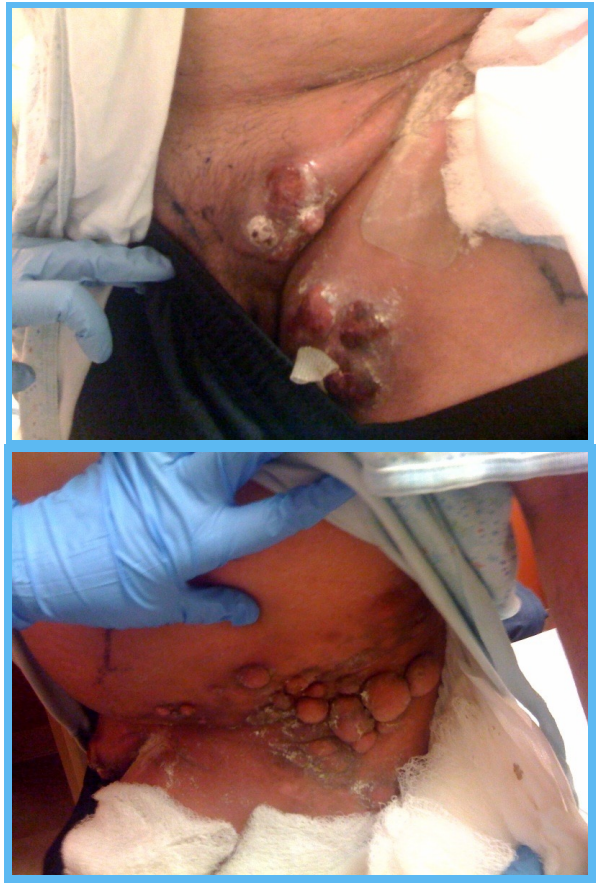
Brentuximab Vedotin Mechanism of Action



SGN 35 Trial

Refractory sALCL with skin involvement: Baseline

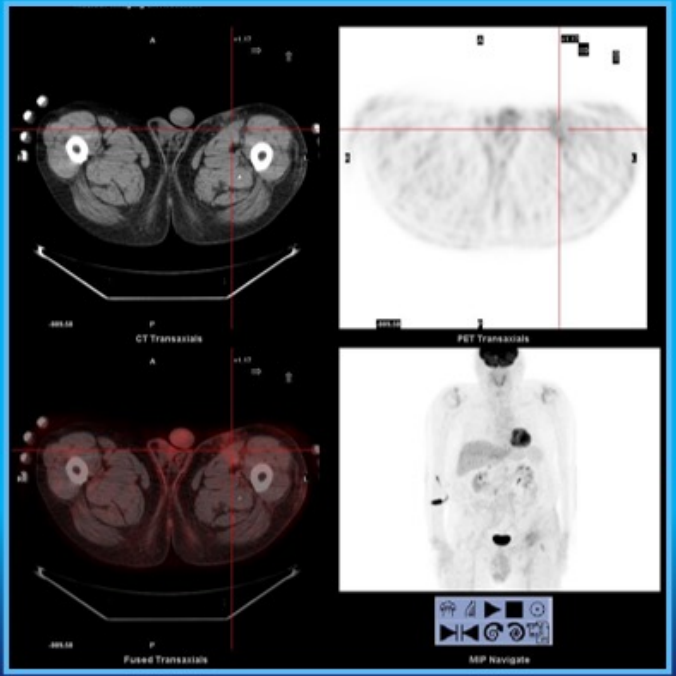


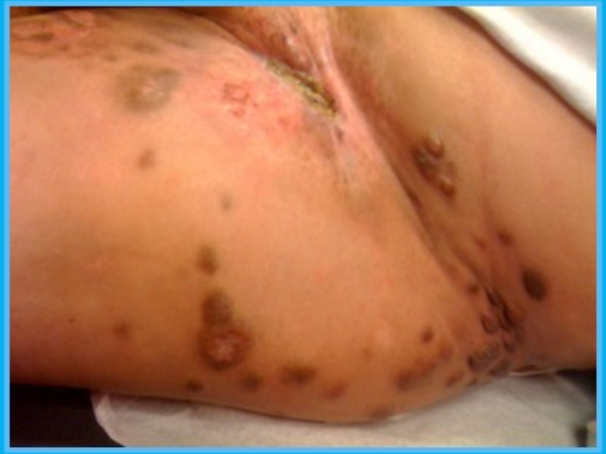


Refractory sALCL with skin involvement treated with SGN 35:

Response Post Cycle 4

PET-CT



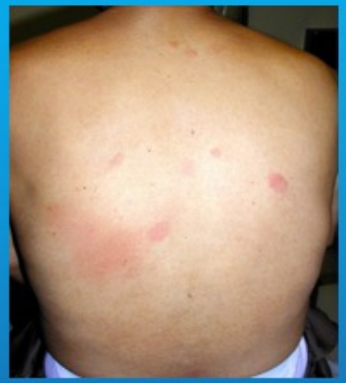


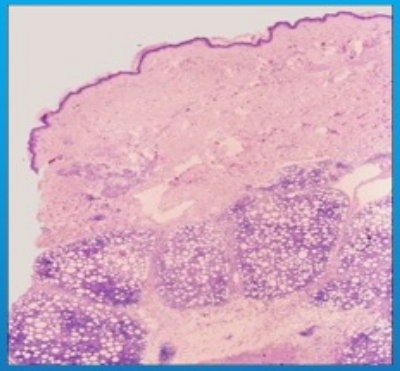
Courtesy of R Advani

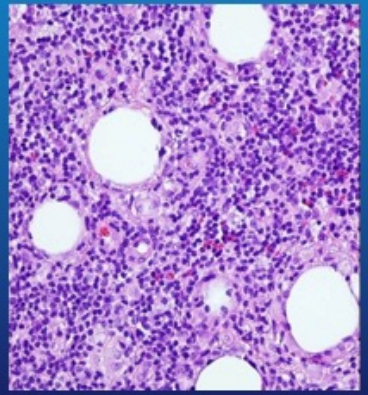
Subcutaneous Panniculitis-like T-Cell Lymphoma

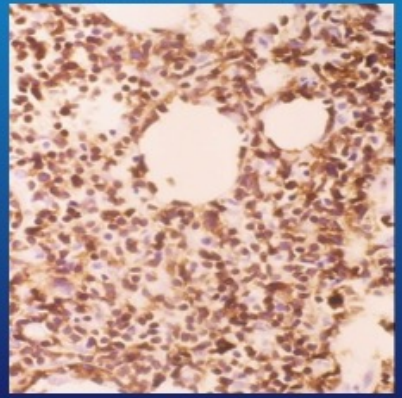
- Subcutaneous nodules often violaceous
- Systemic symptoms (weight loss, fever, fatigue) not uncommon.
- Autoimmune disease (20%) - SLE most common
- α/β TCR rearrangement, CD8+, CD56-, cytotoxic markers - (granzyme B, perforin and TIA-1)
- Hemophagocytic syndrome uncommon
- Five-year survival > 80%
- Therapy: local radiation, immunosuppressive agents (eg. steroids, cyclosporine) and/or single agent chemotherpay (eg. methotrexate, chlorambucil). Combination chemotherapy for aggressive and progressive variants. Romidepsin (anecdotal reports)

Subcutaneous Panniculitis-like T-Cell Lymphoma









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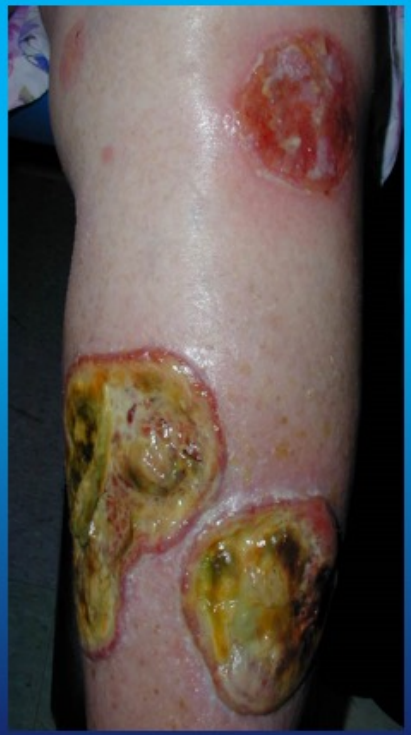
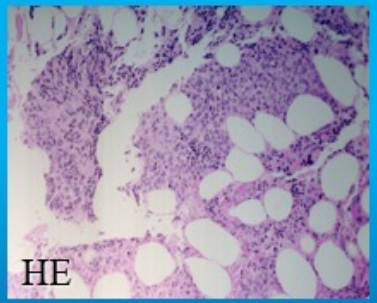
Primary cutaneous gamma-delta Lymphoma

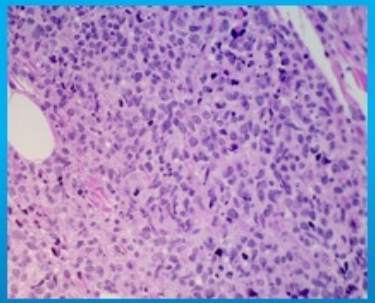
- Disseminated cutaneous ulcerated plaques, nodules and tumors
- Mucosal involvement
- Systemic symptoms universal
- γ/δ TCR rearrangement, $CD3^+$, $CD4^-$, $CD8^-$, $CD56^+$
- STAT5B activating mutations
- Median survival < 2years
- Allogeneic stem cell transplant

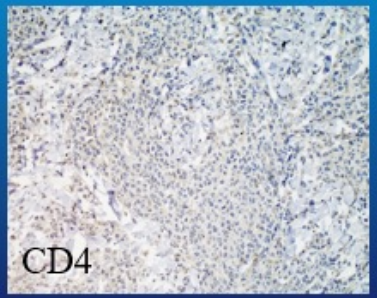
Clinical and histologic features

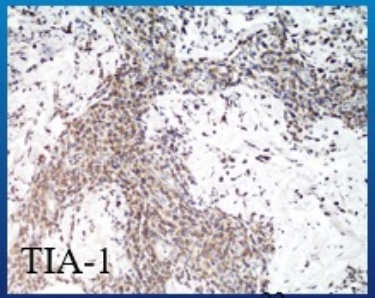


- Medium-sized to large pleomorphic T-cells
- Cytotoxic protein expression
- Apoptosis and necrosis









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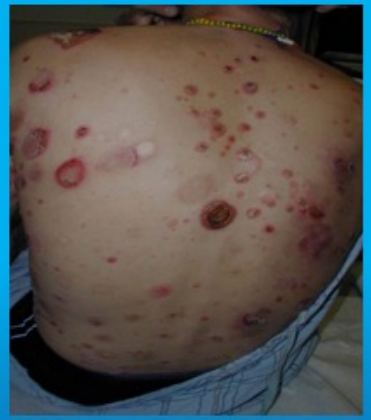
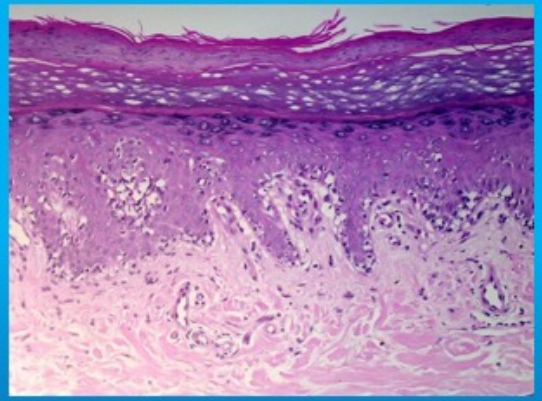
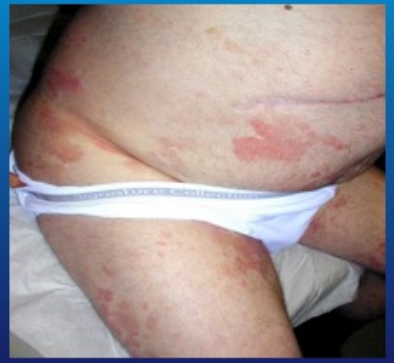
Primary cutaneous CD8-positive Aggressive Epidermotrophic T-Cell Lymphoma

- Generalized ulcerated/necrotic papules, nodules, hyperkeratotic patches/plaques
- Visceral dissemination common (lung, testes, oral mucosa and CNS)
- Nodal involvement uncommon
- $CD3^+$, $CD8^+$, $CD4^-$, cytotoxic markers (granzyme B, perforin and TIA-1)
- Median survival < 3years
- Allogeneic stem cell transplant

Primary cutaneous CD8-positive Aggressive Epidermotrophic T-Cell Lymphoma







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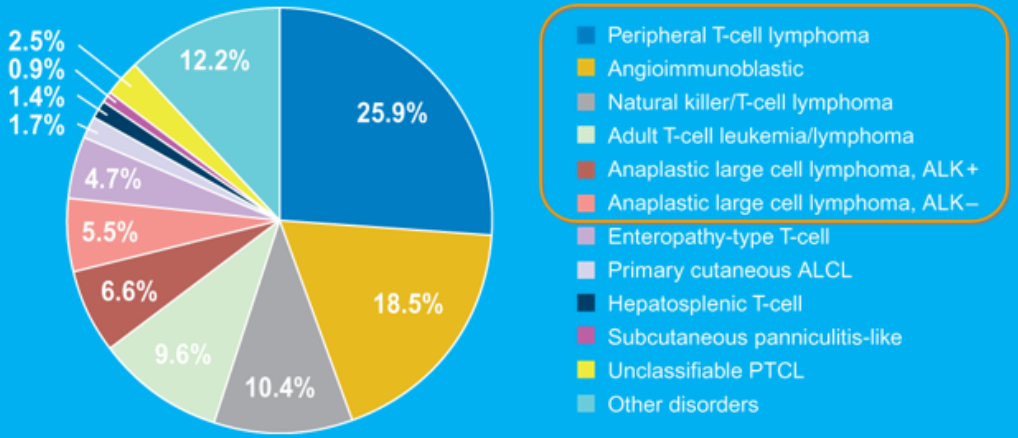
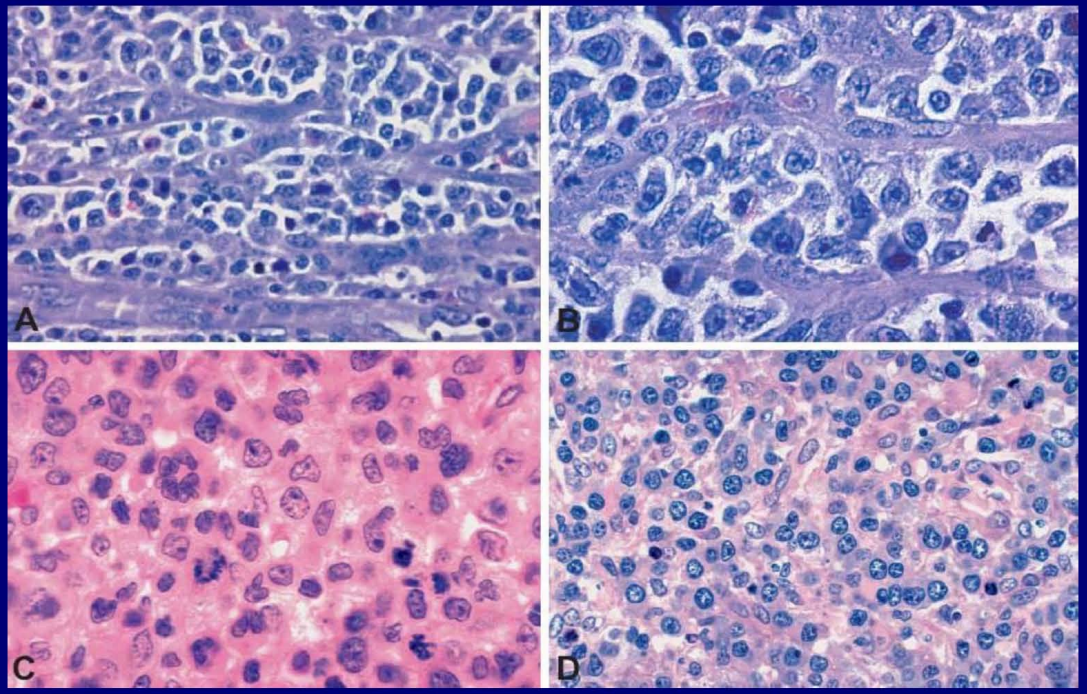
Common Peripheral T-cell Lymphoma Subtypes

- Peripheral T-cell lymphoma – not otherwise specified (PTCL-NOS) is the most common subtype
- Anaplastic large cell lymphoma (ALCL) ALK$^{+/-}$ and angioimmunoblastic lymphoma are also common subtypes



1. Armitage J, et al. *J Clin Oncol.* 2008;26:4124–4130.

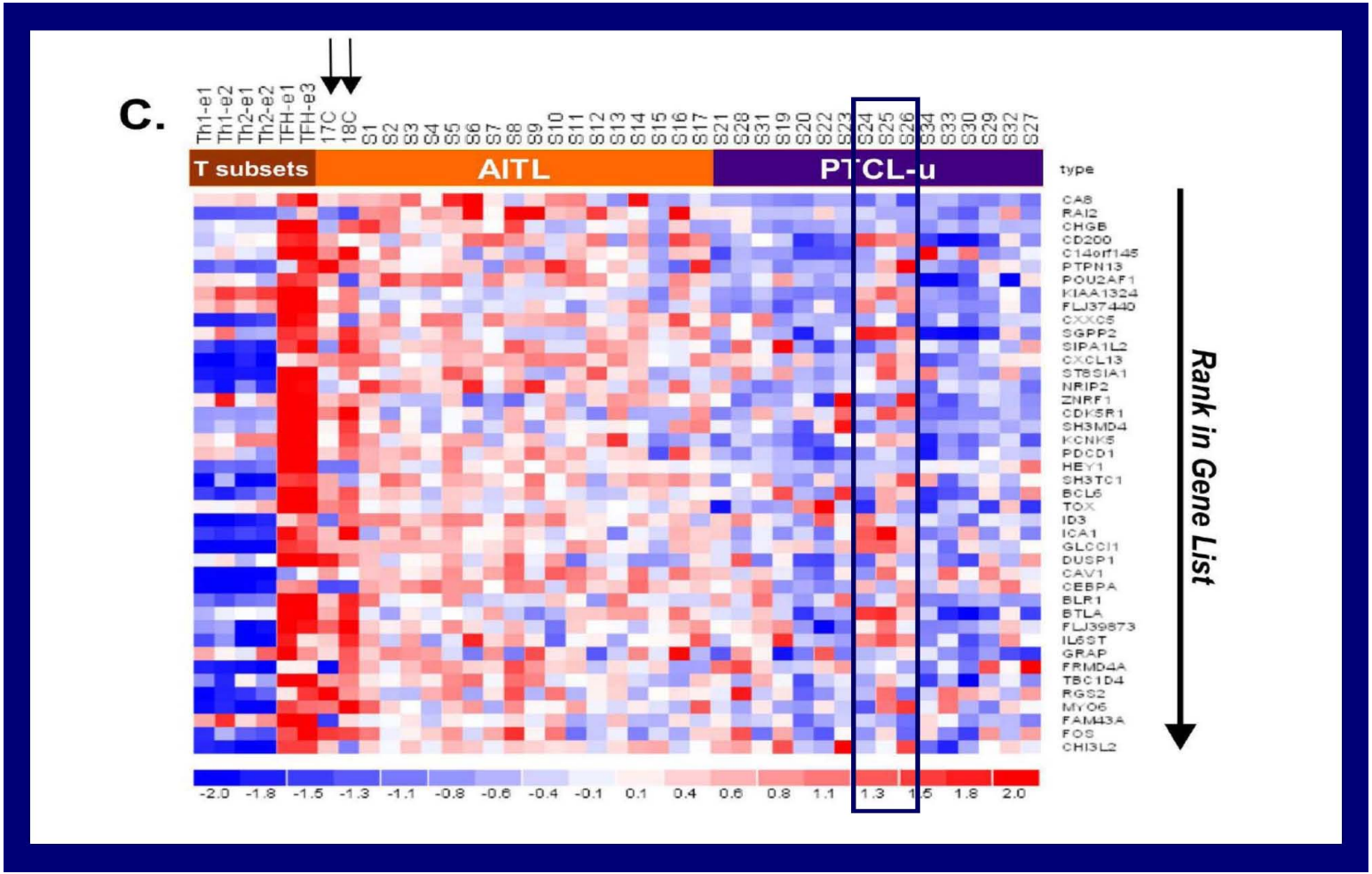
Morphologic spectrum



Variants: T-zone, Lennert's and follicular

Lack of immunophenotypic markers of clonality, although the presence of an aberrant immuno-phenotype assists in the diagnosis.

Neoplasms	CD3	CD4	CD8	CD7	CD5	CD2	TIA1	GrB Per	CD30	CD25	CD56	CD16	CD57	BCL6	CD10	EBV	EMA
T-PLL	+	+	+/-	+	+	+	-	-	-	-	-	-	-	-	-	-	-
T-LGL	+	-	+	-/+	-/+	+	+	+	-	-	-	+	+	-	-	-	-
ATLL	+	+	-	-	+	+	-	-	-/+	++	-	-	-	-	-	-	-
Agg NK	+ c	-	-/+	-	-	+	+	+	-	-	+	-	-	-	-	+	-
ENK/T, Nasal type	+ c	-	-/+	-	-	+	+	+	-	-	+	-	-	-	-	+	-
EATL	+	-	-/+	+	-	+	+	+	-/+	-/+	-/+	-	-	-	-	-	-/+
HSTL	+	-	+/-	+	-	+	+	-	-	-	+	-	-	-	-	-	-
SPTCL	+	-	+	+	-/+	+	+	+	-	-	+	-	-	-	-	-	-
MF/SS	+	+	-/+	-/+	+/-	+	-	-	-	-	-	-	-	-	-	-	-
Primary cutaneous γδ T-cell lymphoma	+	-	-/+	-/+	-	+	+	+	-	-	+	-	-	-	-	-	-
Primary cutaneous CD30+ LPD	+	+	-	-	+/-	+	+	-+	+	+	-	-	-	-	-	-	+/-
AITL	+	+	-	+	+	+	-	-	-	-	-	-	-	+/-	+/-	-	-
PTCL, NOS##	+	+/-	-/+	-/+	-/+	+	-	-	-/+	-	-	-	-	-	-	-	-
ALCL, ALK+	-/+	+/-	-/+	-/+	+/-	+/-	+	+	++	++	+/-	-	-	+	-	-	++
ALCL, ALK-	+/-	+/-	-/+	-/+	+/-	+/-	+/-	+/-	++	++	+/-	-	-	-	-	-	+


C.
Th1-e1
Th1-e2
Th2-e1
Th2-e2
TFH-e1
TFH-e3
17C
18C
S1
S2
S3
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S27
T subsets
AITL
PTCL-u
type
CA8
RAI2
CHGB
CD200
C14orf145
PTPN13
POU2AF1
KIAA1324
FLJ37440
CXXC5
SGPP2
SIPA1L2
CXCL13
ST8SIA1
NRIP2
ZNRF1
CDK5R1
SH3MD4
KCNK5
PDCD1
HEY1
SH3TC1
BCL6
TOX
ID3
ICA1
GLCCI1
DUSP1
CAV1
CEBPA
BLR1
BTLA
FLJ39873
IL6ST
GRAP
FRMD4A
TBC1D4
RGS2
MYO6
FAM43A
FOS
CHI3L2
Rank in Gene List
-2.0
-1.8
-1.5
-1.3
-1.1
-0.8
-0.6
-0.4
-0.1
0.1
0.4
0.6
0.8
1.1
1.3
1.5
1.8
2.0

PTCL Epidemiology

- The relative incidence of PTCL subtypes varies by geography[1,2]
  - Incidence is higher in Asian and Caribbean populations[1,2]

Subtype	Percentage[2]		
	North America	Europe	Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK+	16.0	6.4	3.2
ALCL, ALK-	7.8	9.4	2.6
NK/TCL	5.1	4.3	22.4
ATLL (HTLV-1+)	2.0	1.0	25.0
Enteropathy-type	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Subcutaneous panniculitis-like	1.3	0.5	1.3
Unclassifiable T-cell	2.3	3.3	2.4

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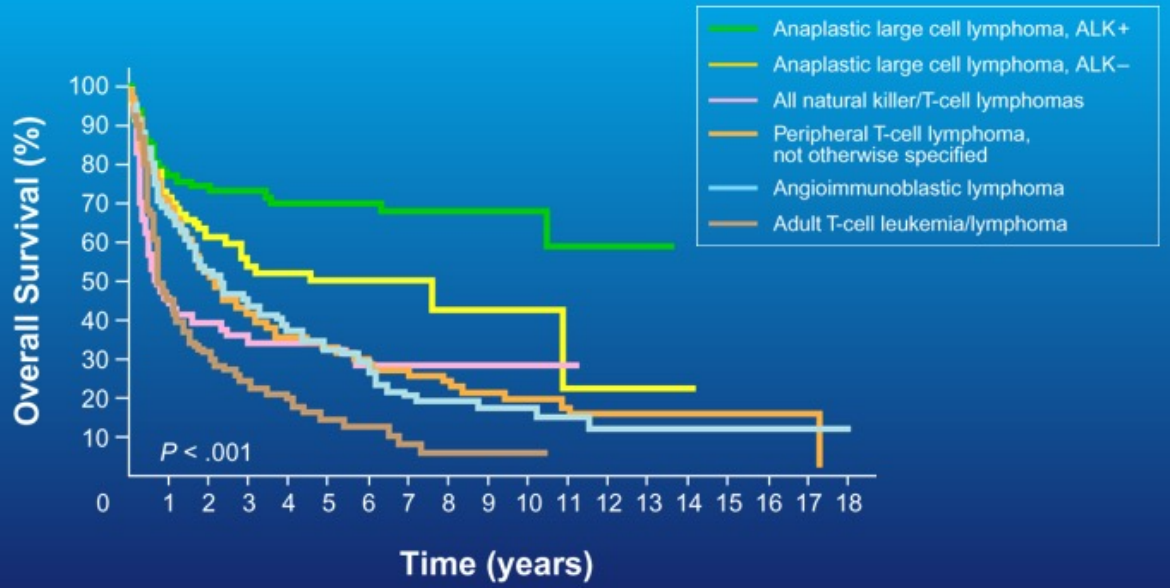
1. Savage KJ. *Hematology*. 2005;10:267–277; 2. Armitage J, et al. *J Clin Oncol*. 2008;26:4124–4130.

PTCL Prognosis by Subtype

- Overall survival varies according to subtype and median ranges from 1-3 years[1]



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Armitage J, et al. *J Clin Oncol.* 2008;26:4124–4130.

Presentation of PTCL

- PTCL most commonly presents with advanced, systemic symptoms[1]
- Compared with B-cell NHL, PTCL is more likely to present with the following:

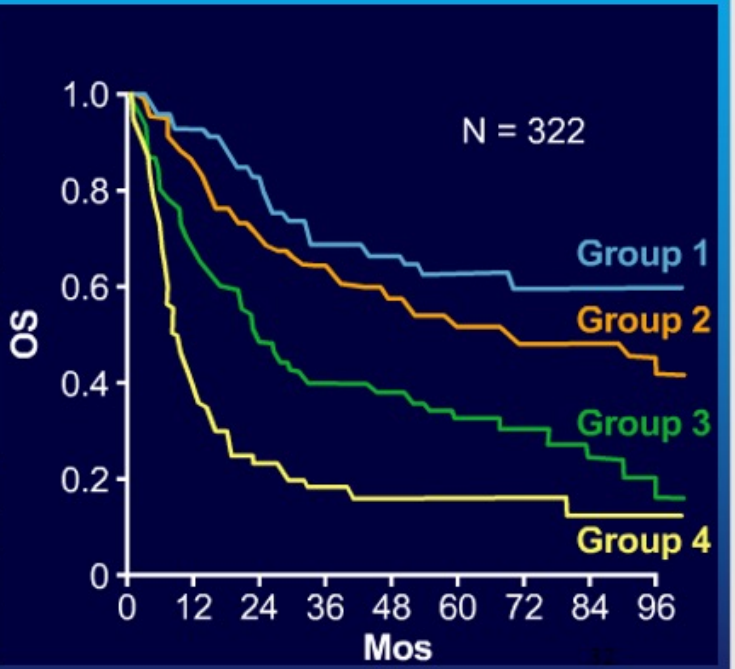
% of Patients With Clinical Characteristics in the LNH87 Trial[2,3]			
Clinical Characteristics	PTCL (n = 288)	BCL (n = 1,595)	*P* Value
Disseminated disease	78	58	
B symptoms	57	40	0.001
Bone marrow positive	31	17	0.001
Skin lesions	21	4	0.001

1. Rodriguez-Abreu D, et al. *Hematol Oncol*. 2008;26:8-20.
2. Gisselbrecht C, et al. *Blood*. 1998;92:76-82.
3. Hermine O, et al. *Blood*. 1996;87:265-272.

Overall Survival According to Prognostic Index for PTCL

Parameter	*P* Value	Relative Risk
Age	< .0001	1.732
PS	< .0001	1.719
LDH level	< .001	1.905
BM attainment	.026	1.454

	Percentage of the Total Population (N = 322)
Group 1—0	20
Group 2—1	34
Group 3—2	26
Group 4—3, 4	20



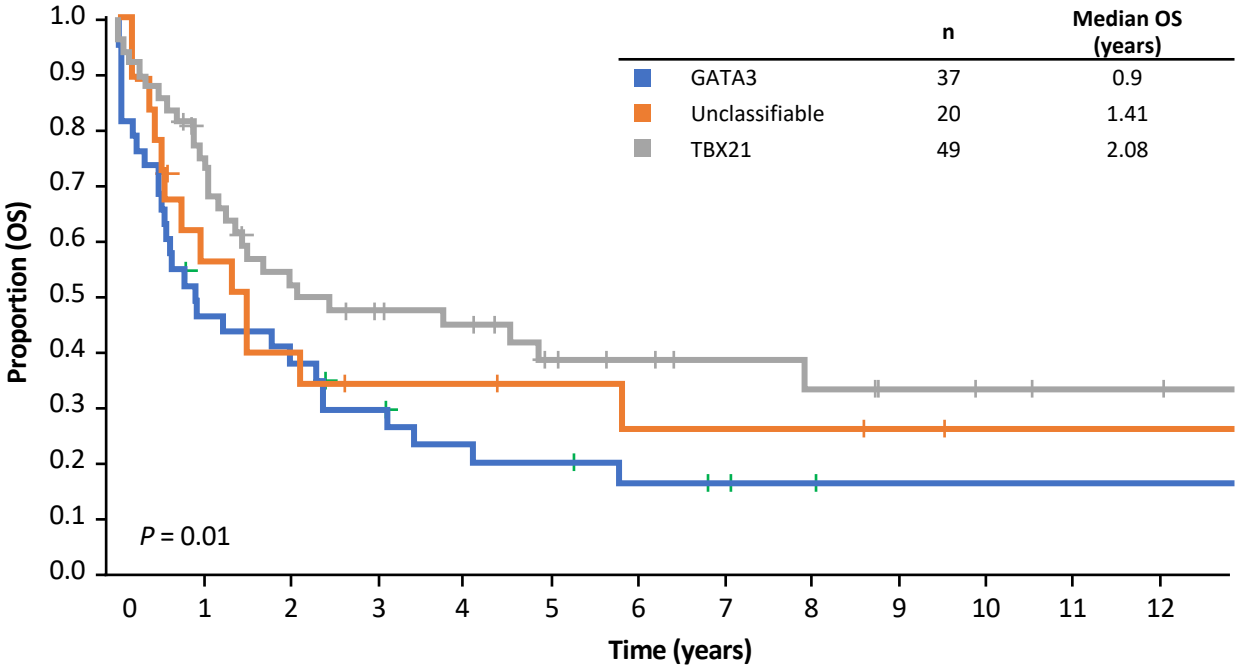
Gallamini A, et al. *Blood.* 2004;103:2474–2479.

Molecularly Defined Subgroups of PTCL-NOS Predict Outcome[1,2]

IHC Algorithm

If PTCL-NOS, cell origin can determine PTCL-TBX21 vs PTCL-GATA3

- TBX21 (IHC; ≥ 20%) or CXCR3 (IHC; ≥ 20%) = PTCL-TBX21
- GATA3 (IHC; ≥50%) or CCR4 (IHC; ≥50%) = PTCL-GATA3
- All others = PTCL-unclassifiable



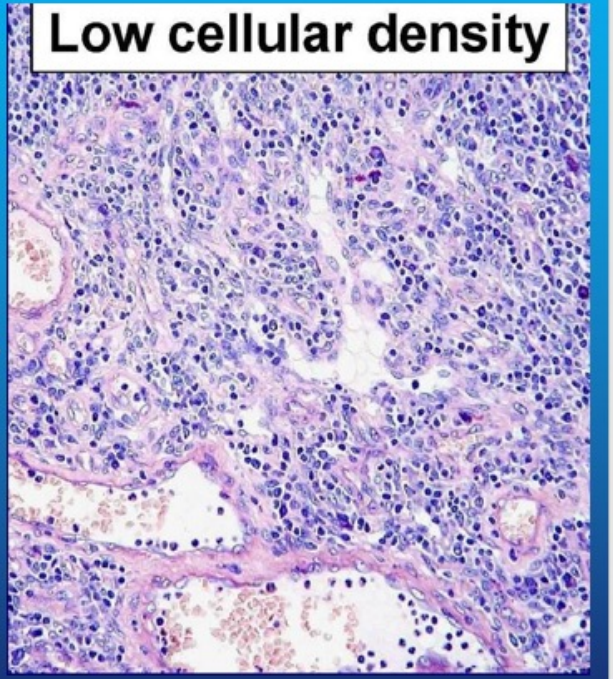
1. Iqbal J, et al. *Blood*. 2014;123:2915-2923. 2. Vega F, et al. *Human Pathol*. 2020;102:104-116.

Angioimmunoblastic T cell lymphoma

Elderly Patients (median age >60y)

Clinical Features

- Generalized lymphadenopathy
- Hepatosplenomegaly
- Skin rash
- BM commonly involved
- Usually advanced clinical stage
- Systemic symptoms
- Polyclonal hypergammaglobulinemia
- Clinical course aggressive
- Median survival: < 3yrs



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Systemic ALCL

- 2-3% NHL
- 6.5% ALK- positive (genetic translocation or inversions; t(2;5) 75%)
- 5.5% ALK- negative : DUSP22 rearrangement 30% (95% OS); TP63 rearrangement 8% (17% OS)
- 2/3 patients with advanced stage
- CD3 +/-; CD5+/-; CD4-/+; CD8-/+; CD25+; CD30+; CD52-/+; EBV- TCR-rearranged

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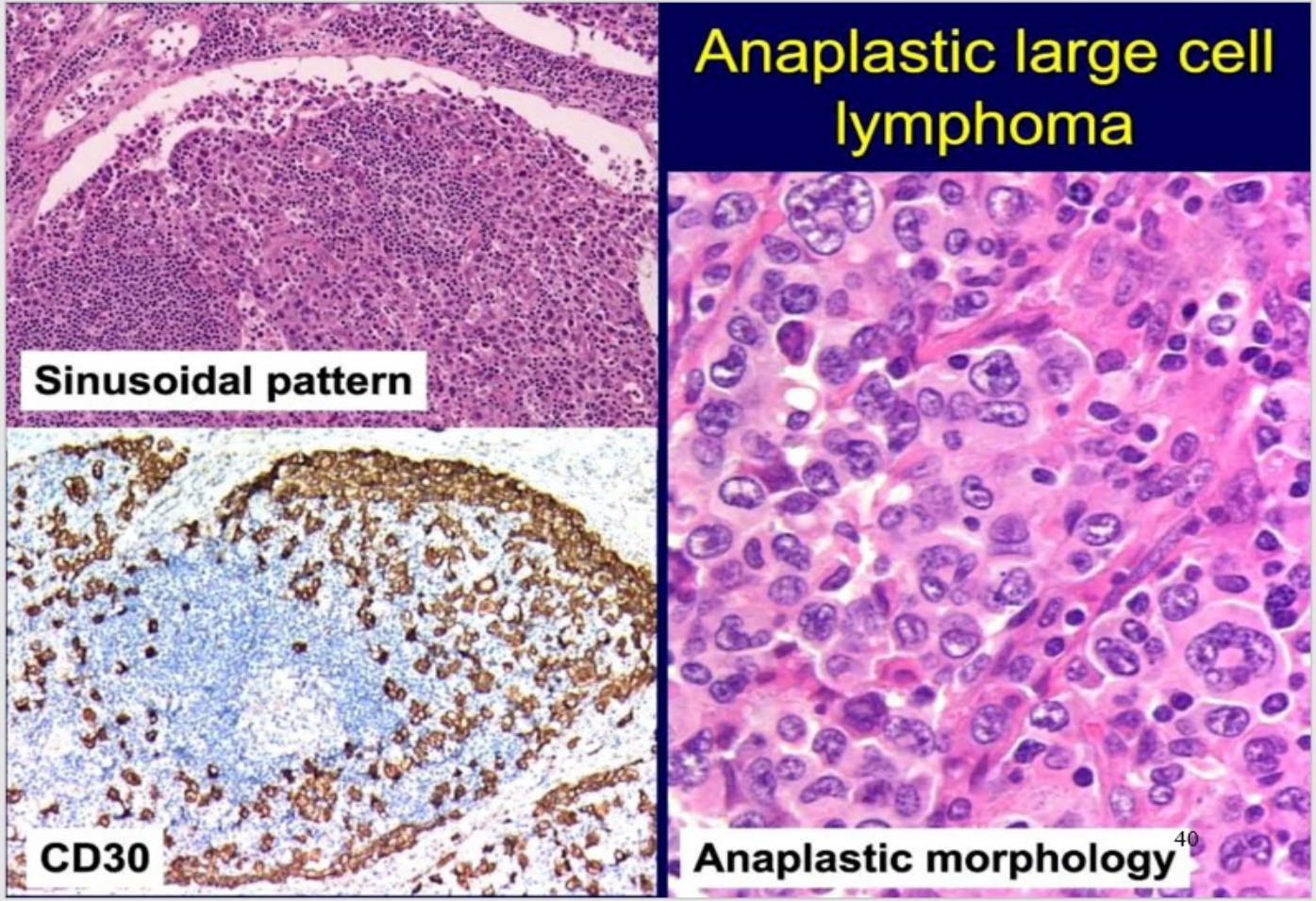
Anaplastic large cell lymphoma
Sinusoidal pattern
CD30
Anaplastic morphology
40

Enteropathy-associated T-Cell Lymphoma

- Classic type associated with celiac disease (HLA DQ2, DQ8 expression and anti-gliadin antibodies)
- Abdominal pain & weight loss
- $CD3^{+}$, $CD4^{-}$, $CD8^{-/+}$
- Poor prognosis
- Autologous Stem Cell transplant

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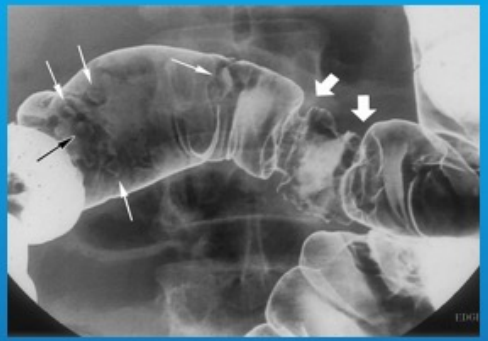
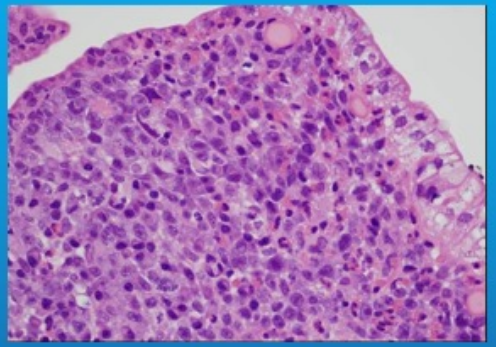
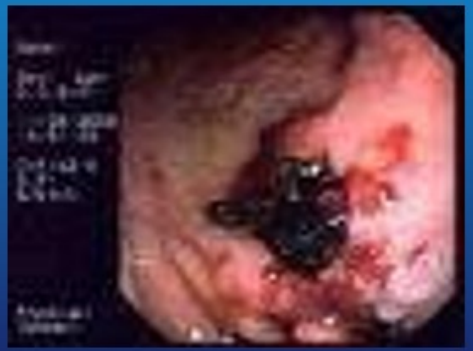
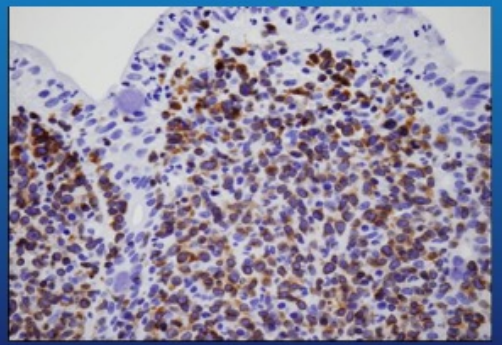
Enteropathy-associated T-Cell Lymphoma









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NCCN Guidelines Version 2.2022
Peripheral T-Cell Lymphomas

SUGGESTED TREATMENT REGIMENS

FIRST-LINE THERAPY	
ALCL	**Preferred regimen** • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) (category 1) **Other recommended regimens** • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) • CHOEP[e] (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
Other histologies (PTCL-NOS; AITL; EATL; MEITL; nodal PTCL, TFH; and FTCL)	**Preferred regimens** (alphabetical order) • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) for CD30+ histologies • CHOEP[e] • CHOP • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) **Other recommended regimens** (alphabetical order) • CHOP followed by IVE (ifosfamide, etoposide epirubicin) alternating with intermediate-dose methotrexate (Newcastle Regimen; studied only in patients with EATL) • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)

FIRST-LINE CONSOLIDATION
• Consider consolidation with high-dose therapy and autologous stem cell rescue.

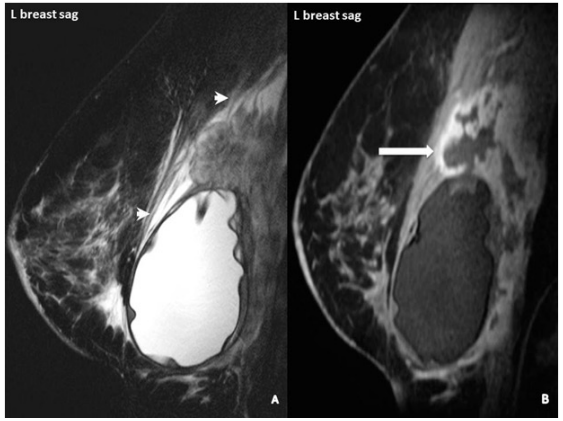
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Peripheral T-Cell Lymphomas

SECOND-LINE TREATMENT REGIMENS

PTCL-NOS; EATL; MEITL	AITL, INCLUDING NODAL PTCL, TFH and FTCL	ALCL
• Clinical trial preferred Preferred regimens (alphabetical order) • Belinostat • Brentuximab vedotin for CD30+ PTCL • Pralatrexate • Romidepsin Other recommended regimens (alphabetical order) • Alemtuzumab • Bendamustine • Bortezomib[j] (category 2B) • Cyclophosphamide and/or etoposide (intravenous [IV] or oral [PO]) • Duvelisib • Gemcitabine • Lenalidomide • RT	• Clinical trial preferred Preferred regimens (alphabetical order) • Belinostat • Brentuximab vedotin for CD30+ AITL • Romidepsin Other recommended regimens (alphabetical order) • Alemtuzumab • Bendamustine • Bortezomib (category 2B) • Cyclophosphamide and/or etoposide (IV or PO) • Cyclosporine • Duvelisib • Gemcitabine • Lenalidomide • Pralatrexate • RT	• Clinical trial preferred Preferred regimens • Brentuximab vedotin Other recommended regimens (alphabetical order) • Alectinib (ALK+ ALCL only) • Belinostat • Bendamustine • Bortezomib[j] (category 2B) • Cyclophosphamide and/or etoposide (IV or PO) • Crizotinib (ALK+ ALCL only) • Duvelisib • Gemcitabine • Pralatrexate • RT • Romidepsin

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Breast Implant-Associated ALCL

SUGGESTED TREATMENT REGIMENS
(alphabetical order)

SYSTEMIC THERAPY
• Brentuximab vedotin • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) • CHOP • CHOEP • Dose-adjusted EPOCH

Adult T-cell leukemia/lymphoma

- HTLV-1 associated
- $CD3^+$, $CD4^+$, $CD8^-$, $CD25^+$ T-cell phenotype
- Endemic in Southern Japan, Caribbean islands, South America, Central Africa
- Chronic/smoldering ATLL (<5% ATLL cells)
  - Slow progression
  - Frequent skin manifestations (MF-like)
- Acute/lymphomatous ATLL
  - Rapid progression
  - Leukemia, lymphadenopathy, organomegaly, hypercalcemia
  - 50% skin manifestations (tumor, nodules, papules, plaques)

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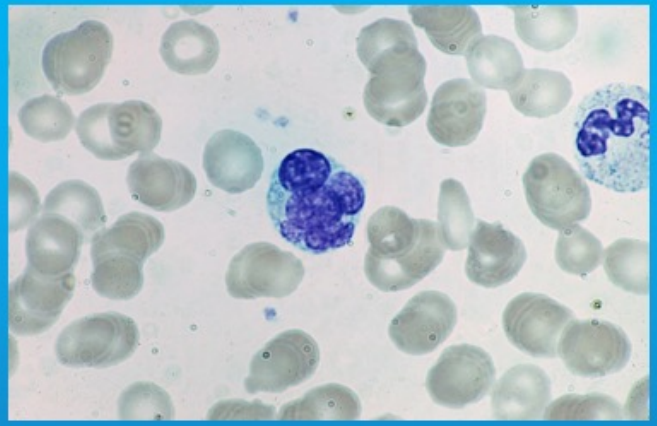

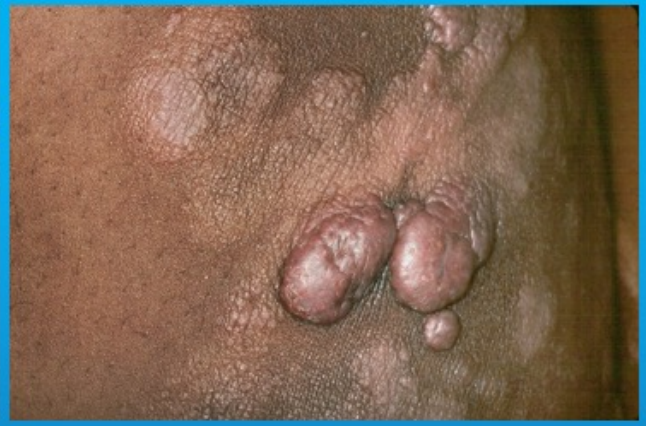

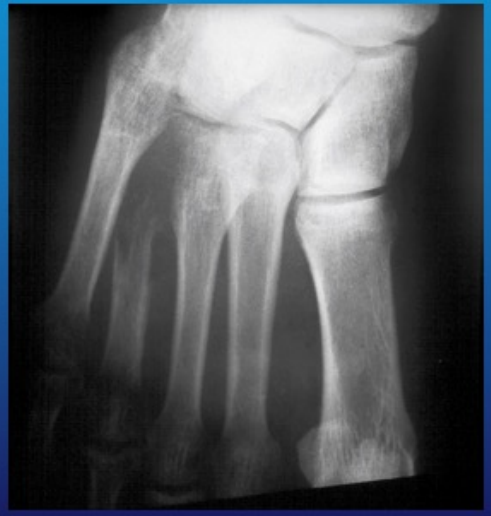

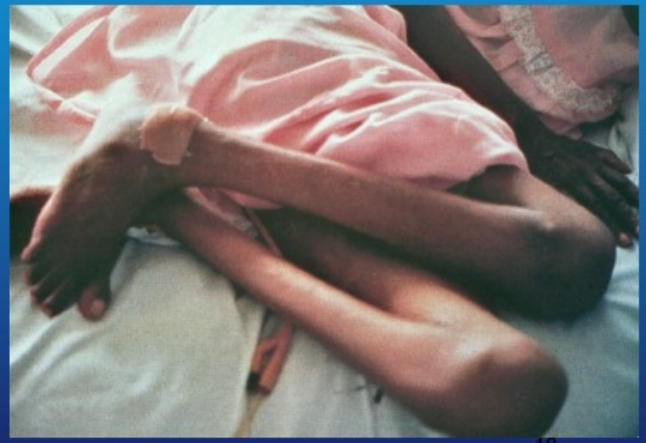

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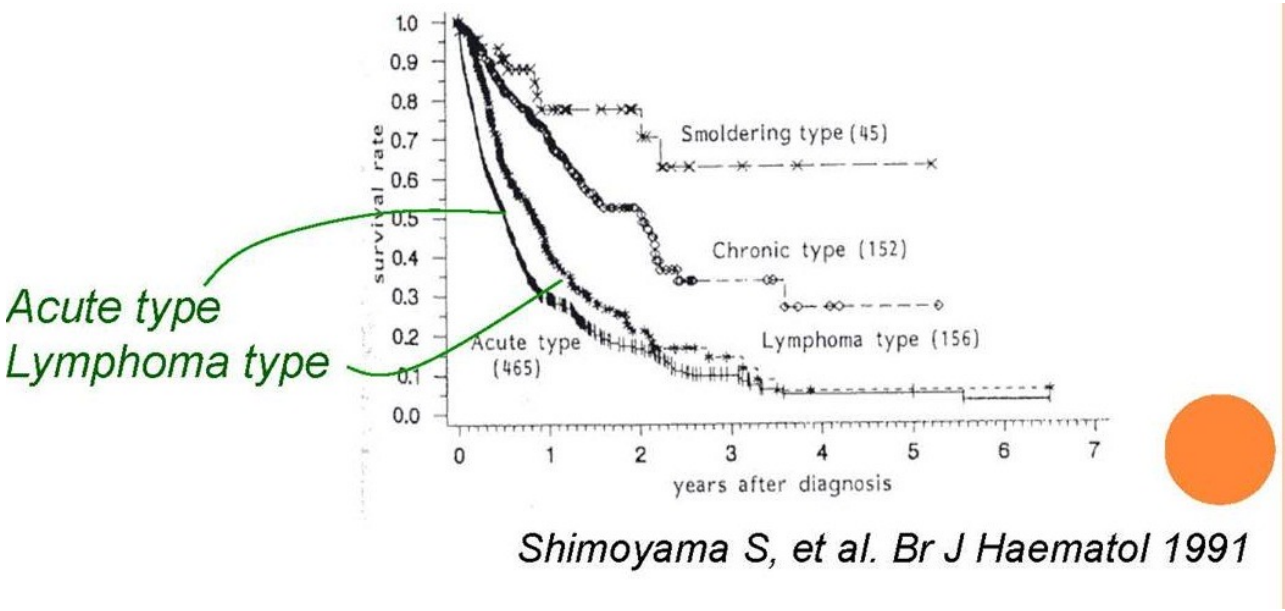
Adult T cell leukemia/lymphoma (ATL)



Shimoyama S, et al. Br J Haematol 1991

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Adult T-Cell Leukemia/Lymphoma

SUGGESTED TREATMENT REGIMENS

INITIAL THERAPY

- Clinical trial

Preferred regimens

- Chemotherapy
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
  - Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) for CD30+ cases
- Zidovudine and interferon (acute and chronic/smoldering subtypes)

Other recommended regimens (alphabetical order)

- CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine

Useful in certain circumstances

- CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) (unable to tolerate intensive regimen or non-CD30 expressing ATLL)

SECOND-LINE THERAPY OR SUBSEQUENT THERAPY

- Clinical trial preferred

Preferred regimens (alphabetical order)

- Single agents
  - Brentuximab vedotin for CD30+ cases
  - Lenalidomide
  - Mogamulizumab
- Combination regimens
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
  - ICE (ifosfamide, carboplatin, etoposide)
  - Zidovudine and interferon (acute and chronic/smoldering subtypes)

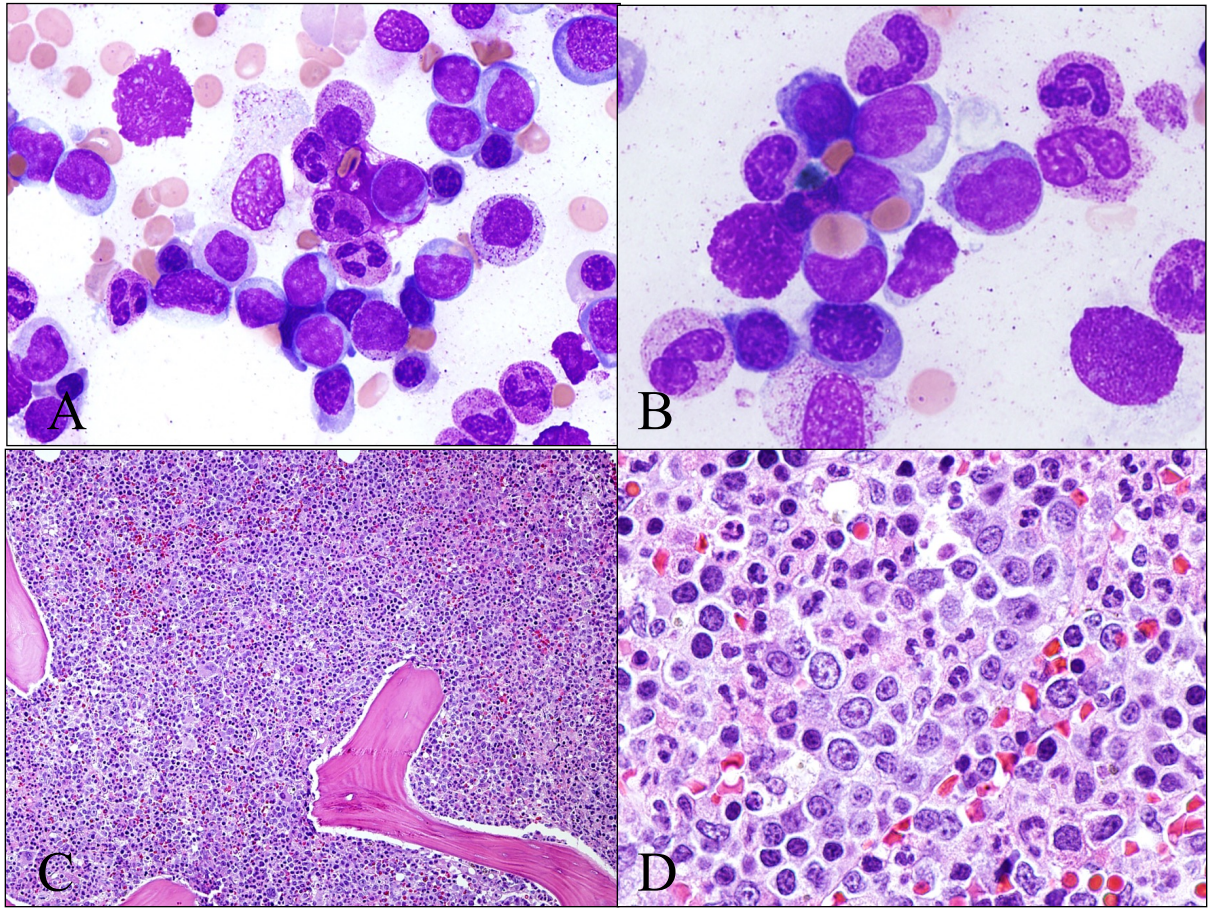
Alternative regimens (alphabetical order)

- Single agents
  - Alemtuzumab
  - Arsenic trioxide
  - Belinostat
  - Bendamustine
  - Bortezomib
  - Gemcitabine
  - Pralatrexate
  - RT in selected cases with localized, symptomatic disease

Hepatosplenic T-Cell Lymphoma

- Male predominance, young adults
- Systemic symptoms
- Hepatosplenomegaly, lymphadenopathy and pancytopenia
- Previous immune suppression or compromise (10-20%)
- Infiltrates liver, splenic red pulp and bone marrow
- Erythrophagocytosis in 25-50%
- γ/δ TCR rearrangement, $CD3^{+}$, $CD4^{-}$, $CD8^{-}$, $CD56^{+/-}$
- Isochrome 7 q translocation
- STAT5B activating mutations
- Dismal prognosis
- Allogeneic stem cell transplant

Hepatosplenic T-Cell Lymphoma



Extranodal nasal NK/T-cell lymphoma, nasal type

- Accounts for 3 to 10% of malignant lymphomas in East Asia (< 1% in western countries)
- 2/3 of patients have localized diseases (stage I or II) in the nasal region (nasal NK/T-cell lymphoma): 5yr-OS (15-40%)
- Localized disease treated with chemotherapy combined with radiation
- Epstein-Barr virus (EBV) – associated lymphoid malignancy
- Tumor cells express P-glycoprotein/MDR1
- B symptoms, stage III/IV, elevated sLDH level, and regional LN involvement are known to be unfavorable prognostic factors

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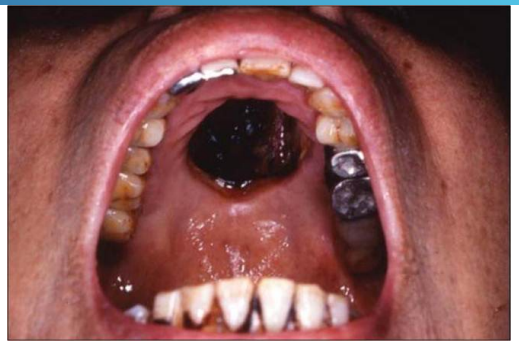
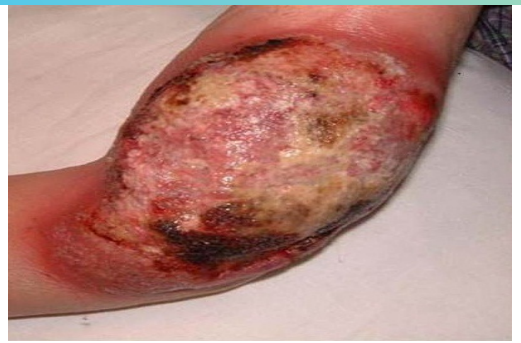
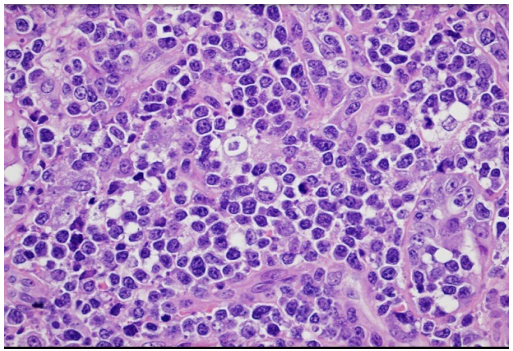
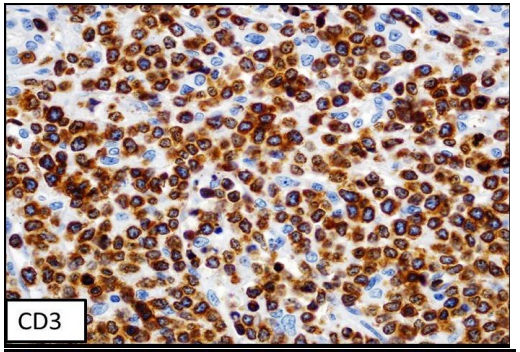
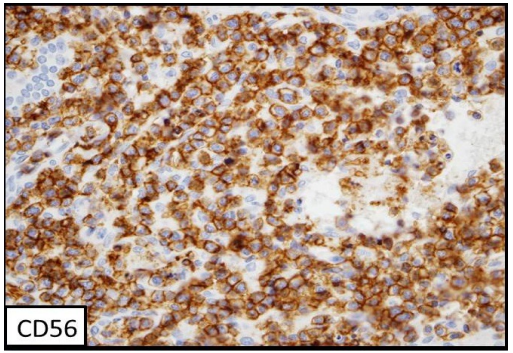
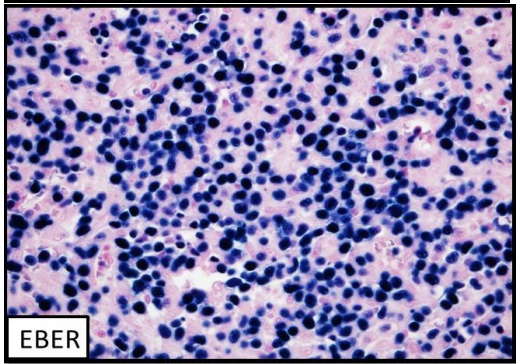







CD3


CD56


EBER

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Extranodal NK/T-Cell Lymphomas

PROGNOSTIC INDEX OF NATURAL KILLER LYMPHOMA (PINK)

RISK FACTORS

Age >60 y
Stage III or IV disease
Distant lymph-node involvement
Non-nasal type disease

	Number of risk factors
Low	0
Intermediate	1
High	≥2

PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA WITH EPSTEIN-BARR VIRUS DNA (PINK-E)[a]

RISK FACTORS

Age >60 y
Stage III or IV disease
Distant lymph-node involvement
Non-nasal type disease
Epstein-Barr virus DNA

	Number of risk factors
Low	0–1
Intermediate	2
High	≥3

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Extranodal NK/T-Cell Lymphomas

SUGGESTED TREATMENT REGIMENS

INDUCTION THERAPY	
Combination chemotherapy regimen (asparaginase-based)	**Preferred regimens** • Modified SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide) x 4–6 cycles for advanced stage • P-GEMOX (gemcitabine, pegaspargase, and oxaliplatin) • DDGP (dexamethasone, cisplatin, gemcitabine, pegaspargase) **Useful in certain circumstances** • AspaMetDex (pegaspargase, methotrexate, and dexamethasone)
Combined modality therapy	Concurrent chemoradiation therapy (CCRT) **Preferred regimen** • RT and 3 courses of DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) **Other recommended regimen** • RT and cisplatin followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)
	Sequential chemoradiation • For stage I, II, modified SMILE x 2–4 cycles followed by RT
	Sandwich chemoradiation • P-GEMOX x 2 cycles followed by RT followed by P-GEMOX x 2–4 cycles

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Extranodal NK/T-Cell Lymphomas

SUGGESTED TREATMENT REGIMENS

RELAPSED/REFRACTORY THERAPY

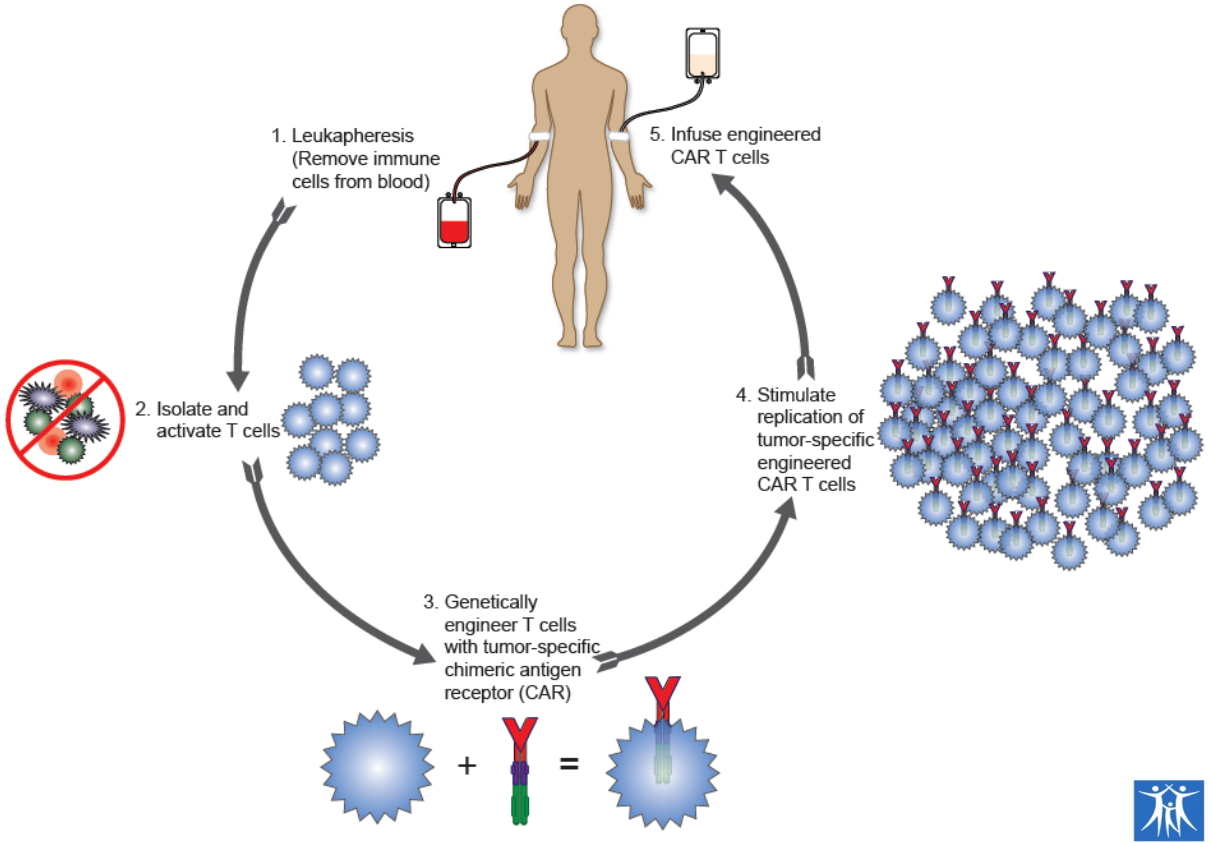
- Clinical trial

Preferred regimens
- Pembrolizumab
- Nivolumab

Other recommended regimens (alphabetical order)
- Single agents
  - Brentuximab vedotin for CD30+ disease
  - Pralatrexate
- Combination regimens (alphabetical order)
  - Asparaginase-based combination chemotherapy regimen (1 of 3) not used in first-line therapy
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

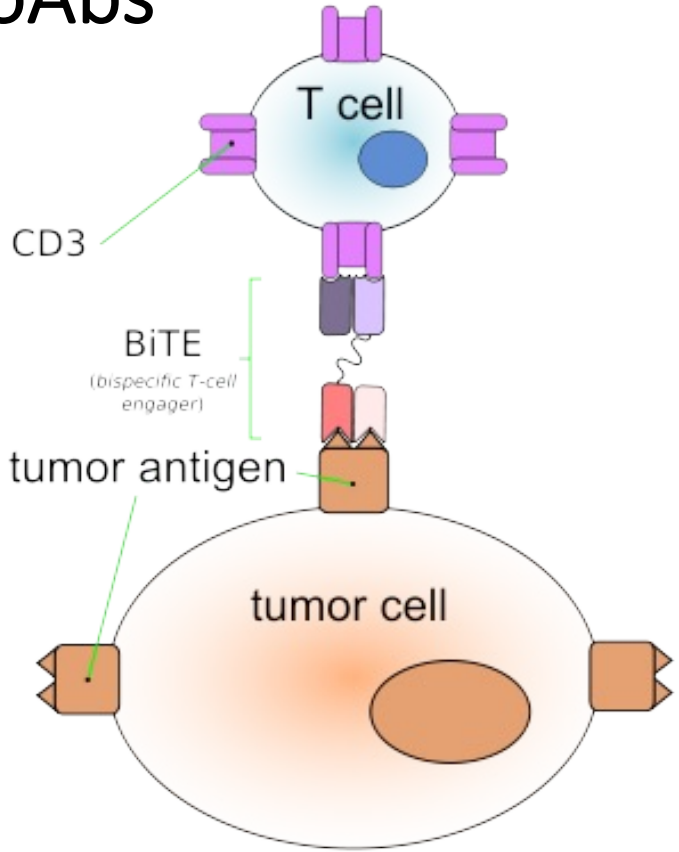
Useful in certain circumstances
- RT
- Belinostat
- Romidepsin

Adoptive Therapy using CAR-Engineered T cells



City of Hope

Bi-Specific MoAbs



Potential Targets

CD1a
CD3
CD4
CD5
CD7
CD30
CD37
TCR

THANK YOU

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