PTCL – Diagnosis & Treatment Update

LEUKEMIA & LYMPHOMA SOCIETY®
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Welcome & Introductions

Treatment and Clinical Trials for PTCL

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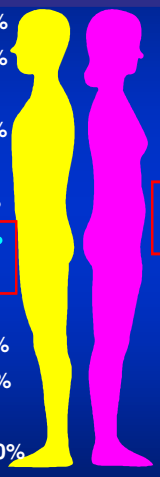
UNMC

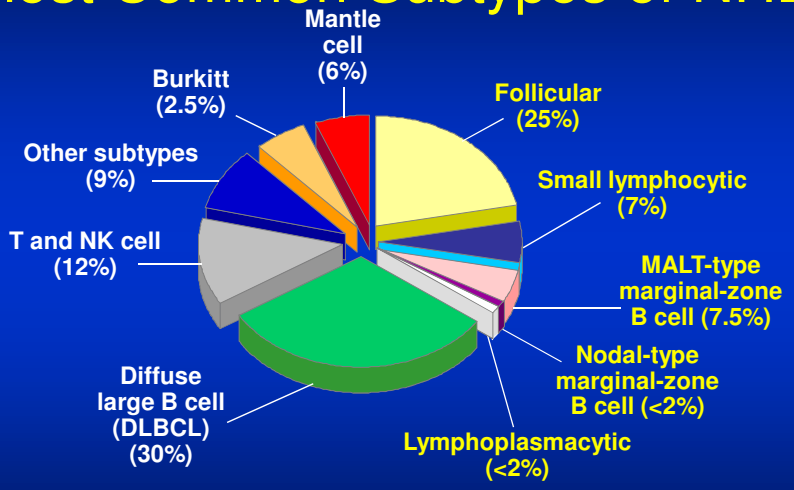
2013 Estimated US New Cancer Cases

Males			Females		
Prostate	238,590	27.9%	Breast	232,340	28.8%
Lung & bronchus	118,080	13.8%	Lung & bronchus	110,110	13.7%
Urinary bladder	54,610	6.4%	Colon	52,390	6.5%
Colon	50,090	5.8%	Uterine corpus	49,560	6.1%
Melanoma of skin	45,060	5.3%	Thyroid	45,310	5.6%
Kidney & renal pelvis	40,430	4.7%	Non-Hodgkin lymphoma	32,140	4.0%
Non-Hodgkin lymphoma	37,600	4.4%	Kidney & renal pelvis	24,720	3.1%
Oral cavity & pharynx	29,620	3.5%	Melanoma of skin	31,630	3.9%
Leukemia	27,880	3.3%	Pancreas	22,480	2.8%
Pancreas	22,740	2.7%	Ovary	22,240	2.8%
ALL SITES	854,790	100%	ALL SITES	805,500	100%



American Cancer Society. *Cancer Facts & Figures 2013*. Available online at http://www.cancer.org/research/cancerfactsfigures/cancerfactsfigures/cancer-facts-figures-2013

Most Common Subtypes of NHL



Percentages are of all NHLs.
MALT=mucosa-associated lymphoid tissue; NK=natural killer.

Lichtman MA. *Williams Hematology*. 7th ed. New York, NY: McGraw Hill. 2006;1408.

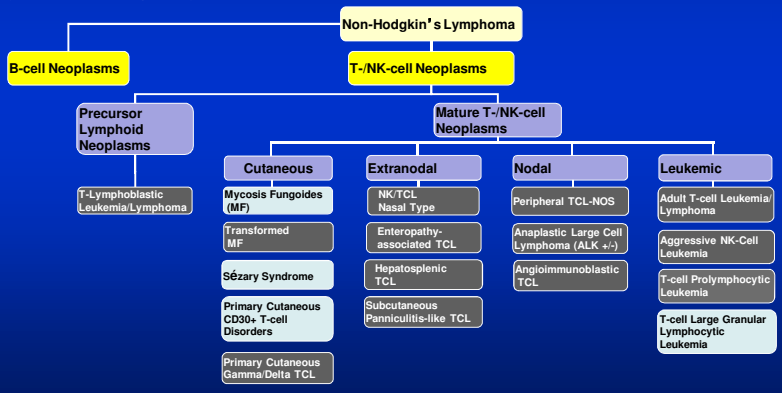
T-cell Lymphomas

- T-cell lymphomas account for ~15% of all NHLs
- Less common than B-cell lymphomas
- Can be indolent or clinically aggressive
- Similarly heterogeneous in their clinical presentation, features, and prognosis
- Challenges in treatment:
  - Increasing number of subtypes, making it very difficult to understand and to keep track of these entities
  - Each entity is encountered infrequently

Gisselbrecht C, et al. Blood. 1998;92:76-82; Armitage J, et al. *J Clin Oncol.* 1998;16:2780–2795.

Classification of Peripheral T-cell Lymphoma (PTCL)

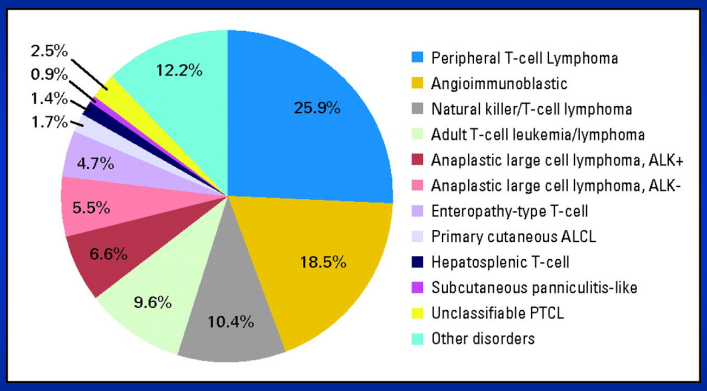
- PTCL is a heterogeneous group of aggressive mature T-/NK-cell lymphomas[1]
  - PTCL does not refer to anatomic sites, but rather to the involvement of more mature (post-thymic) T cells vs pre-thymic or immature T cells[1]



Adapted from Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* 2008.

Aggressive | Indolent

Fig 1. Distribution of 1,314 cases by consensus diagnosis



International T-Cell Lymphoma Project, Vose, et al: J Clin Oncol; 26:4124-4130 2008

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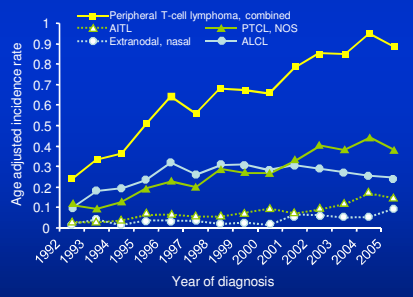
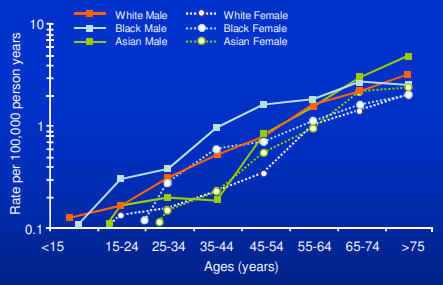
PTCL Incidence

- PTCL represents 10-15% of new NHL cases per year[1]
- By some estimates, the incidence of PTCL is growing significantly[2,3]
- The growth in PTCL incidence may be driven by an aging population[3]





1. O'Leary HM, Savage KJ. *Curr Oncol Rep.* 2008;10:404-411.
2. Abouyabis AN, et al. *Leuk Lymphoma.* 2008:49:2099-2107.
3. Morton LM, et al. *Blood.* 2006;107:265-276.

Staging of PTCL
Ann Arbor Classification System

PTCL most commonly presents with advanced, systemic symptoms (stage III-IV).[1]

Ann Arbor Classification for Hodgkin's and non-Hodgkin's Lymphoma[2]	
Principal stages	
Stage I	Cancer is located in a single region, (eg, 1 lymph node and the surrounding area)
Stage II	Cancer is located in 2 separate regions but confined to 1 side of the diaphragm
Stage III	Cancer has spread to both sides of the diaphragm, including 1 organ or area near the lymph nodes or the spleen
Stage IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs, including any involvement of the liver, bone marrow, or nodular involvement of the lungs
Modifiers	
A	Absence of constitutional (B-type) symptoms
B	Presence of B-type symptoms
E	Extranodal disease

[1] Rodriguez-Abreu D, et al. *Hematol Oncol.* 2008;26:8–20. [2] Carbone PP, et al. *Cancer Res.* 1971;31:1860–1861

Prognostic Indices for PTCL

- The IPI for NHL is commonly utilized in PTCL[1]

International Prognostic Index (IPI)	
All patients	• Age (≤60 years vs >60 years) • Serum LDH (≤1 x ULN vs >1x ULN) • Performance status (0 or 1 vs 2–4) • Stage I or II [(localized) vs III or IV (advanced)] • Extranodal involvement (≤1 site vs >1 site)
Age-adjusted index (age ≤60 years)	• Stage (I or II vs III or IV) • Serum LDH (≤1 x ULN vs >1x ULN) • Performance status (0 or 1 vs 2–4)

The IPI is calculated based on the sum of the number of risk factors present at diagnosis.

0-1 Low
2 Low/intermediate
3 High/intermediate
4-5 High

- The Prognostic Index for PTCL (PIT) is also in use[2]

Prognostic Risk Factors for PTCL (PIT)
• Age >60 years • ECOG Performance Status (score ≥2) • Elevated LDH • Bone marrow involvement

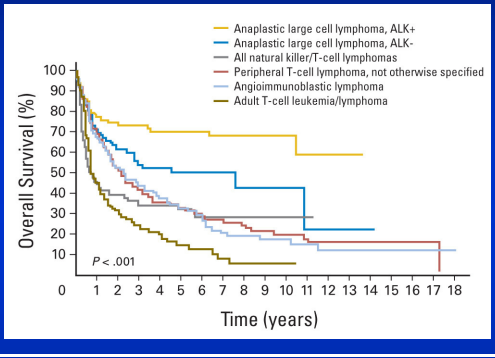
The PIT is based on number of risk factors present at diagnosis

Group 1 0 risk factor (62% 5-yr OS)
Group 2 1 risk factor (53% 5-yr OS)
Group 3 2 risk factors (33% 5-yr OS)
Group 4 3-4 risk factors (18% 5-yr OS)

1. International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Eng J Med.* 1993;329:987-994.
2. Gallamini A, et al. *Blood.* 2004;103:2474-2479.

The International PTCL and NK/TCL Study: OS in PTCL

- Majority of patients (>85%) received an anthracycline-containing regimen



	PTCL Subtypes					
	ALK+ ALCL	ALK– ALCL	PTCL-NOS	AITL	NK/TCL	ATLL
5-yr OS rate	70%	49%	32%	32%	32%	14%

International T-Cell Lymphoma Project. Vose, et al:*J Clin Oncol*. 26:4124-4130, 2008.

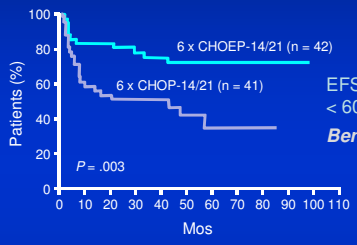
NCCN Guidelines for Initial Treatment of PTCL

Patient Population	Induction Therapy	Consolidation Therapy
ALK-positive ALCL	CHOP -21 CHOEP-21	Not needed if in remission
All other subtypes: stage I-II (low/low intermediate risk)	• **Clinical trial preferred** • Multiagent chemotherapy* (4-6 cycles) with adjuvant locoregional RT	Consider consolidation with high-dose therapy and stem cell rescue for all patients except low-risk (aaIPI)
All other subtypes: stage I-II (high/high-intermediate risk), stage III-IV	• **Clinical trial preferred** • Multiagent chemotherapy (6-8 cycles) ± RT	

*Suggested regimens:
- **CHOP** (cyclophosphamide, doxorubicin, vincristine, prednisone)
- **CHOEP** (cyclophsophamide, doxorubicin, vincristine, etoposide, prednisone)
- **HyperCVAD** (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine
- **CHOP followed by ICE** (ifosfamide, carboplatin, etoposide) **or IVE** (ifosfamide, etoposide, and epirubicin) alternating with intermediate-dose methotrexate [New Castle Regimen]
- **Dose-adjusted EPOCH** (etoposide, prednisone, vincristine,cyclophosphamide, doxorubicin)

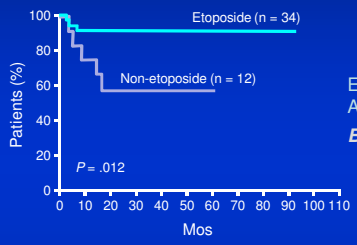
NCCN. Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphoma. Version 1.2013. Available at http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

Adding Etoposide to CHOP: German Prospective High-Grade NHL Studies



EFS, aged < 60 yrs

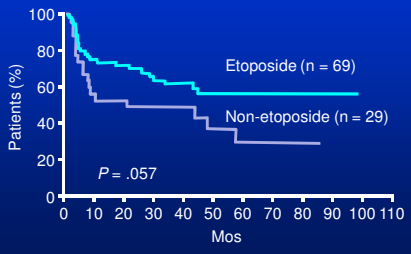
Benefit



EFS, ALCL, ALK+

Benefit

PTCL Subtype	n
ALCL, ALK+	78
ALCL, ALK-	113
PTCL-NOS	70
AITL	28
Other	31
Total	320

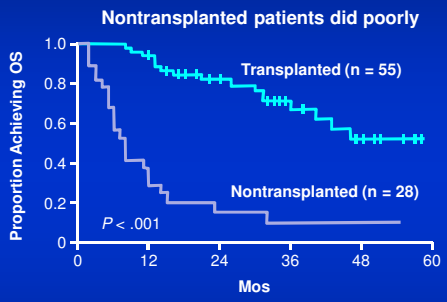


EFS, other subtypes

No Benefit

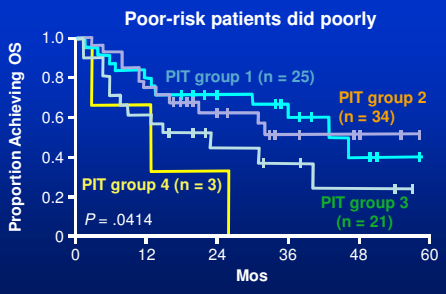
Schmitz N, et al. Blood. 2010;116:3418-3425.

German Prospective Trial of ASCT in First Remission



- PIT group 1: 0 risk factors
- PIT group 2: 1 risk factor
- PIT group 3: 2 risk factors
- PIT group 4: 3-4 risk factors

- N = 83 untreated patients
- CHOP x 4-6
- If ≥ PR, dexaBEAM or ESHAP
- dexaBEAM or ESHAP ± TBI, ASCT
- Median follow-up: 33 mos



Reimer P, et al. J Clin Oncol. 2009;27:106-113.

NCCN Treatment Guidelines for Relapsed/Refractory PTCL

- NCCN recommends **clinical trials** for treatment of relapsed or refractory PTCL
- Patients may be evaluated as candidates for high-dose therapy
- Patients who are not candidates for high-dose therapy may receive experimental treatments

Suggested Treatment Regimens for Second-line Therapy of PTCL (in alphabetical order)[1]

Candidates for Transplant	Non-candidates for Transplant
Clinical trial preferred	**Clinical trial preferred**
Brentuximab vedotin (systemic ALCL only)	Alemtuzumab
DHAP (dexamethasone, cisplatin, cytarabine)	Bortezomib
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)	Brentuximab vedotin (systemic ALCL only)
Dose-Adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)	Cyclosporine (AITL only)
GDP (gemcitabine, dexamethasone, cisplatin)	Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
GemOx (gemcitabine, oxaliplatin)	Gemcitabine
ICE (ifosfamide, carboplatin, etoposide)	Pralatrexate
MINE (mesna, ifosfamide, mitoxantrone, etoposide)	Radiation therapy
Pralatrexate (category 2B)	Romidepsin
Romidepsin	

NCCN. Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphoma. Version 1.2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

Relapsed/Refractory PTCL: FDA-Approved Agents

Agent	Regimen	N	ORR, %	CR, %	Response Duration, Mos
Romidepsin[1] (NCI)	14 mg/m^2 weekly x 3 every 28 days	47	38	18	8.9
Romidepsin[2] (pivotal)	14 mg/m^2 weekly x 3 every 28 days	131	25	14	17.0
Pralatrexate[3] (pivotal)	30 mg/m^2 weekly x 6 of 7 wks	111	29	11	10.1
Brentuximab vedotin[4] (ALCL)	1.8 mg/kg every 21 days	58	86	57	12.6

1. Piekarz RL, et al. Blood. 2011;117:5827-5834. 2. Coiffier B, et al. J Clin Oncol. 2012;30:631-636.
3. O'Connor OA, et al. J Clin Oncol. 2011;29:1182-1189. 4. Pro B, et al. J Clin Oncol. 2012;30:2190-2196.

Pralatrexate Mechanism of Action

Pralatrexate is a selective antifolate designed to accumulate preferentially in cancer cells

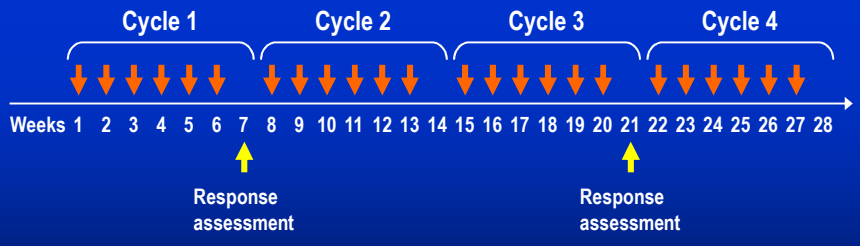
Entry	Pralatrexate selectively enters cells expressing RFC-1, a protein that is overexpressed on cancer cells compared to normal cells	
Accumulation	Once inside cancer cells, pralatrexate is efficiently polyglutamylated, which leads to high intracellular drug retention	
Inhibition	Acting on the folate pathway, pralatrexate interferes with DNA synthesis and triggers cancer cell death	

Sirotnak et al. *Cancer Chemother Pharmacol.* 1998;42(4):313-318.
Wang ES, et al. *Leuk Lymphoma.* 2003;44:1027-1035.
Krug LM, et al. *Clin Cancer Res.* 2000;6:3493-3498.

PROPEL: A Multi-center Phase 2 Open-label Study of Pralatrexate with Vitamin B_{12} and Folic Acid Supplementation in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

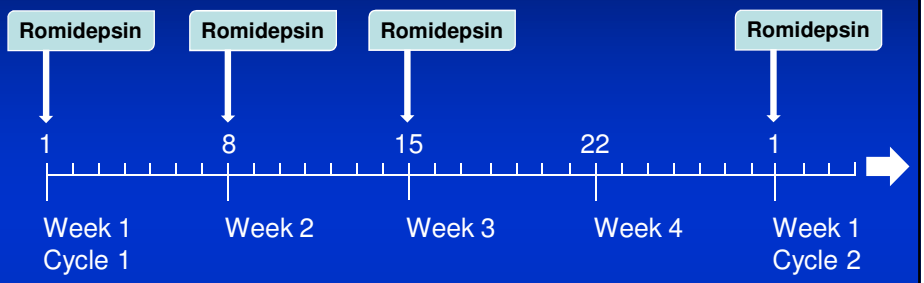
Out-patient dosing schedule

- **PDX 30 mg/m² once weekly IV push × 6 weeks**
- **Vitamin B_{12} 1 mg IM q 8 - 10 weeks**
- **Folic acid 1.0 - 1.25 mg PO QD**



Treat until progression or intolerance

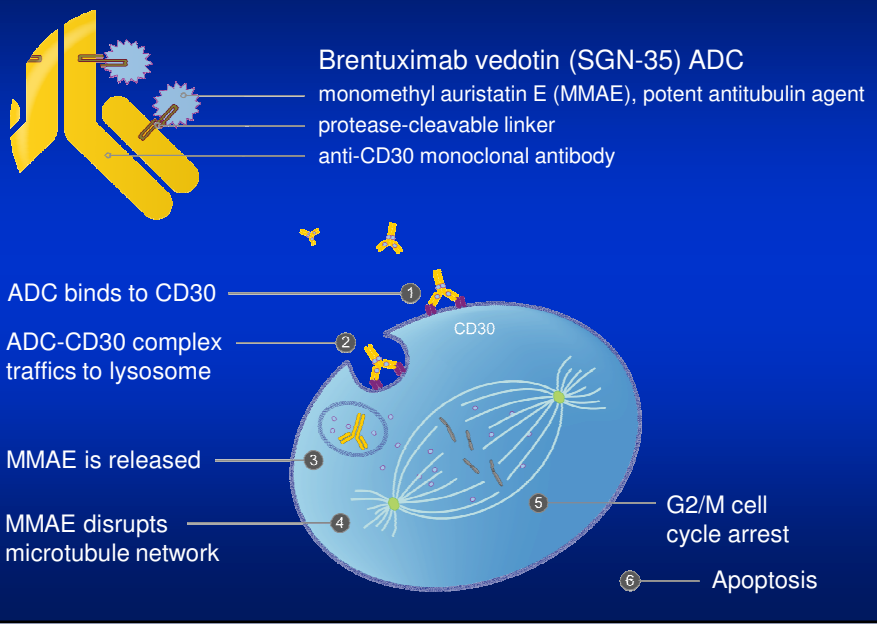
Depsipeptide in Rel/Ref PTCL: Treatment Schedule



Schedule:

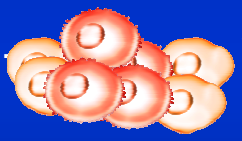
4-hour infusion 14 mg/m^2 on days 1, 8, & 15 every 28 days

Brentuximab Vedotin Mechanism of Action



Targeting T-cell Lymphoma

Surface Antigens/Receptors
CD2
CD4
CD25
CD30
Chemokine receptors..



Microenvironmental Factors
Angiogenesis
Immunomodulation
Viral Pathogens

Cellular Survival Mechanisms
Proteasome Inhibition
HDAC inhibition
Death Receptors & Ligands
Cell Cycle Arrest
Signal Transduction Inhibition

New Agents for T-cell Lymphoma

Nucleoside analogs/pathway inhibitors
- Gemcitabine
- Fludarabine
- Cladribine
- Forodesine
- Clofarabine
- Nelarabine

HDAC inhibitors
- Depsipeptide
- Vorinostat
- Panabinostat
- Belinostat

Antifolate
- Pralatrexate

Proteasome inhibitors
- Bortezomib
- Carfilzomib

Immunomodulators
- Lenalidomide

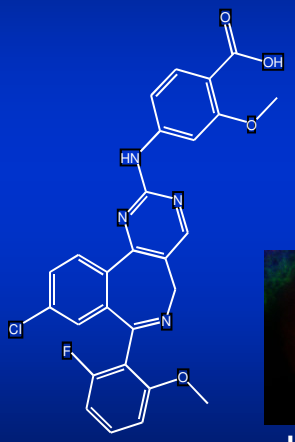
Monoclonal antibodies
- Alemtuzumab
- Anti-CD30
- Zanolimumab
- Siplizumab

Immunotoxins /immunoconjugates
- Denileukin difitox
- SGN-35
- Daclizumab

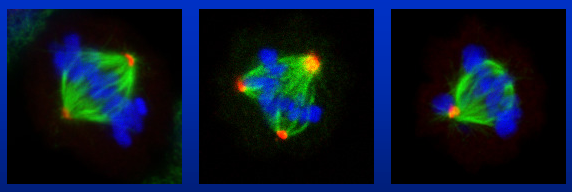
Syk inhibitors
- Fostamatinib disodium

Kinase Inhibitors
-- PDGFRβ inhibitor
-- TKI/Src inhibitors
-- JAK2-Stat inhibitors

Alisertib: Investigational Aurora A Kinase Inhibitor



- Results in mitotic defects
  - Abnormal spindles
  - Unseparated centrosomes
  - Delayed mitotic progression
- Apoptosis or senescence



Untreated **Treated** **Treated**

Anti-CCR4 Antibody: KW-0761

- Defucosylated humanized IgG1 MoAb
- Targets CCR4
  - Shown to be overexpressed on tumor cells
    - 88% of patients with ATLL
    - 38% of patients with PTCL
  - CCR4 expression associated with unfavorable prognosis in both diseases
- Phase II studies under way in relapsed/refractory ATLL and PTCL patients

Lenalidomide in Relapsed/Refractory Aggressive NHL: Results

Histology	n	ORR	PFS (mo.)
DLBCL	108	28%	2.3
Mantle	57	42%	5.7
Follicular (grade 3)	19	42%	6.3
T-cell	33	45%	4.6

ORR in patients with prior SCT = 37% (27/73)

Gr 3-4 neutropenia 41%, thrombocytopenia 19%

Witzig et al. Blood 2009; 114: ASH Abstract #1676

Gene Expression Profiles (GEP) in PTCL-nos

- PTCL-nos can be separated into 3 subgroups on the basis of gene expression profiles (U1, U2, and U3)
- It has not been established whether these subgroups correlate with clinical outcome
  - Preliminary findings indicate that PTCL-U1 tended to have a worse outcome than PTCL-U2 or -U3

Molecular subgroup	Gene expression signature
U1	Included genes involved with poor outcome in other tumors (CCND2)
U2	Over-expression of genes involved in T-cell activation and apoptosis (NFKB1, BCL-2)
U3	Over-expression of genes involved in IFN/JAK/STAT pathway

1. Ballester B, et al. *Oncogene.* 2006;25:1560-1570.

Future for PTCL Therapy

- Standard CHOP – does not work well
- Need to identify novel agents or combinations
- GEP may help us identify specific targets
- Induction therapy, consolidation , and/or maintenance therapy may be needed
- Consider PSCT for selected patients
- Novel therapies added to PSCT also an option
- Clinical trials essential for all PTCL patients

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Question and Answer Session

Dr. Vose's slides are available for download at www.LLS.org/programs

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The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified lymphoma patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE: www.LLS.org/copay**
- **TOLL-FREE PHONE: (877) LLS-COPAY**

For more information about peripheral T-cell lymphoma and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**