Clinical Updates and Issues: T-Cell Lymphomas

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Learning Objectives

- Summarize the current and evolving therapeutic options for the treatment of T-cell lymphomas.
- Construct a treatment plan for the management of newly-diagnosed and relapsed PTCL.
- Discuss the role of stem-cell transplantation in treatment of T-cell lymphomas.

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Lymphoma 101

- Of all cancers, lymphomas represent 4.9% cases in US
  - 81,000 new cases in US in 2015[1]
  - Most common hematologic malignancy
- Neoplasms arising from cells of the lymphoid lineage
- Based on pathologic and clinical features
  - REAL classification[2]
  - NHL v. HL
  - Aggressive v. indolent
- Risk factors not fully understood
- There are >70 types of lymphoma[2]
  - Majority are NHL

1. National Cancer Institute SEER fact sheet, 2015
2. Swerdlow SH, Campo E, Harris NL, et al. (Eds). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Press, Lyon 2008.

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Peripheral T-Cell Lymphomas

- Represent ~10-15% of all cases of NHL[1]
- 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%

1. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124-4130.
2. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918

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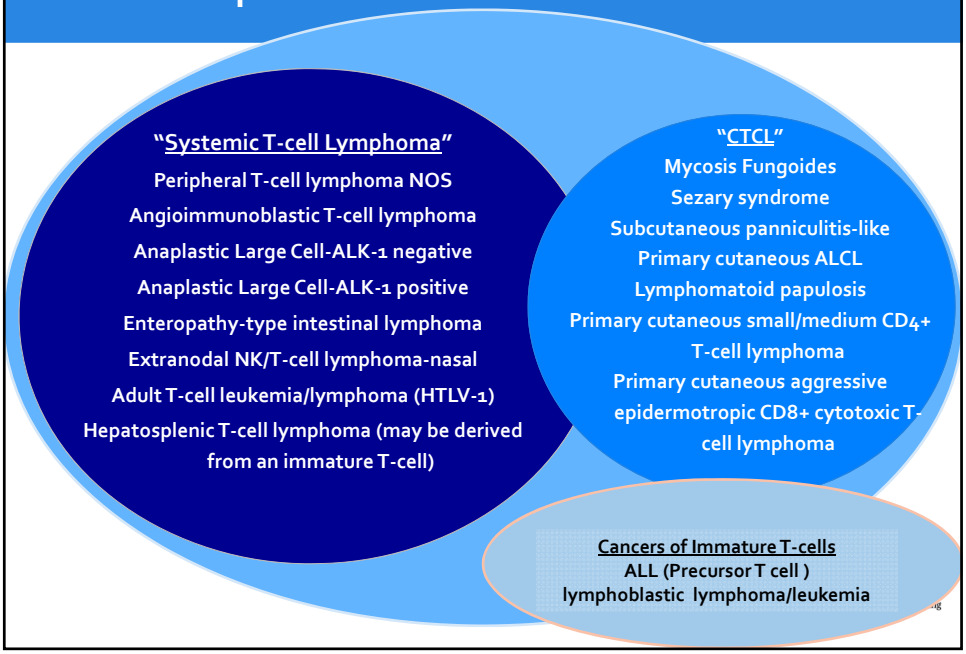
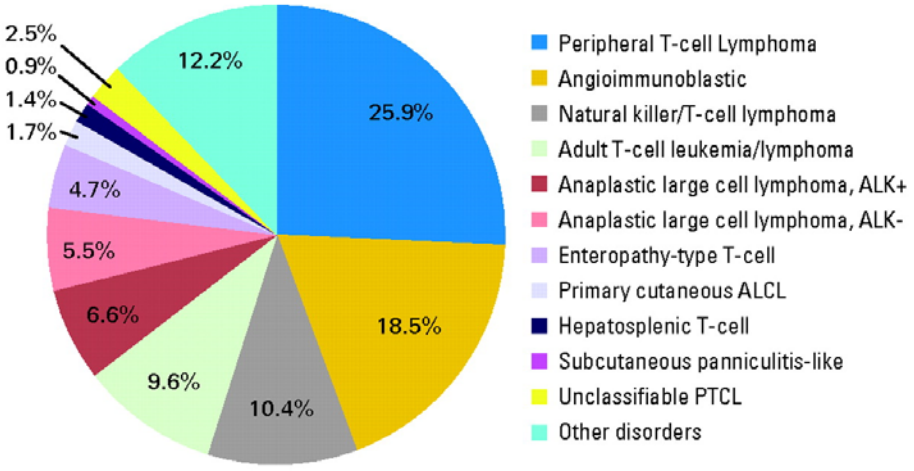
T-Cell neoplasms



Distribution of subtypes among 1,314 cases



International T-Cell Lymphoma Project JCO 2008;26:4124-4130

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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)[1]
  - Age
  - LDH
  - Performance status
  - Ann Arbor Stage
  - # extranodal sites
- Prognostic Index for PTCL-U (PIT)[2]
  - Age
  - LDH
  - Performance status
  - BM involvement

1 The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive Model for aggressive NHL. *N Engl Med* 1993;329:987-994
2 Gallamini, A., et al Peripheral T-Cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. *Blood* 2004;103:2474-2479

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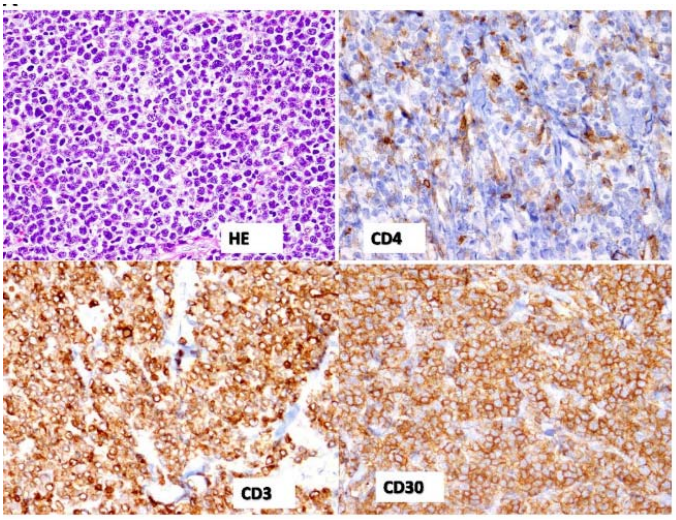
Pathology example



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Cutaneous T-Cell Lymphomas

Cutaneous T-Cell Lymphomas (CTCL)

- 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

1. Talpur, R. et al. Long term outcomes of 1263 patients with mycosis fungoides and Sézary syndrome from 1982 to 2009. *Clin Cancer Res*. 2012; 18:5051-5060.
2. Alberti-Violetti S, et al. Advanced stage mycosis fungoides and Sezary syndrome: survival and response to treatment. *Clin Lymphoma Myeloma Leuk*. 2015; 15:105-112

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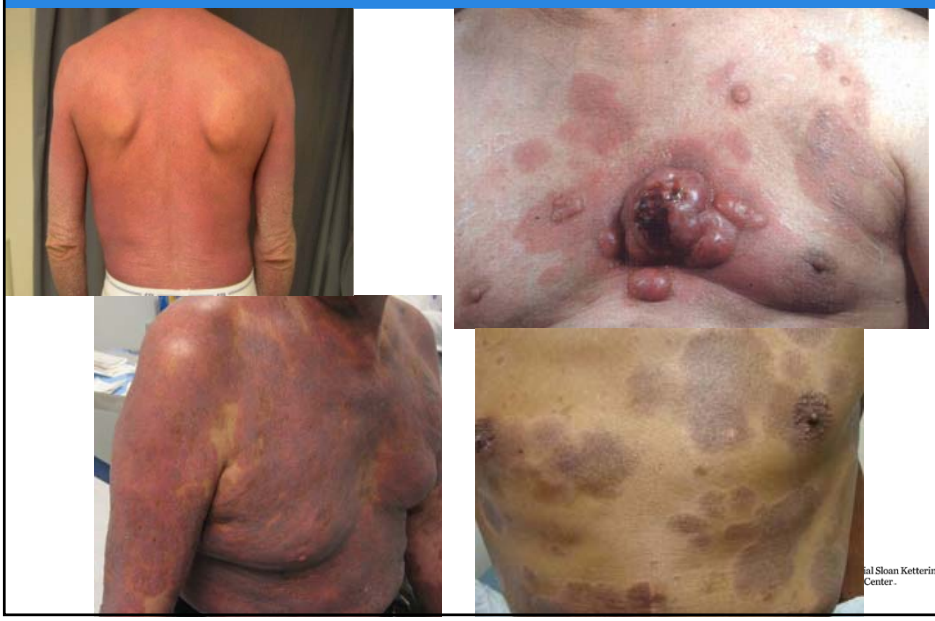
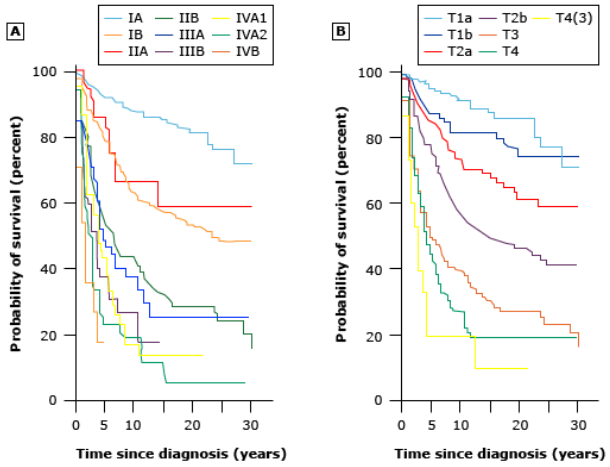
CTCL: skin lesions



Mycosis Fungoides



Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol 2010*; 28:4730.

MF/SS Therapy: Skin-directed

Limited

- Steroids
- Topical chemotherapy (mechlorethamine)
- Local radiation
- Topical retinoids (bexarotene)
- Phototherapy (UVB/PUVA)
- Topical immune response modifiers (imiquimod, resiquimod)

Generalized

- Steroids
- Topical chemotherapy (mechlorethamine)
- Phototherapy (UVB/PUVA)
- Total skin electron beam therapy (TSEBT)
- Topical tacrolimus

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MF/SS: Systemic Therapy

- Biologic response modifiers
  - interferon (IFN-α2a)
  - Oral retinoids (isotretinoin, bexarotene)
- HDAC inhibitors
  - Vorinostat
  - romidepsin
- Extracorporeal photopheresis (ECP)
- Methotrexate
- Steroids
- Targeted therapy
  - brentuximab vedotin
  - denileukin diftitox
- Chemotherapy
  - gemcitabine
  - liposomal doxorubicin
  - pralatrexate
  - chlorambucil
  - pentostatin
  - Bortezomib
- Allo transplant?

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MF/SS: newer agents

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

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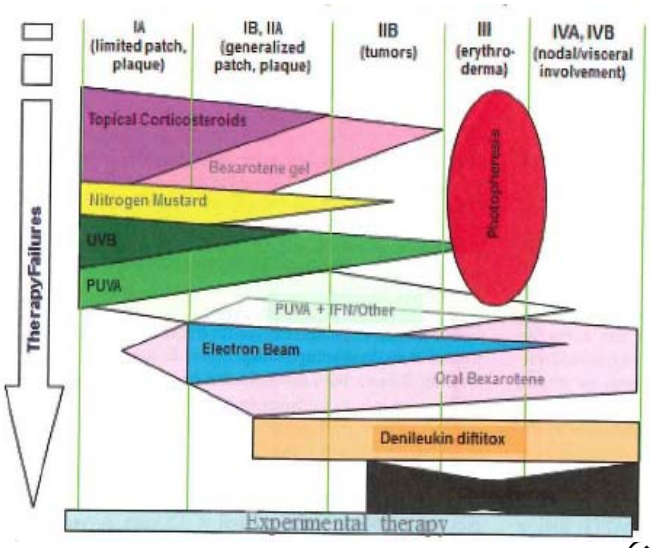
CTCL treatment map



Used with permission. Duvic, M. Choosing a systemic treatment for advanced stage CTCL: mycosis fungoides and Sezary syndrome. American Society of Hematology Education Program 2015; 529-544

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Agents in the pipeline

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

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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

Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124-4130.

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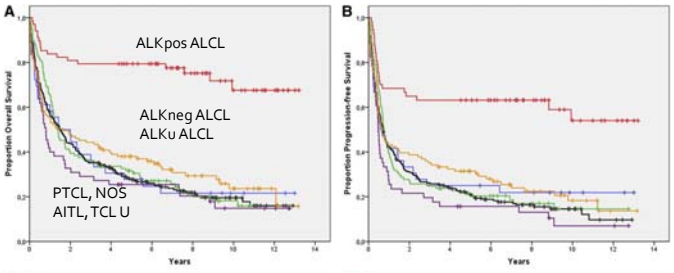
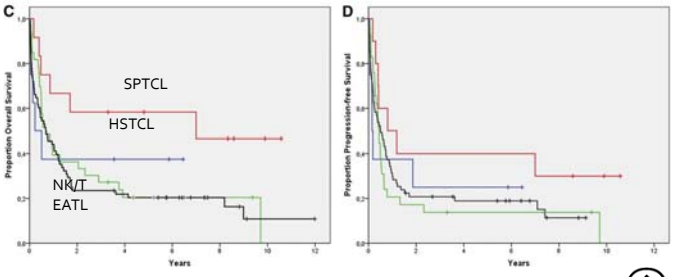
Swedish Registry: Population- based PTCL cohort

OS nodal PTCL



PFS nodal PTCL

OS extra-nodal PTCL



PFS extra-nodal PTCL

Ellin , F. et al. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. *Blood* 2014;124:1570-1577

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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

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CHOP: The regimen of choice

Citation	Regimen	Population	N	ORR	CR	PFS/EFS
Savage, et al.	CHOP (retrospective)	PTCL-NOS	117	84%	64%	29% (5 yr)
Reimer, et al.	CHOP→ ASCT	PTCL/AITL/ALCL	83	79%	39%	36% (3 yr), with ASCT
Simon, et al.	CHOP v. VIP-rABVD	PTCL/AITL/ALCL	43	62%	39% (29% in PTCL)	41% (2yr)

Savage KJ, et al. *Ann Oncol. 2004;15(10):1467-1475;*
Reimer P, et al. J Clin Oncol. 2009;27(1):106-113;
Simon A, et al. *Br J Haematol. 2013;151(2):159-166.*

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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

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Improving upon CHOP

Swedish Lymphoma Registry

	CHOP (n=145)	CHOEP (n=107)	p
ORR	70%	81%	0.052
5 yr OS	30%	47%	ns
5 yr PFS	23%	40%	ns*

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

Fredrik Ellin et al. *Blood* 2014;124:1570-1577

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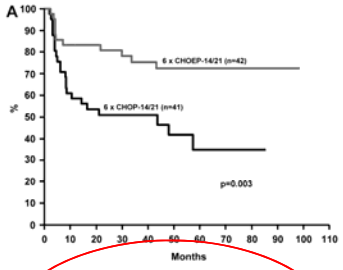
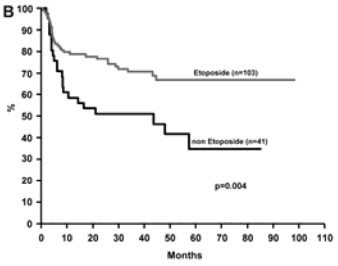
German High -Grade NHL Study Group (DSHNHL) Trials

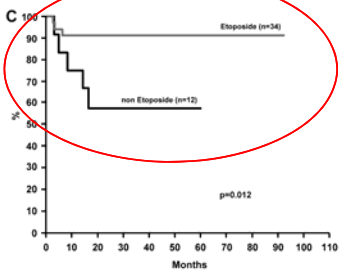
NHL-B1 trial

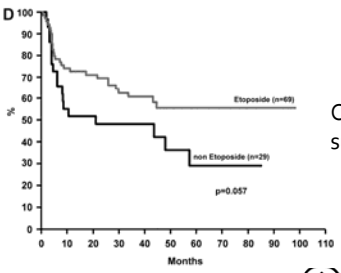




NHL-B1 & Hi-CHOEP trials

ALCL, ALK positive





Other subtypes

Schmitz, N., et al. *Blood* 2010;116:3418-3425

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Additional attempts to improve CHOP

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

Gallamini A, et al. *Blood*. 2007;110(7):2316-2323; Kim SJ, et al. *Eur J Cancer*. 2013;49(4):904-910; Simon A, et al. *Br J Haematol*. 2010;151(2):159-166; Dupuis J, et al. *Hematological Oncology*. 2013; 31 (suppl1): 135; Mahadevan D, et al. *Cancer*. 2013;119(2):371-379; Advani, RH, et al. *Br J Haematol*. 2015; 172:535-544

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

Treatment schema	Patients	ORR	CR
Sequential treatment: BV x2 -> CHOPx6 -> BV x8	13 ALCL	85%	62%
Combination treatment BV plus CHP x6 -> BV x 10	19 ALCL 7 non-ALCL	100%	88%

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

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Studies building upon CHOP in PTCL

Trial	NCT	Study Title
ECHELON-2	01777152	A Comparison of Brentuximab Vedotin and CHP With Standard-of-care CHOP in the Treatment of Patients With CD30-positive Mature T-cell Lymphomas
Ro-CHOP	01796002	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
A-CHOP-14	00725231	Immunotherapy in Peripheral T Cell Lymphoma - the Role of Alemtuzumab in Addition to Dose Dense CHOP
Pralatrexate	01420679	Study of Pralatrexate Versus Observation Following CHOP-based Chemotherapy in Previously Undiagnosed Peripheral T-cell Lymphoma Patients
RADCHOP	01198665	RAD001 (everolimus) Combined With CHOP in Newly Diagnosed Peripheral T-cell Lymphomas

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Upfront consolidation with autologous transplant

Swedish Lymphoma Registry[1]

Outcome	Auto-SCT ITT (n=128)	Non-auto-SCT (n=124)	p-value
5 year PFS (%)	41	20	0.002
5 year OS (%)	48	26	0.004

MSKCC series – PTCL patients with intent for front-line transplant[2]

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

[1]Fredrik Ellin et al. *Blood* 2014;124:1570-1577
[2]Neha Mehta, et al. A retrospective analysis of PTCL treated with intention to transplant in the first remission. *Clinical Lymphoma, Myeloma & Leukemia*, 2013; 13: 664-670

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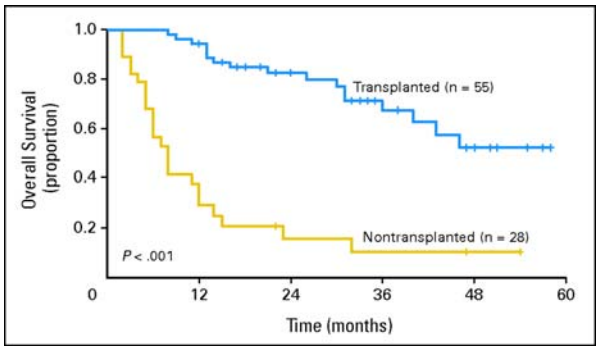
Prospective phase II study: Up-front auto-SCT

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

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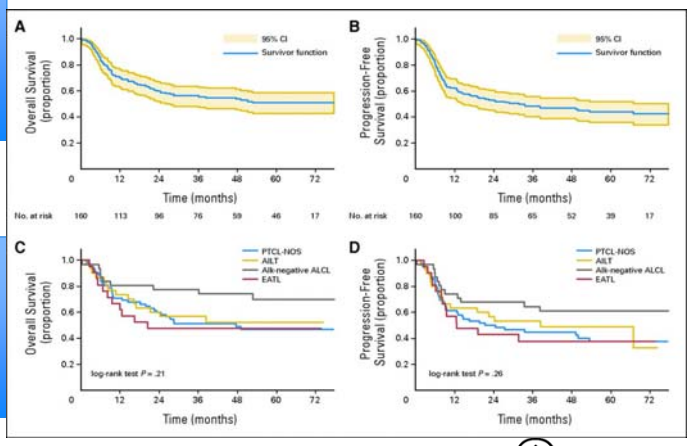
CHOEP followed by auto-SCT - Nordic Lymphoma Group Trial 1

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

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

5 yr OS 51%

5 yr PFS 44%



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

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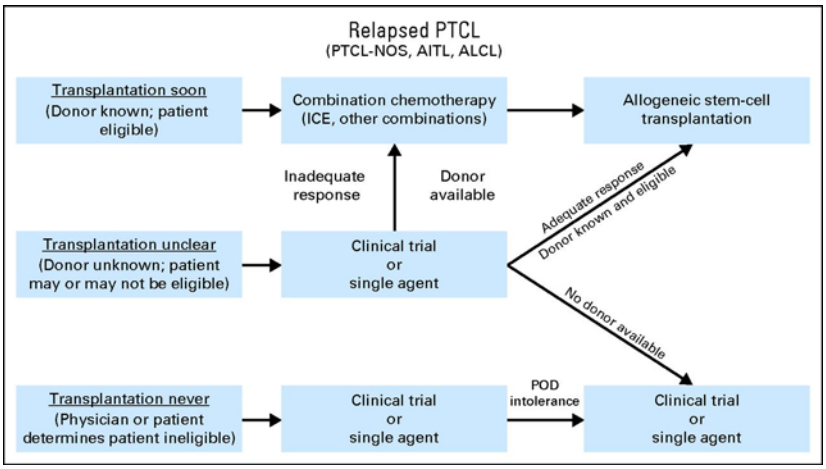
Relapsed/Refractory PTCL

Treatment Strategy for Relapsed/Refractory Disease



Lunning et al. JCO 2013;31:1922-1927

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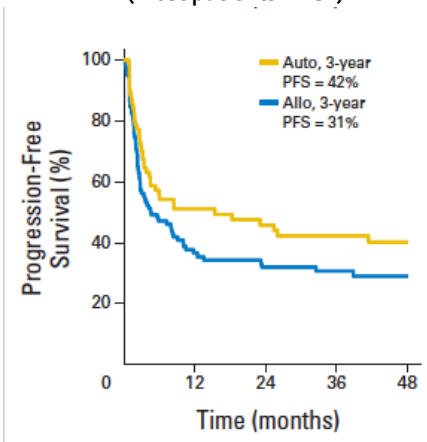
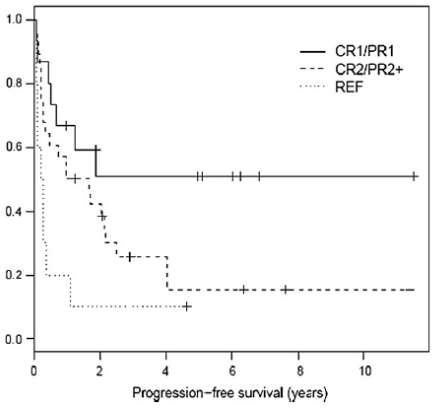
Autologous Transplantation in Relapsed PTCL

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



Stanford



CIBMTR, Center for International Blood and Marrow Transplant Research
Smith S, et al. *JCO 2013; 31(25): 3100-3109;* Chen AI, et al. *Biol Blood Marrow Transplant.* 2008;14(7):741-747.

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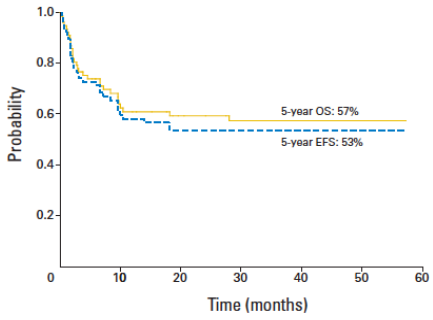
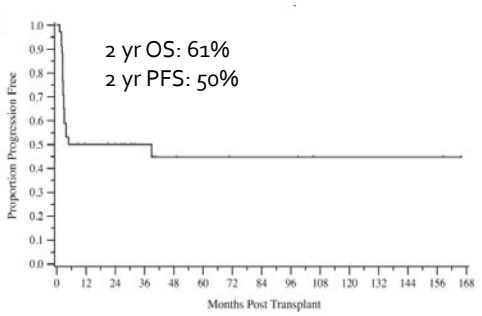
Allogeneic stem cell transplant

French Registry N = 77, TRM 34%



MSKCC N = 34, TRM 18%



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

Le Gouill S, et al. *J Clin Oncol.* 2008;26:2264-2271
Goldberg J, et al. *Leuk Lymphoma.* 2012

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Single-agent activity in Relapsed/Refractory PTCL

Agent	n	ORR	CR	DOR (mo)	Reference
Romidepsin	130	25%	15%	17	Coiffer, et al. JCO 2012
Belinostat	129	26%	10%	8.3	O'Connor, et al. JCO 2015
Pralatrexate	111	29%	13%	10.5	O'Connor, et al. JCO 2011
Bendamustine	60	50%	28%	3.5	Damaj, et al. JCO 2013
Brentuximab vedotin (ALCL)	58	86%	57%	12.6	Pro, et al. JCO 2012
Brentuximab (non-ALCL)	35	41%	23%	7.6	Horwitz, et al. Blood 2014
Gemcitabine	20	55%	30%		Zinzani, et al. Annals of Oncology 2010
Lenalidomide	40	26%	8%	13	Toumishey, et al. Cancer 2015

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Recent promising studies in PTCL

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

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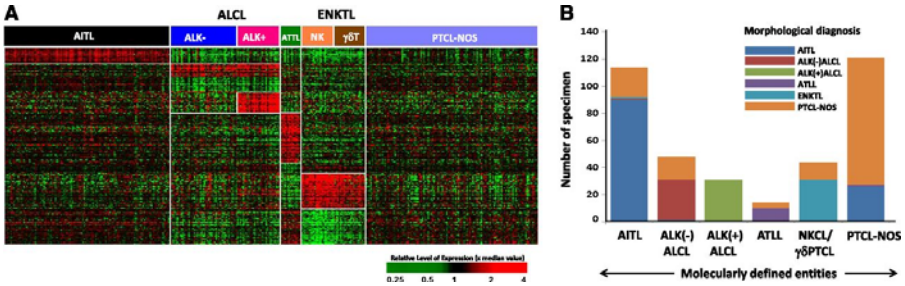
The Future….

PTCL: Gene expression signatures - towards more precise classification



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

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

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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

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

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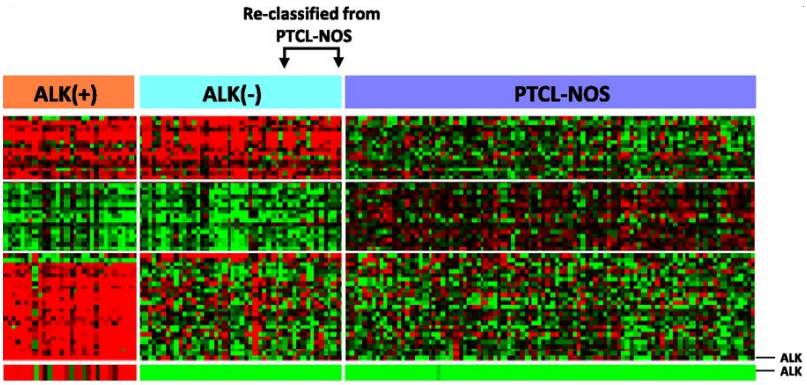
Distinct molecular signatures



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

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

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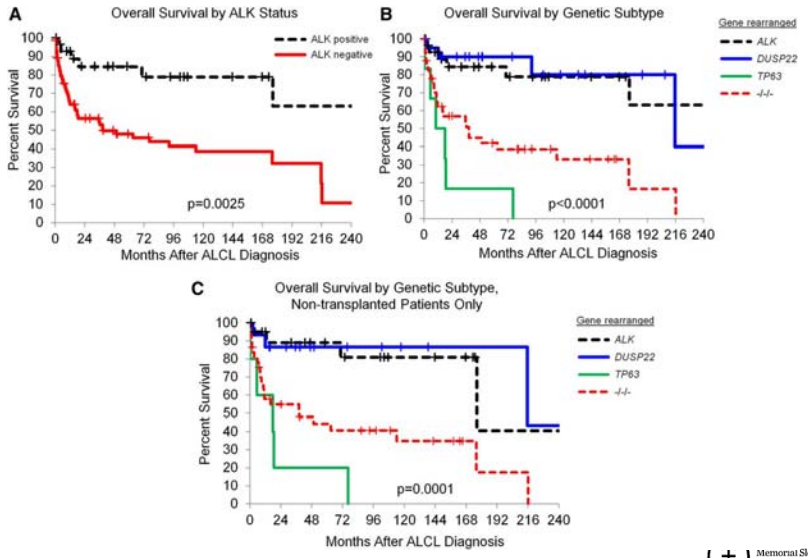
ALK negative ALCL: Prognostic impact of DUSP22 and TP63 rearrangements



Edgardo R. Parrilla Castellar et al. *Blood* 2014;124:1473-1480

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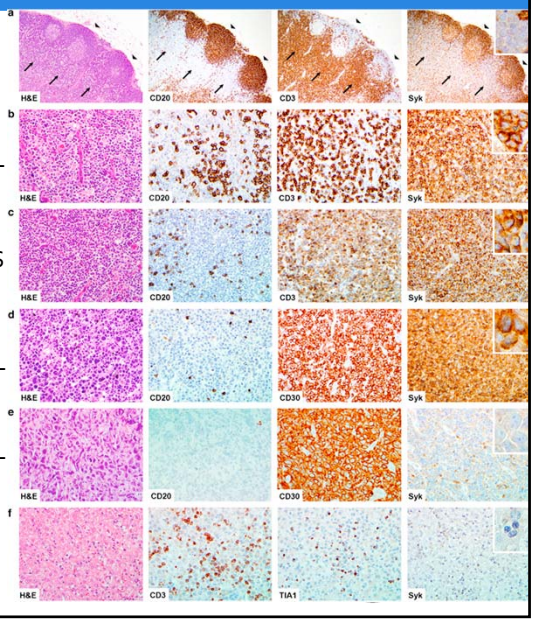
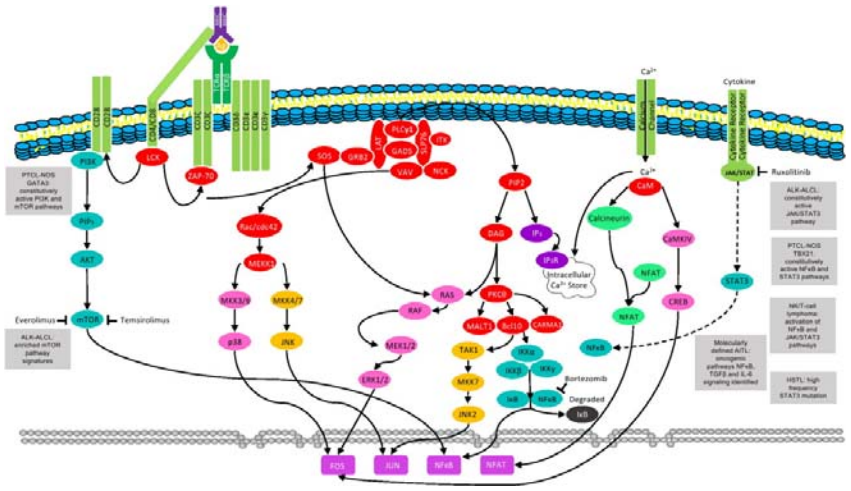
SYK as a target in PTCL

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



Feldman, et al. Leukemia (2008) 22, 1139–1143
Wilcox, et al. Leukemia (2010) 24, 229–232

Pathways and potential targets in PTCL



Iqbal et al. Genomic signatures in T-cell lymphoma: How can these improve precision in diagnosis and inform prognosis? *Blood Reviews*, 2015, Available online 18 August 2015

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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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