
Update on PTCL
someday is today
LEUKEMIA & LYMPHOMA SOCIETY
fighting blood cancers
Welcome and Introductions


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someday is today
LEUKEMIA & LYMPHOMA SOCIETY
fighting blood cancers
Lauren C. Pinter-Brown, MD, FACP
Clinical Professor of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, CA
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Disclosures

- Consulting
  - Millennium, Celgene

T-cell Lymphomas

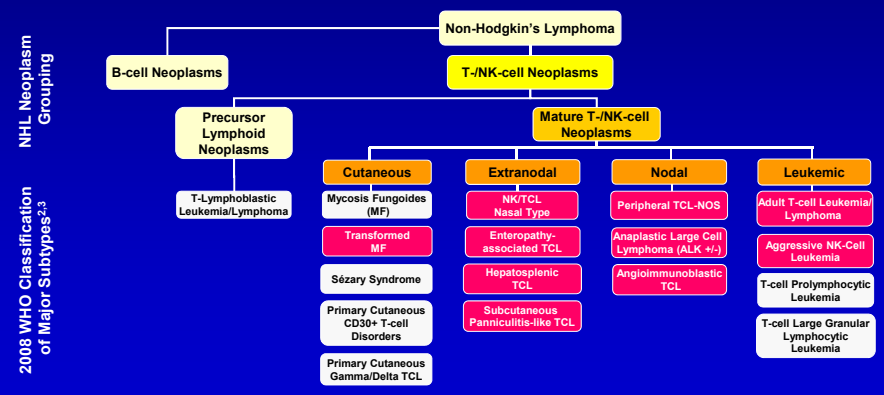
- T-cell lymphomas account for ~15% of all NHLs in the US; the majority of NHLs in the US are B-cell lymphomas
- Like their B-cell counterparts, T-cell lymphomas are heterogeneous in their clinical presentation, pathologic features, biologic behavior and prognosis
- Interpretation of pathologic material may be difficult; to ensure appropriate management, an accurate diagnosis is necessary
- Classification (subtypes) is changing as more knowledge acquired
- There is no "standard" therapy
- The treatments that work well for B-cell lymphomas do not always work as well in the treatment of T-cell lymphomas, underscoring the need for novel therapies for this patient population

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

4

Classification of PTCL

- Peripheral T-cell lymphoma (PTCL) = **Mature T-cell lymphoma**

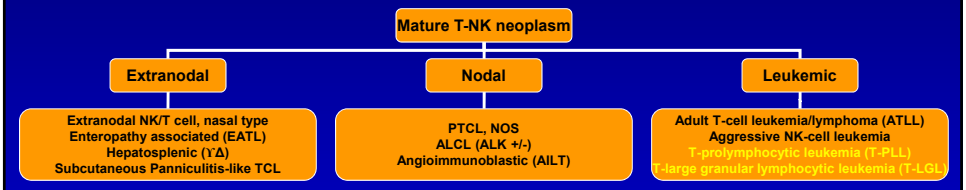


1. Armitage JO, et al. *Ann Oncol*. 2004;15:1447–1449.
2. Adapted from Rodriguez J, et al. *Crit Rev Oncol Hematol*. 2008.
3. Adapted from Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2008.

Aggressive | Indolent

5

Classification of PTCL (cont.)



6

Classification of PTCL (cont.)

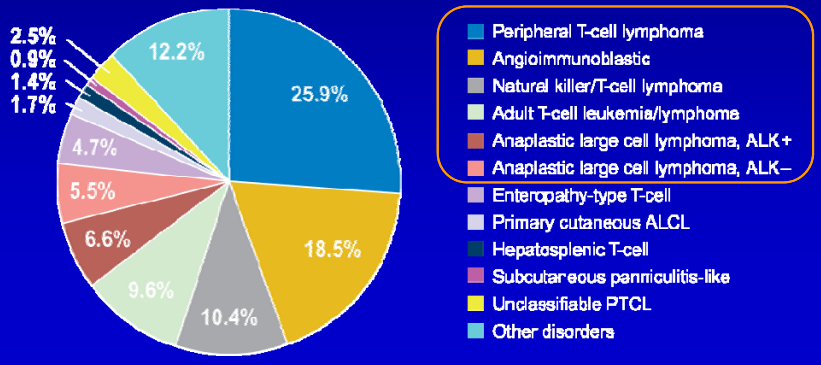
Cutaneous

Mycosis fungoides/Sézary syndrome (MF/SS)
CD30+ lymphoproliferative disorders
CD4+ small/medium pleomorphic T-cell lymphoma
Cutaneous PTCL, NOS
Cutaneous aggressive CD8+ T-cell lymphoma
Cutaneous NK/T cell lymphoma, nasal type

7

Common Peripheral T-cell Lymphoma Subtypes (excluding CTCLs)

- 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.

8

PTCL Epidemiology

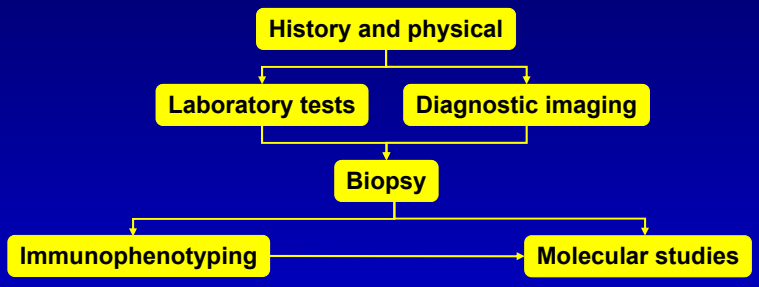
- The relative incidence of PTCL subtypes varies by geography[1,2]
  - Incidence is higher in Asian and Caribbean populations[1,2]

	Percentage[2]		
Subtype	North America	Europe	Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	20.7	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

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

9

Diagnostic Workup of a Patient



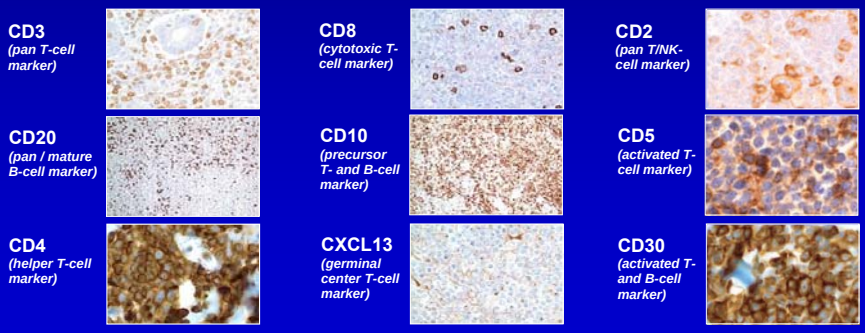
- Access to an accurate and sufficient patient history is necessary to aid in an accurate diagnosis
- This information guides which diagnostic tests should be run and how to interpret the results of those tests
- In select cases, cytogenetic studies may be useful
- Molecular studies (T-cell gene rearrangement) by themselves do not make a diagnosis!

10

Diagnosis of PTCL

- Approximately 10% of PTCL cases are incorrectly diagnosed[1]
- Diagnosis of PTCL routinely involves immunophenotypic analysis in conjunction with cellular morphology, analysis of lymph node architecture, and molecular genetic assays[2,3]
  - Excisional biopsy is usually required[4]

Common immunohistochemistry stains for the diagnosis of PTCL[2,3]



1. Armitage J, et al. *J Clin Oncol*. 2008;26:4124–4130; 2. Warnke RA, et al. *Am J Clin Pathol*. 2007;127:511–527;
3. Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2008; 4. Kocjan G. *J Clin Pathol*. 2005;58:561–567.

11

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-IV	• **Clinical trial preferred** • Multiagent chemotherapy* (6 cycles)	Clinical trial or Consider consolidation with high-dose therapy with stem cell rescue or Observe

*Suggested regimens:

- CHOP-14 or 21 (cyclophosphamide, doxorubicin, vincristine, prednisone)
- CHOEP (cyclophosphamide, 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. 2014.
Available at: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

12

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

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) or systemic CD30+ PTCL	Alemtuzumab
DHAP (dexamethasone, cisplatin, cytarabine)	Bortezomib
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)	Brentuximab vedotin (systemic ALCL or CD30+ PTCL)
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 (in AITL has limited activity)
MINE (mesna, ifosfamide, mitoxantrone, etoposide)	Radiation therapy
Pralatrexate (category 2B)	Romidepsin
Romidepsin	

NCCN. Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphoma. Version 1.2014. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

13

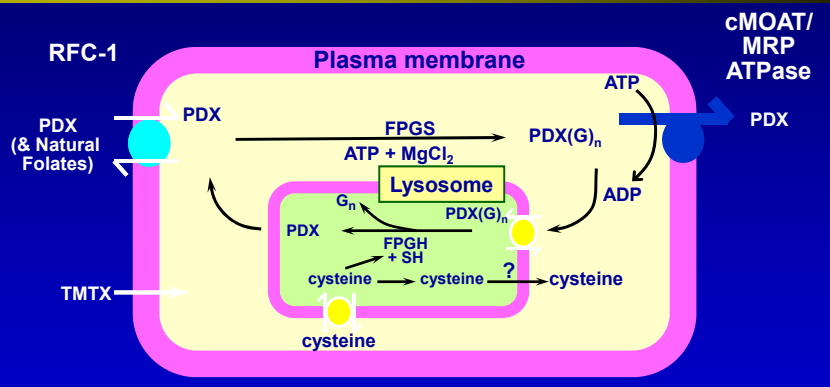
Relapsed/Refractory PTCL: FDA-Approved Agents

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.

14

Pralatrexate



Compared to MTX
PDX more efficiently enters tumor cells (RFC-1) and is more readily polyglutamylated (FPGS)

15

HDAC Inhibitors in MF/SS

Vorinostat[1]

- Orally bioavailable
- FDA approved only for CTCL
- AEs
  - Diarrhea (most disabling and dose related)
  - Fatigue
  - Anorexia >20%
  - Anemia, thrombocytopenia, increased creatinine less common

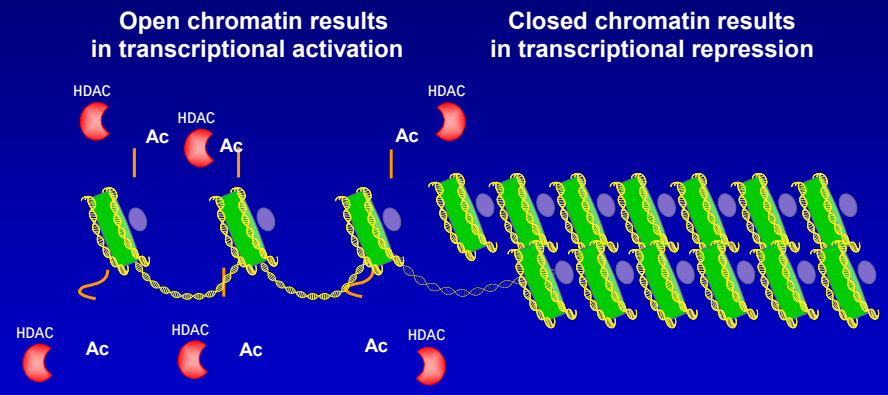
Romidepsin[2,3]

- IV preparation
- FDA approved for CTCL and PTCL
- AEs
  - Prolonged QT with concomitant use of other drugs that inhibit CYP3A4
  - Nausea
  - Fatigue
  - Vomiting
  - Anorexia
  - Lymphopenia
  - Granulocytopenia

1. Olsen, et al. *JCO.* 2007; 2. Piekarz, et al. *JCO.* 2009; 3. Whittaker, et al. *JCO.* 2010.

16

Histone Deacetylation Results in Transcriptional Repression

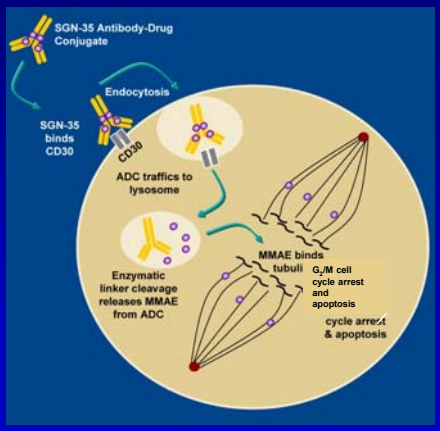


Adapted from Johnstone RW. *Nat Rev Drug Discov.* 2002;1:287–299.

17

Brentuximab Vedotin (SGN-35) Antibody-Drug Conjugate

- 3 components:
  - Chimeric antibody SGN-30
  - Synthetic analog (MMAE) of the antitubulin agent dolastatin 10
  - Stable drug linker
- Proposed mechanism of action
  - Binds to CD30
  - Internalized into the tumor cell
  - MMAE is released
  - Tumor cell undergoes G2/M phase cell cycle arrest and apoptosis
- Preclinical activity observed both in vitro and in vivo
- Administered IV



ADC=antibody-drug conjugate; MMAE= monomethylauristatin E.

Reproduced with permission from Seattle Genetics, Inc.; Pro. *2009 ASCO Educational Book*. Alexandria, VA: American Society of Clinical Oncology. 2009;486; Younes. *EHA*. 2009 (abstract 0503).

18

Ongoing Phase III Trials PTCL

Intervention	Patient Population	Primary Endpoints	Status
Alemtuzumab + CHOP14 + G-CSF vs CHOP14 + G-CSF [1]	Newly diagnosed PTCL	EFS	Recruiting
Alisertib vs pralatrexate or gemcitabine or romidepsin [2]	Relapsed/Refractory PTCL	ORR, PFS	Recruiting
Brentuximab vedotin + CHP vs CHOP [3]	CD30+ PTCL	PFS	Recruiting
CHOP → pralatrexate [4]	Newly diagnosed PTCL	PFS, OS	Recruiting
Romidepsin + CHOP vs CHOP [5]	Newly diagnosed PTCL	PFS	Recruiting
Heliostat+ CHOP vs CHOP	Newly diagnosed PTCL	PFS	To open soon

1. ClinicalTrials.gov NCT00646854.
2. ClinicalTrials.gov NCT01482962.
3. ClinicalTrials.gov NCT01777152.
4. ClinicalTrials.gov NCT01420679.
5. ClinicalTrials.gov NCT01796002.

19

Ongoing Phase III Trials CTCL

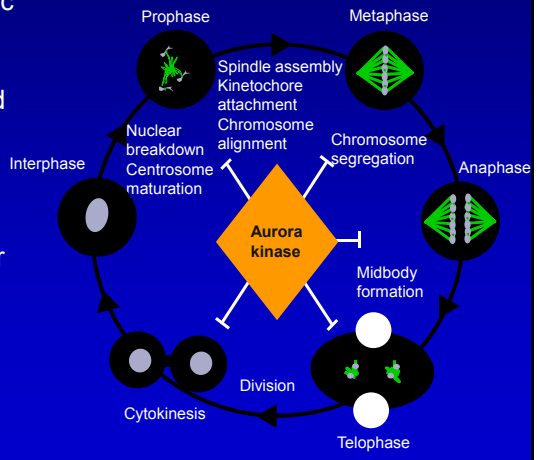
Intervention	Patient Population	Primary Endpoints	Status
B. vedotin vs investigator's choice (methotrexate or bexarotene) [1]	CD30+ CTCL	ORR lasting ≥4 months	Recruiting
KW-0761 vs vorinostat [2]	Relapsed/Refractory CTCL	PFS	Recruiting

1. ClinicalTrials.gov NCT01578499.
2. ClinicalTrials.gov NCT01728805.

20

Alisertib: Kinase Inhibitor

- Aurora kinases regulate mitotic signaling
- Inhibition of AAK is associated with mitotic errors, apoptosis, and senescence
- Alisertib is an **oral**, investigational ATP competitor and AAK inhibitor

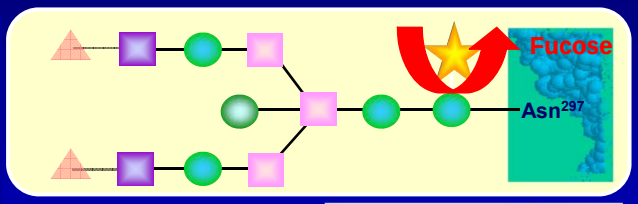


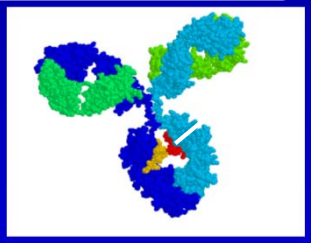
Friedberg J, et al. *ASH 2011*. Abstract 95.

21

Mogamulizumab (KW-0761): Anti-CCR4 Monoclonal Antibody

: N-acetylglucosamine
: bisec GlcNAc
: Mannose
: Galactose
: Sialic acid
: Fucose





- Approved in Japan for treatment of ATLL (Adult T-cell leukemia/lymphoma)

22

Drugs to watch out for

- PI3-kinase inhibitors (GS 1101 and others)
- PD-1 inhibitors
- Dual PI3-kinase/MTOR inhibitors

23

How might we treat in the future? How are we treating now?

- Increasing attention should be paid to whether a lymphoma is a T-cell vs B-cell lymphoma
- Increasing attention should be paid to subtype of T-cell lymphoma. Examples of specific treatments that work better for specific subtypes are:
  - T/NK nasal lymphoma: SMILE regimen
  - ATLL: Mogamulizumab
  - EATL: Newcastle regimen
  - AITL: Cyclosporine; HDACi over pralatrexate
  - ALCL: B. vedotin

24

Functional Subsets of PTCL

- Report from the lymphoma workshop of the XVIth meeting of the EAHP and SHP…
- "In past years, genomic techniques have been applied to both normal and neoplastic T-cells leading to the recognition of distinctive functional subsets"
  - (1) AITL and T-follicular-helper cell-associated lymphomas
  - (2) CD30+ T-cell lymphomas/lymphoproliferative diseases
  - (3) Extranodal T-cell and NK-cell neoplasms
  - (4) EBV-associated T-cell/NK-cell lymphomas/lymphoproliferative diseases
  - (5) PTCL, NOS, PTLD, and mimics

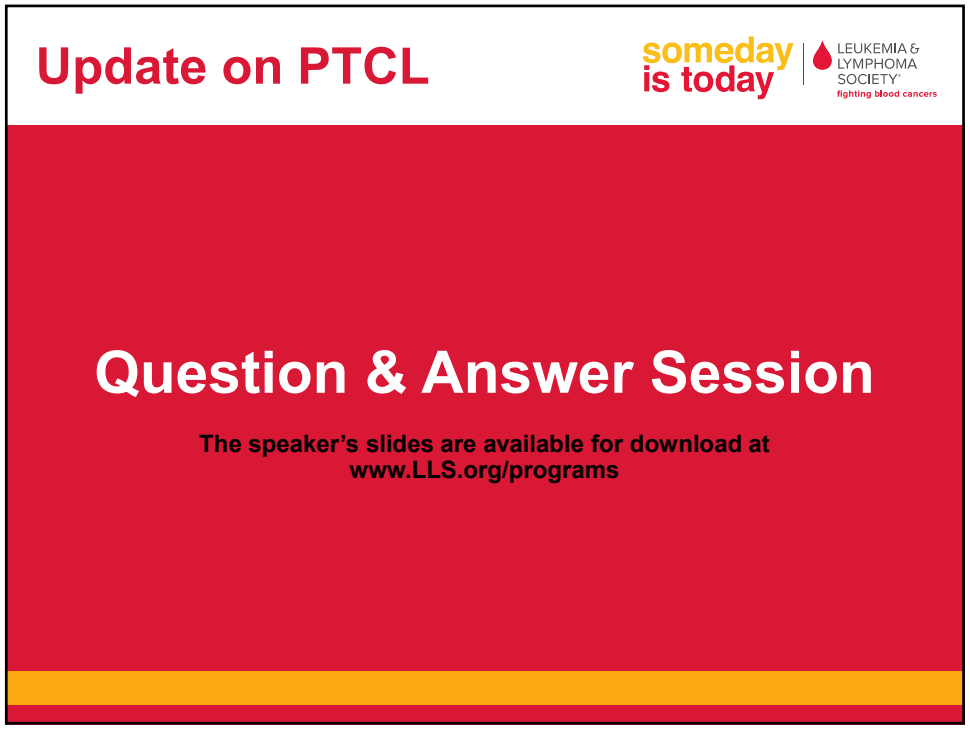
Attygalle AD, et al. *Histopathology*. 2014;64(2): 171–94.

25

Communication Among Patients And Healthcare Providers

- **Open communication with your treatment team is essential to understanding your diagnosis and in making informed treatment decisions.**
- **Don't be afraid to ask your treatment team questions** (What exactly is my diagnosis? Is there a standard treatment for my disease? Are you the right doctor for my disease? Are there clinical trials available for my disease?)
- **Should I get a second opinion?** It's okay to let your doctor know that you'd like a second opinion; most doctors are used to patients seeking second opinions and even encourage it.
- **Feel free to speak with your treatment team regarding time and effort commitment: travel, parking, work, life events, etc.**

26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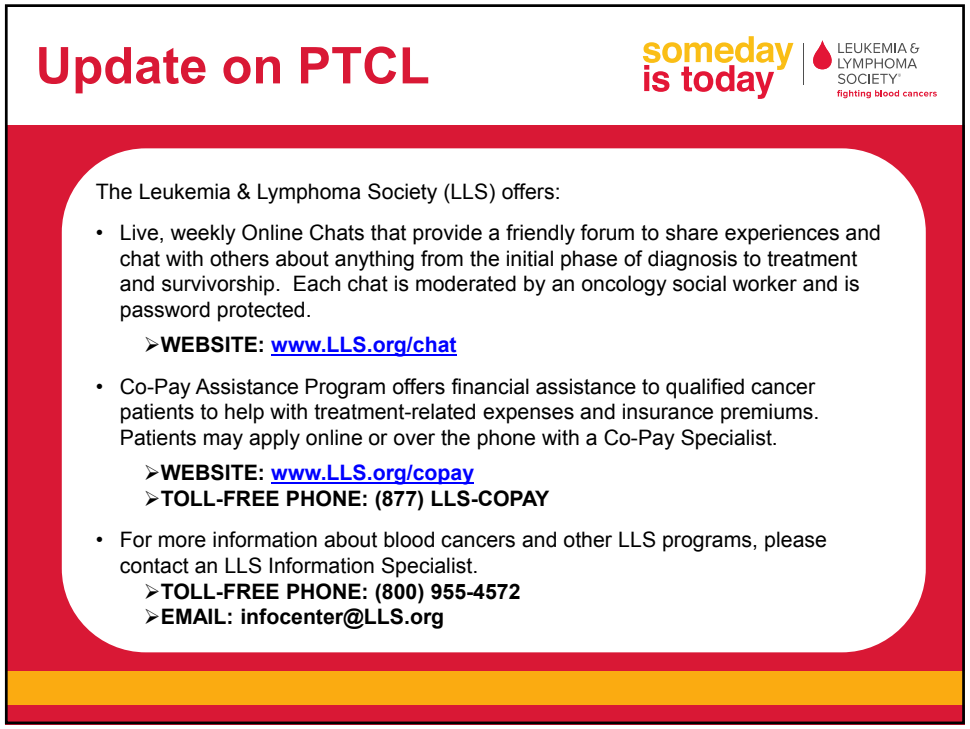
Question & Answer Session
The speaker's slides are available for download at www.LLS.org/programs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The Leukemia & Lymphoma Society (LLS) offers:
• Live, weekly Online Chats that provide a friendly forum to share experiences and chat with others about anything from the initial phase of diagnosis to treatment and survivorship. Each chat is moderated by an oncology social worker and is password protected.
➢WEBSITE: www.LLS.org/chat
• Co-Pay Assistance Program offers financial assistance to qualified cancer 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 blood cancers and other LLS programs, please contact an LLS Information Specialist.
➢TOLL-FREE PHONE: (800) 955-4572
➢EMAIL: infocenter@LLS.org