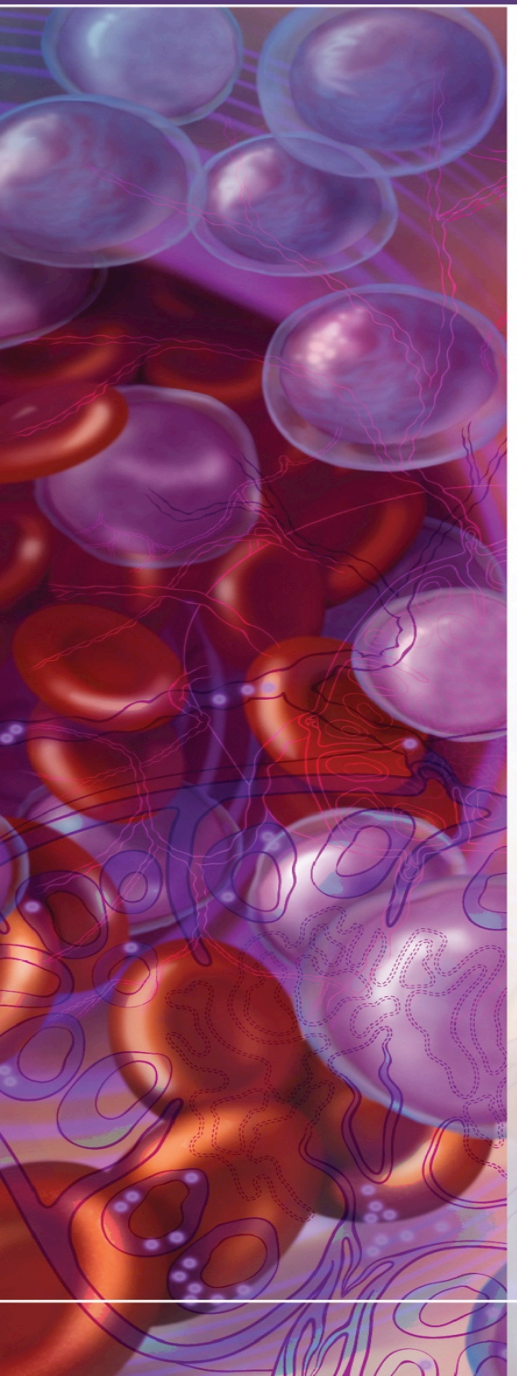


Meeting the Challenge of Managing Rare Hematologic Malignancies: Mantle Cell Lymphoma, T-Cell Lymphoma, and Myelodysplastic Syndromes

Ellen Neylon, MSN, FNP-BC, RN, OCN®

Oncology Nurse Practitioner, Center for Lymphoid Malignancies
Columbia University Medical Center, New York, New York

Sandra E. Kurtin, RN, MS, AOCN®, ANP-C

Nurse Practitioner, Clinical Assistant Professor of Medicine and Nursing
The University of Arizona Cancer Center, Tucson, Arizona

Disclosure

- Ms. Neylon has received honoraria and served on speakers bureaus for Seattle Genetics, Genentech, Celgene, and Spectrum Pharmaceuticals.
- Ms. Kurtin has acted as a consultant for Celgene, Onyx, Millennium, Incyte, and Novartis.

Supported in part by an
unrestricted educational grant from Celgene

Learning Objectives

- Discuss the molecular and clinical features of rare hematologic malignancies such as mantle cell lymphoma (MCL), T-cell lymphoma (TCL), and myelodysplastic syndromes (MDS)
- Describe the diagnosis and potential risk factors for the non-Hodgkin lymphoma subtypes MCL and TCL as well as for MDS
- Evaluate the optimal therapeutic regimens available for the treatment of rare hematologic malignancies
- Become familiar with the latest clinical trials involving novel treatment options for patients with MCL, TCL, and MDS
- Craft supportive care strategies for patients receiving therapies for rare hematologic malignancies to help them remain on treatment to achieve optimal benefits while coping with side effects
- Summarize the key considerations in symptom management of patients with rare hematologic malignancies, focusing primarily on common infectious pathogens and infection preventive strategies

Mantle Cell Lymphoma: Overview of Disease States and Treatment

Ellen Neylon, MSN, FNP-BC, OCN®
Oncology Nurse Practitioner
Center for Lymphoid Malignancies
Columbia University
New York, New York

Overview of MCL

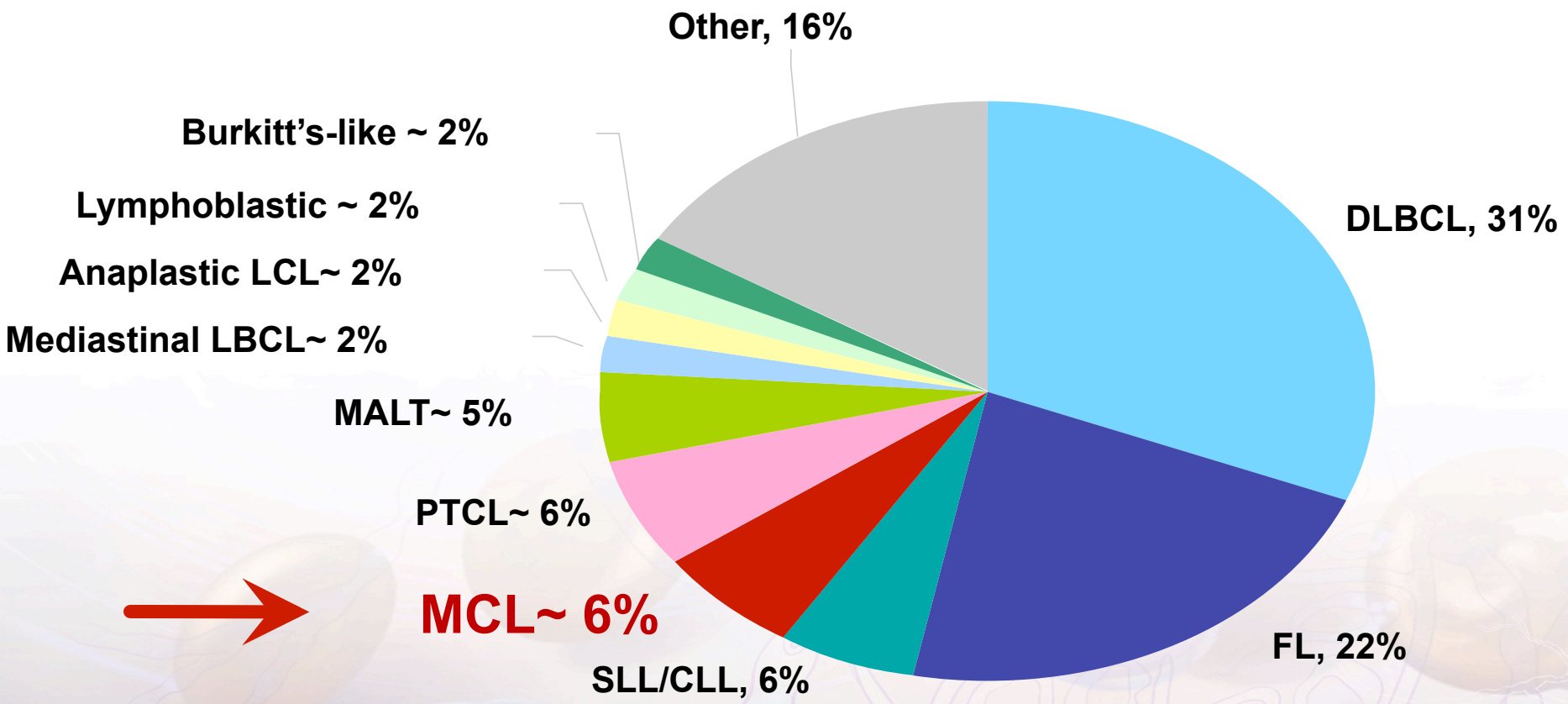
- Understanding the biologic basis of disease
- Risk stratification
- Are there treatment principles for the upfront setting?
  - The role of high-dose cytarabine
  - The role of auto-stem cell transplantation consolidation
  - The role of monitoring and treating minimal residual disease
- New “paradigm-changing” approaches: Let’s see
- The emerging new drugs for patients with relapsed disease

Definition and Epidemiology of MCL

- MCL is a mature B-cell non-Hodgkin lymphoma (NHL)[1,2]
  - More aggressive than other forms of NHL: Median overall survival only 4–5 years
- Epidemiology[1]
  - Relatively rare: Accounts for approximately 7% of all cases of adult NHL cases in the US and Europe (3,000–4,000 cases per year in the US)
  - Incidence: ≈ 4–8 cases per million persons per year
  - Three-fourths of affected patients are male
  - Whites affected twice as frequently as African Americans
  - Median age at diagnosis: 68 years

1. Freedman AS et al. Clinical manifestations, pathologic features, and diagnosis of mantle cell lymphoma. In: UpToDate® [database online] Wolters Kluwer Health 2014. www.uptodate.com/home/. Accessed August 4, 2014.
2. Hitz F et al. Swiss Med Wkly. 2013;143:w13868.

Real Classification of NHL Subtypes



Armitage JO, et al. *J Clin Oncol*. 1998;16:2780-2795.

Clinical Manifestations of MCL

- Approximately 70%–88% of patients with MCL have advanced disease at diagnosis[1,2]
- Approximately 75% of patients present with lymphadenopathy; the remaining 25% present with extranodal disease
  - Common sites of involvement include
    - Lymph nodes
    - Spleen (45%–60%)
    - Bone marrow (> 60%)
    - Blood (13%–77%)
    - Extranodal sites (GI tract, breast, pleura, and orbits)
  - Splenomegaly frequently seen in the absence of lymphadenopathy
  - Up to one-third of patients have systemic B symptoms (e.g., fever, night sweats, unintentional weight loss) at presentation

1. Freedman AS, et al. Clinical manifestations, pathologic features, and diagnosis of mantle cell lymphoma. In: UpToDate® [database online] Wolters Kluwer Health 2014. www.uptodate.com/home/
2. Argatoff LH, et al. *Blood*. 1997;89:2067-2078.

Clinical Features of MCL

Feature	% Patients
Median age	58
Gender ratio	Male:female 2:1
Generalized adenopathy	71–90
Bone marrow involvement	53–93
Splenomegaly	35–81
GI tract involvement	15–28
Hepatomegaly	18–35
Lymphocytosis	10–69
B symptoms	35–55
Elevated LDH	30–50
β_2 microglobulin	54

Which of the following diagnostic findings is indicative of mantle cell lymphoma?

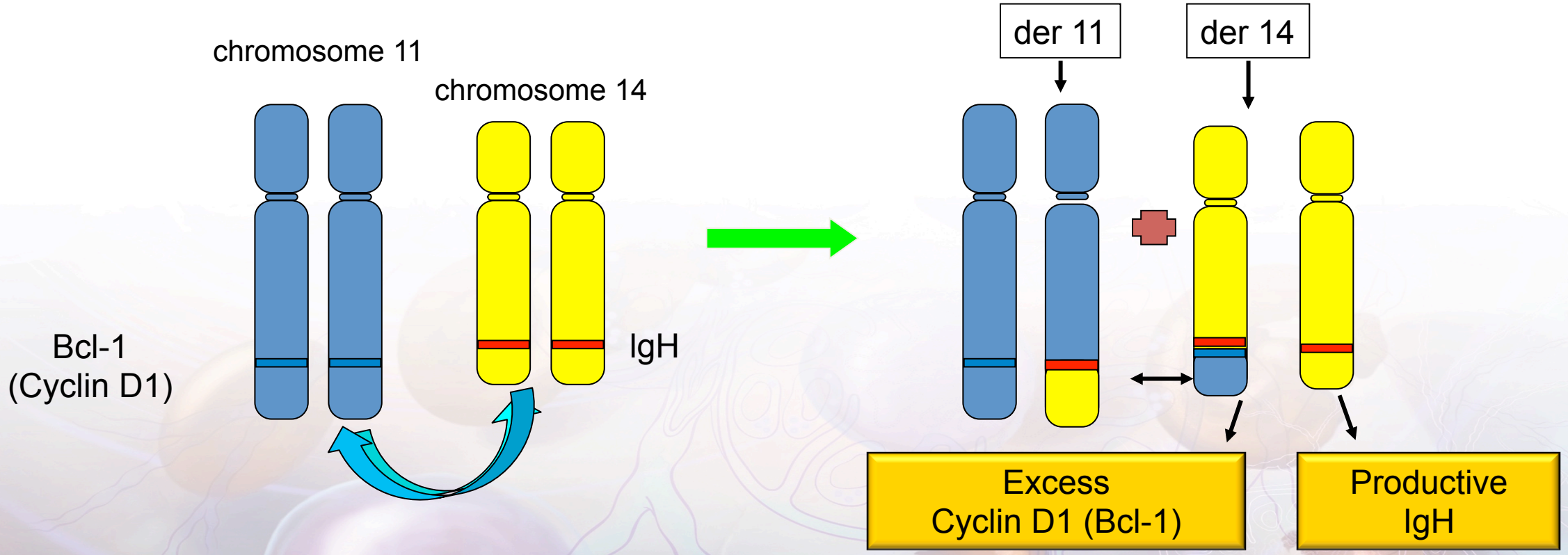
A. t9;22

B. t11;14

C. Del5q

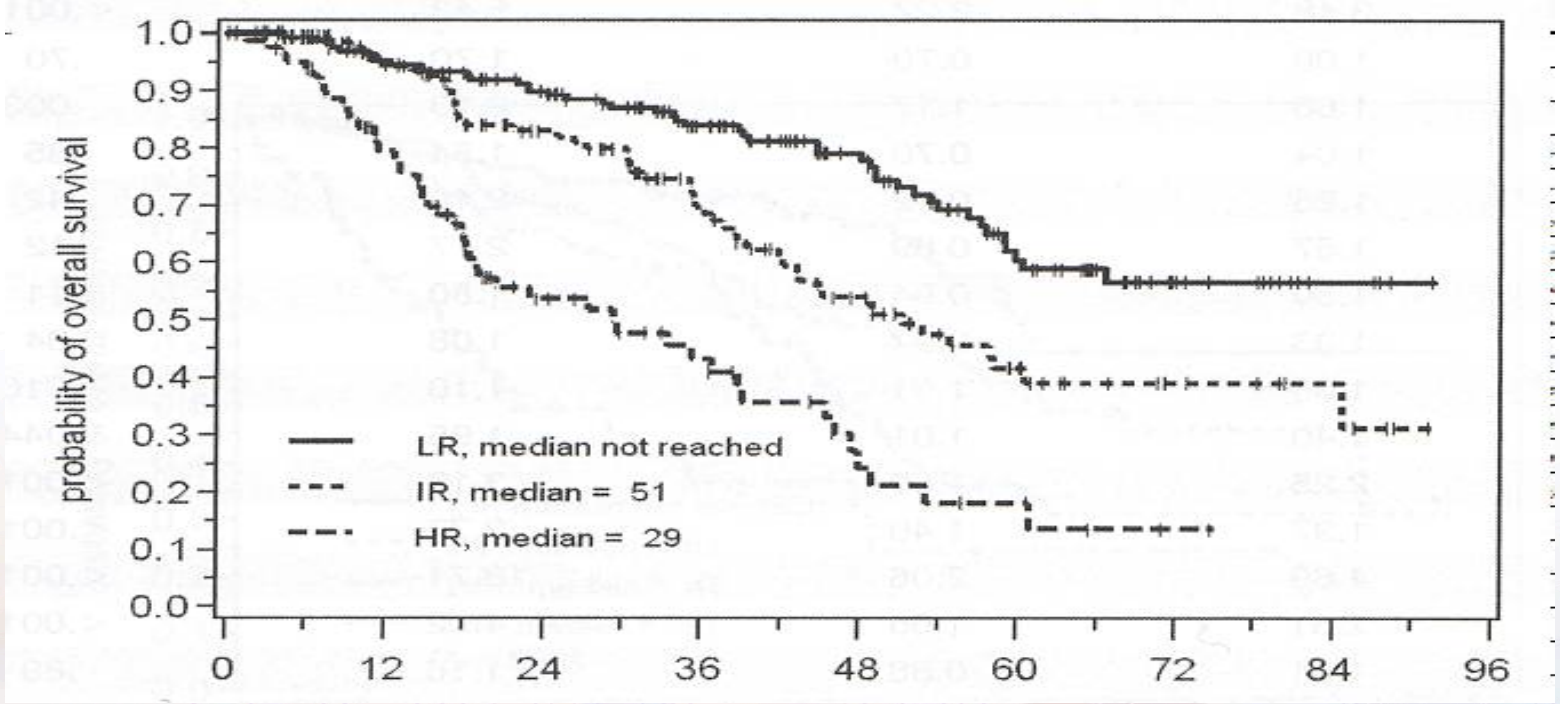
D. +8

MCL Is Characterized by a Pathognomonic Reciprocal Chromosomal Translocation t(11;14)(q13;q32)



Clinical Prognostic Features: MCL International Prognostic Index (MIPI)

- Factors associated with overall survival
  - Age
  - Performance status
  - LDH
  - WBC
- Risk distribution
  - Low: 44% (< 5.7)
  - Int: 35% (5.7–6.1)
  - High: 21% (> 6.1)



Available at: http://www.qxmd.com/calculate-online/hematology/prognosis-mantle-cell-lymphoma-mipi

Hoster E et al. Blood. 2008;111:558-565.

Deciphering the Diagnosis by Immunohistochemistry (IHC): The Small Lymphocytic Lymphomas (SLL)

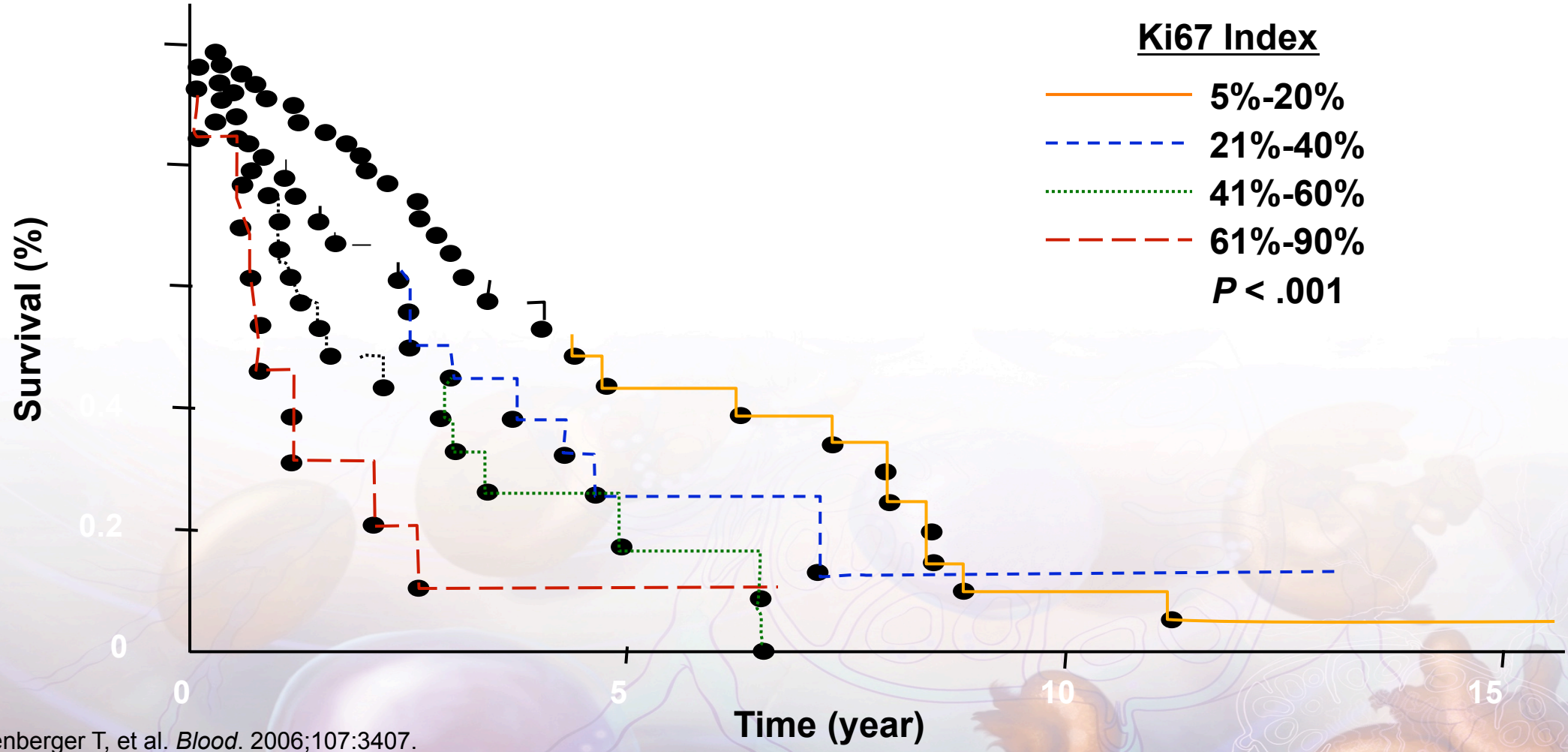
Surface marker	MCL	FL	SLL	MZL
CD5	++	-	++	-
Surface Ig	++	+++	+	+
CD19	++	++	++	++
CD20	+++	++	+ (weak)	++
CD10	-	+ (80%)	-	-
CD23	-	+/-	+	-
Cyclin D1	+++	-	-	-
Cytogenetics	t(11:14)	t(14:18)	-	t(11:18)

FL = follicular lymphoma; MZL = marginal zone lymphoma; Ig = immunoglobulin

Progress in MCL

- Diagnosis: Now routine
  - Immunophenotype, cyclin D1, t(11;14)
- Targets and pathways
  - Cell cycle, apoptosis, epigenetic, NFκB, BCR
- Improvements in overall survival
  - Median 2.7 (1975–1986) → 4.8 years (1996–2004)
  - Recent series indicate median 6+ years
- Treatment options expanding fast
  - Chemoimmunotherapy, targeted agents

Ki67 Index as a Marker of Cell Proliferation in 134 Patients With MCL



Katzenberger T, et al. *Blood*. 2006;107:3407.

Indolent MCL

Clinical Features

- Splenomegaly
- Minimal or no adenopathy
- Leukemic phase
- May be confused with CLL
- Watchful waiting often a reasonable option

Molecular Features

- Mutated IgVH genes
- No p53 mutations
- Few chromosomal changes other than t(11;14)
- SOX11 negative
- Unique 13-gene signature vs classic MCL

Martin P, et al. *J Clin Oncol.* 2009;27:1209-1213; Fernàndez V, et al. *Cancer Res*. 2010;70:1408-1418.

MCL Risk Stratification: Summary

- Biologic and clinical heterogeneity
  - Some patients with indolent MCL can be observed
- MIPI is a useful scoring system
  - Helpful for comparing results across trials
  - Low-risk MIPI patients may do well with intensive strategies
- Ki67 is predictive
  - Not standardized for routine use

MCL: Induction Treatment Regimens

Stage	Suggested regimens (in alphabetical order)
Stage I, II (localized presentation, extremely rare)[#] Or Stage II bulky, III, and IV (induction treatment involves clinical trials or regimens suggested in last column or observation in selected cases)	**Aggressive therapy** • CALGB regimen[a] ▪ Treatments 1, 2, and 2.5[b]: rituximab + methotrexate with augmented cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) ▪ Treatment 3: etoposide, cytarabine, rituximab ▪ Treatment 4: cyclophosphamide/autologous stem cell rescue ▪ Treatment 5: rituximab maintenance • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab • NORDIC regimen[a] (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine) • Alternating R-CHOP/R-DHAP[a] (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine) • Sequential R-CHOP/R-ICE[a] (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, ifosfamide, carboplatin, etoposide) **Less aggressive therapy** • Bendamustine + rituximab • Bortezomib • CHOP + rituximab followed by consolidation with rituximab maintenance (375 mg/m^2 every 8 weeks until disease progression) • Cladribine + rituximab • Modified rituximab-hyperCVAD with rituximab maintenance in patients > 65 years

[a]Regimens include first-line consolidation with high-dose therapy and autologous stem cell rescue
[b]Treatment 2.5 given if pretreatment 3 bone marrow contains >15% MCL
[#]For select patient with stage 1 disease radiation therapy is a consideration

NCCN Guidelines. Non-Hodgkin's Lymphomas. Version 2.2014. www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

MCL: Second-Line Treatment Regimens[a]

Stage	Suggested regimens (in alphabetical order)
Stage I, II (localized presentation, extremely rare) Or Stage II, bulky, III, and IV (second-line therapy involves clinical trials or radiation therapy or regimens suggested in last column)	• Bendamustine ± rituximab • Bortezomib ± rituximab • Cladribine + rituximab • FC (fludarabine, cyclophosphamide) ± rituximab • FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) • FCMR (fludarabine, mitoxantrone, rituximab) • Ibrutinib • Lenalidomide ± rituximab • PCR (pentostatin, cyclophosphamide, rituximab) • PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab

[a]Second-line consolidation therapy involves allogeneic stem cell transplant (nonmyeloablative or myeloablative).

NCCN Guidelines. Non-Hodgkin's Lymphomas. Version 2.2014. www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

MCL: Investigational Therapeutic Agents

Name of agent	Class of agent	Status
IPI-145	Inhibitor of phosphoinositide-3-kinase-delta (PI3K-delta) and –gamma	Phase I and phase II studies in NHL ongoing[1]
Navitoclax (ABT-263; later, molecule re-engineered to ABT-199)	Inhibitor of Bcl-2 family of proteins	Phase I and phase II studies of navitoclax in NHL ongoing either alone or in combination with bendamustine/rituximab[1]
Ublituximab	Monoclonal antibody	Multiple phase I/II studies with other agents (eg, lenalidomide and ibrutinib) in progress or recruiting[1]
Everolimus (RAD-001)	Immunomodulatory agent	Two phase II studies have shown antilymphoma activity and acceptable tolerability in patients with relapsed or refractory MCL[2,3]
Temsirolimus (CCI-779)		Multiple phase I-III studies have shown efficacy of temsirolimus as initial agent for refractory/relapsed MCL either alone or in combination with agents such as rituximab or cladribine[4-6]

1. Clinical Trials.gov
2. Wang M, et al. *Br J Haematol*. 2014;165:510-518.
3. Renner C, et al. *Haematologica*. 2012;97:1085-1091.
4. Inwards DJ, et al. *Ann Oncol*. 2014;25:2020-2024.
5. Ansell SM, et al. *Lancet Oncol*. 2011;12:361-368.
6. Hess G, et al. *J Clin Oncol*. 2009;27:3822-3829.
7. García-Noblejas A, et al. *Ann Hematol*. 2014;93:1551-1558.
8. Flinn IW, et al. *Blood*. 2014;123:2944-2952.
9. Rummel MJ ,et al. *Lancet*. 2013;381:1203-1210.
10. Visco C, et al. *J Clin Oncol*. 2013;31:1442-1449.

MCL Front-Line Therapy: Summary

- Standard of care not established → clinical trials
- Younger, fit patient
  - R-HiDAC-based regimen → ASCT
  - R-Chemo → maintenance rituximab?
- Older patient[1] or patient with significant comorbid illness
  - R-bendamustine vs. R-CVP or R-CHOP
  - Maintenance rituximab every 2 months × 2+ years

[1]Kluin-Nelemans HC, et al. *N Engl J Med.* 2012;367:520-531.

…Though Challenges Remain

- Improve understanding of pathogenesis
  - Epigenetics – genetic – microenvironment axis
- How do we “risk-adapt” treatment?
  - Dealing with the biologic heterogeneity (proliferation)
  - Prognostic factors (MIPI, Ki67, MRD)
- Timing and type of therapy
  - Induction therapy for younger/fit vs. older/less fit
  - Role of dose-intensive regimens and SCT
- Does therapeutic sequencing matter?
- How do we integrate the plethora of options?
- Rare disease, limited patients for clinical trials

Principles of Front-Line Treatment of Indolent and Mantle Cell Lymphoma

- Obtain a deep and durable remission with initial therapy
- Maximize the time between cytotoxic treatments
- Don’t burn bridges to future treatment options
- Minimize early and late toxicities

Approach to Patient With Relapsed MCL

- Clinically compromised?
  - Consider low-intensity regimen for those > age 65 and/or for those with significant comorbid disease
    - Bortezomib, lenalidomide, rituximab, bendamustine
    - When possible, refer for clinical trial
- A good candidate for aggressive therapy?
  - First relapse:
    - Consider dose-intensified regimen followed by allogeneic stem cell transplant
- Refractory disease?
  - Early referral for clinical trial

Building on What We Know to Define a Path Forward in MCL

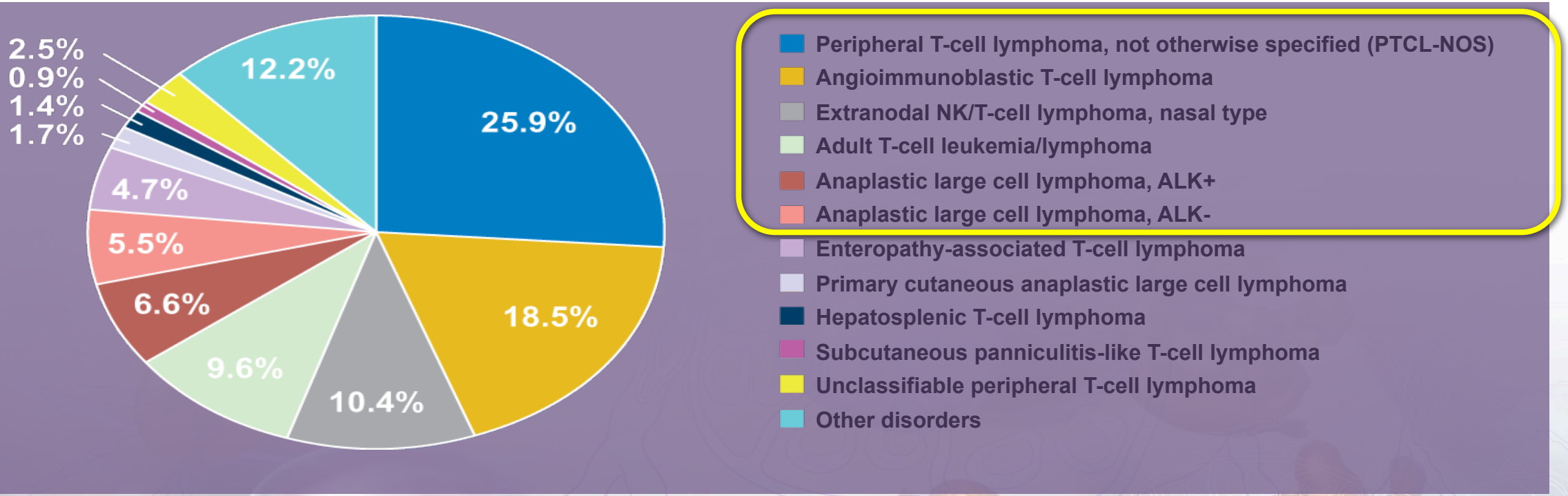
- Cytarabine likely improves long-term benefit
- Autologous stem cell transplantation as consolidation in first remission likely improves long-term benefit
- Maintenance therapy probably matters, because…
- Monitoring minimal residual disease and treating it likely improves long-term benefit
- In nontransplant-eligible patients, adding bortezomib improves progression-free survival
- A plethora of active new drugs has created a “what combination conundrum”

T-Cell Lymphoma (TCL): Overview of Disease States and Treatment

Ellen Neylon, MSN, FNP-BC, OCN®
Oncology Nurse Practitioner
Center for Lymphoid Malignancies
Columbia University
New York, New York

Most Common Peripheral TCL (PTCL) Subtypes

- PTCL-NOS is the most common subtype
- Anaplastic large cell lymphoma (ALCL) ALK+/- and angioimmunoblastic lymphoma are also common subtypes



Source: Adapted from Vose J et al. J Clin Oncol. 2008;26:4125.
Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

1. Vose J, et al. *J Clin Oncol.* 2008;26:4124-4130.

WHO Classification of Lymphoid Neoplasms: Partial List of 26 to ~70 Types

Precursor cell lymphoma

- Lymphoblastic lymphoma, T cell
- Lymphoblastic lymphoma, B cell

Peripheral B-cell lymphoma

- SLL/CLL type
- B-prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Mantle cell lymphoma
- Follicular lymphoma
- Marginal zone lymphoma, MALT
- Marginal zone lymphoma, nodal
- Marginal zone lymphoma, splenic
- Hairy cell leukemia
- Diffuse large B-cell lymphoma
- Burkitt's lymphoma

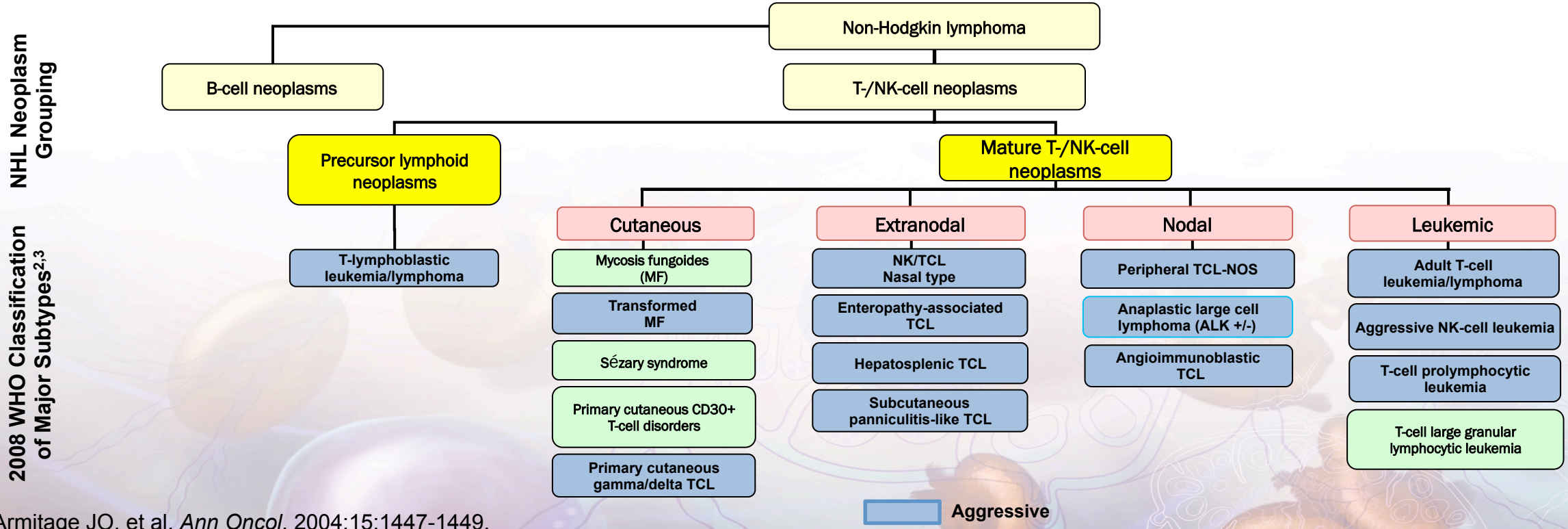
Peripheral T and NK lymphomas

- T-cell prolymphocytic leukemia
- Granular lymphocytic leukemia
- NK cell leukemia
- Mycosis fungoides/Sézary syndrome
- Peripheral T-cell lymphoma, not otherwise specified
- Angioimmunoblastic lymphoma
- NK/T cell, nasal
- Enteropathy-associated lymphoma
- Hepatosplenic gamma/delta lymphoma
- Subcutaneous panniculitis-like
- Anaplastic large cell lymphoma, systemic
- Anaplastic large cell lymphoma, cutaneous
- Adult T-cell lymphoma/leukemia

Post-transplant lymphoproliferative disorders

Classification of PTCL

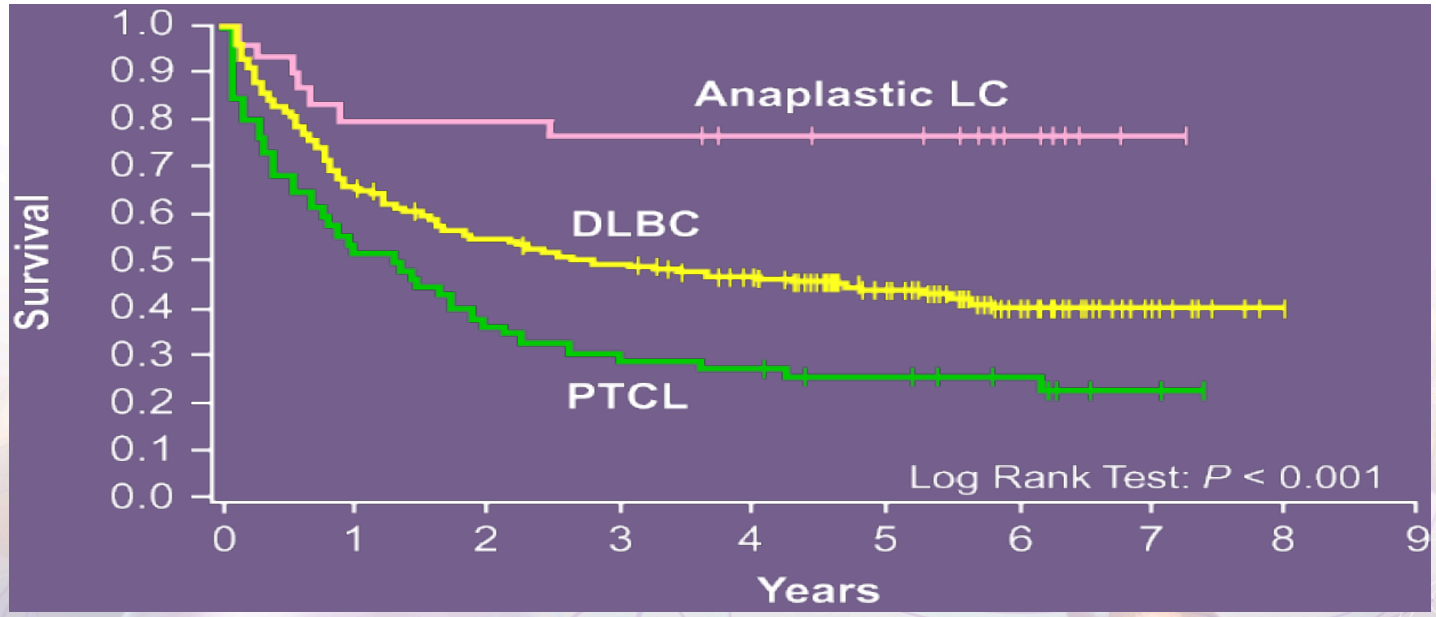
- PTCL is a heterogeneous group of aggressive mature T-/NK-cell lymphomas[1]
  - PTCL does not refer to anatomic sites but rather to the involvement of more mature T cells (post-thymic) vs. immature T cells (prethymic)[1]



1. Armitage JO, et al. *Ann Oncol*. 2004;15:1447-1449.
2. Adapted from Rodriguez J, et al. *Crit Rev Oncol Hematol*. 2008;71:181-198.
3. Adapted from Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. 2008.

PTCL Prognosis

- Most PTCL subtypes have a worse prognosis than aggressive B-cell NHL
  - Median overall survival for most subtypes of PTCL is 1–3 years[1,2]
  - 5-year overall survival is approximately 26%[3]
  - ALK+ ALCL is an exception, with a 5-year survival of 65%–90%[2]



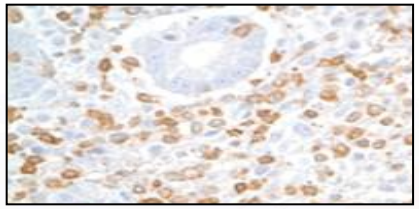
1. Armitage JO, et al. *Ann Oncol*. 2004;15:1447-1449.
2. Savage KJ. *Blood Rev*. 2007;21:201-216.
3. Rüdiger T,,et al. *Ann Oncol*. 2002;13:140-149.

Diagnosis of PTCL

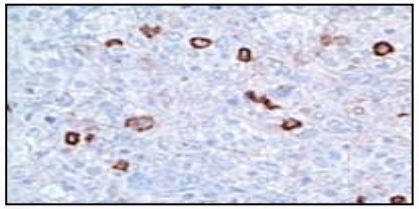
- Approximately 10% of PTCL cases are incorrectly diagnosed[1]
- Diagnosis of PTCL routinely involves immunophenotypic analysis in conjunction with cellular morphology, analysis of lymph node architecture, and molecular genetic assays[2,3]
  - Excisional biopsy is required[4]

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

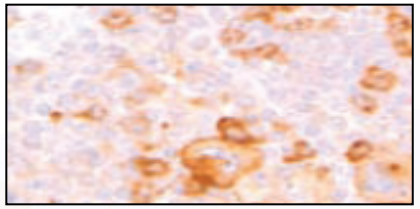
CD3 *(pan T-cell marker)*



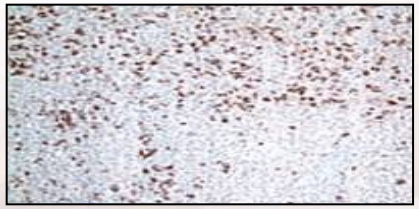
CD8 *(cytotoxic T-cell marker)*



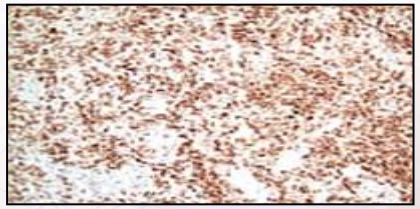
CD2 *(pan T-/NK-cell marker)*



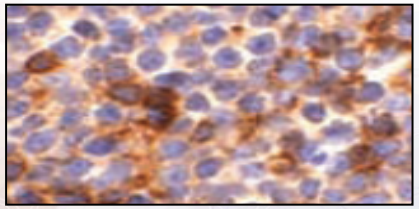
CD20 *(pan/mature B-cell marker)*



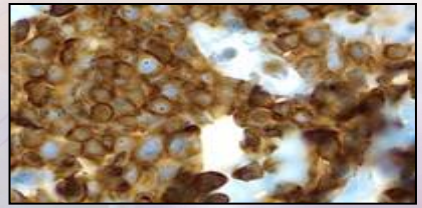
CD10 *(precursor T- and B-cell marker)*



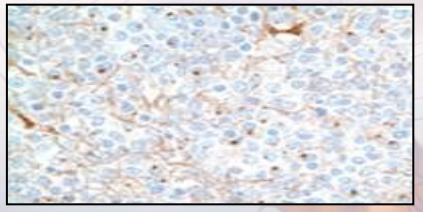
CD5 *(activated T-cell marker)*



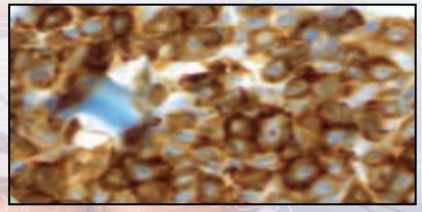
CD4 *(helper T-cell marker)*



CXCL13 *(germinal center T-cell marker)*

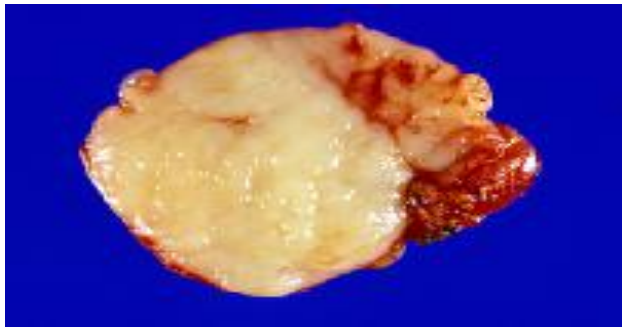


CD30 *(activated T- and B-cell marker)*

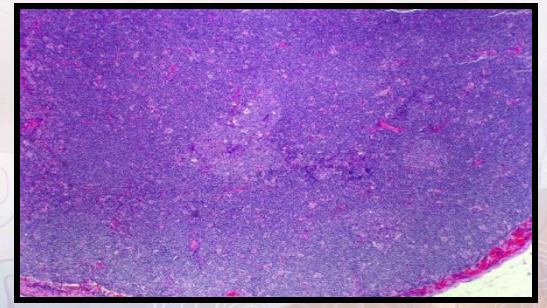


1. Vose J, et al. *J Clin Oncol*. 2008;26:4124-4130.
2. Warnke RA, et al. *Am J Clin Pathol*. 2007;127:511-527.
3. Swerdlow SH et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2008.
4. Kocjan G. *J Clin Pathol*. 2005;58:561-567.

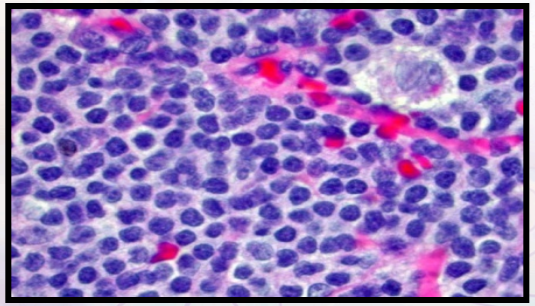
Making the Diagnosis: The More Tissue the Better: Excisional/Incisional Lymph Node Biopsy: The Gold Standard



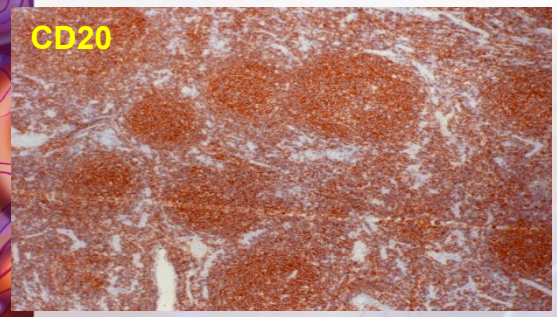
Gross tissue



H&E - architecture

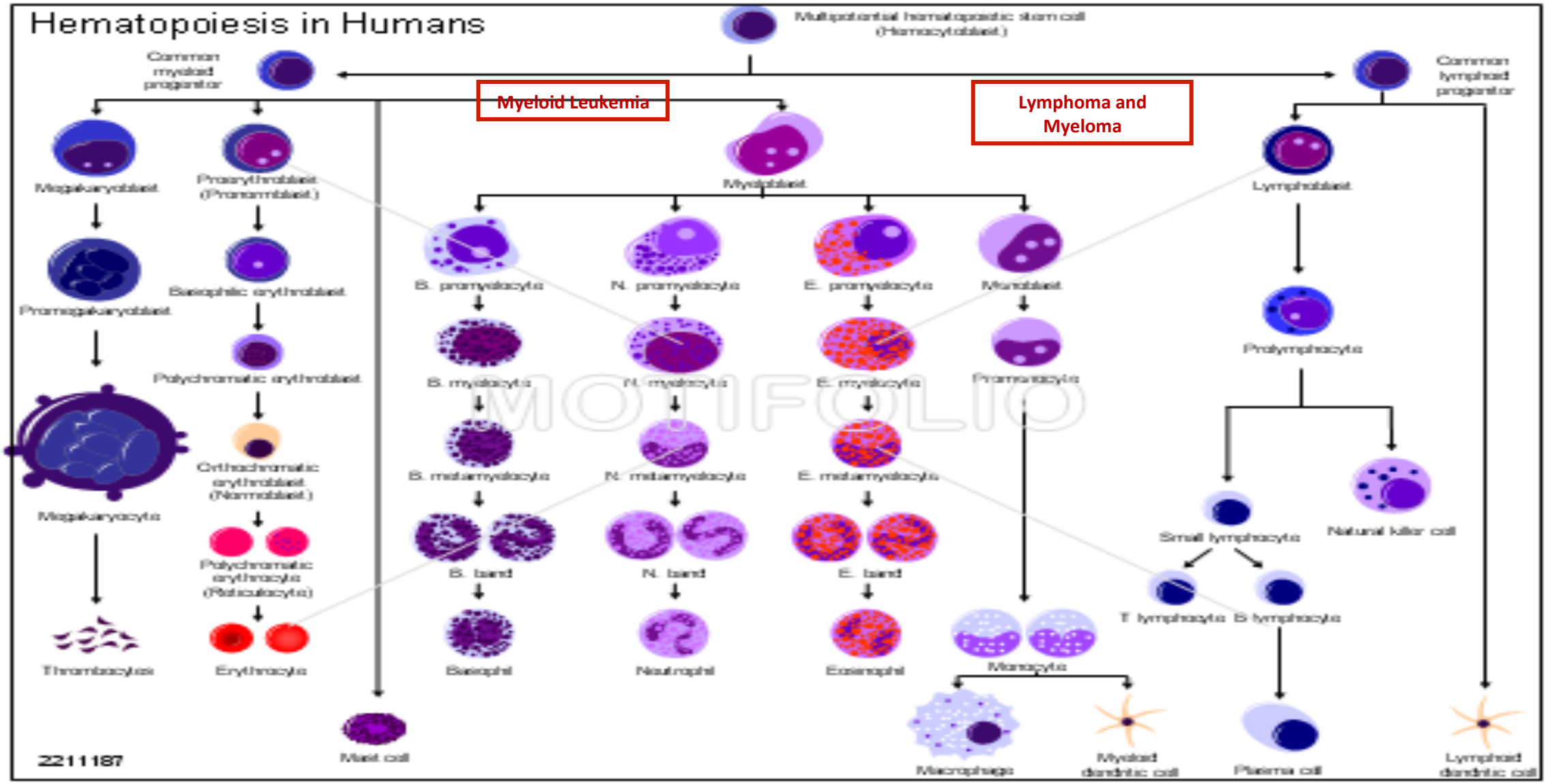


H&E – cellular morphology



Specialized testing (days)

The Diversity of Steps in Hematopoiesis Creates Diversity in Hematologic Malignancies



NCCN: 2014 PTCL Practice Guidelines
First-Line Therapy

First-Line Therapy
Clinical Trial Preferred
CHOP, CHOEP appropriate for ALCL ALK+
CHOEP, CHOP followed by ICE, CHOP followed by IVE
DA EPOCH, hyperCVAD

First-Line Consolidation
For all patients, except those with a low-risk IPI, consider consolidation with high-dose therapy and stem cell rescue
ALCL ALK+ is a subtype with a good prognosis
and does not need consolidative transplant if in remission

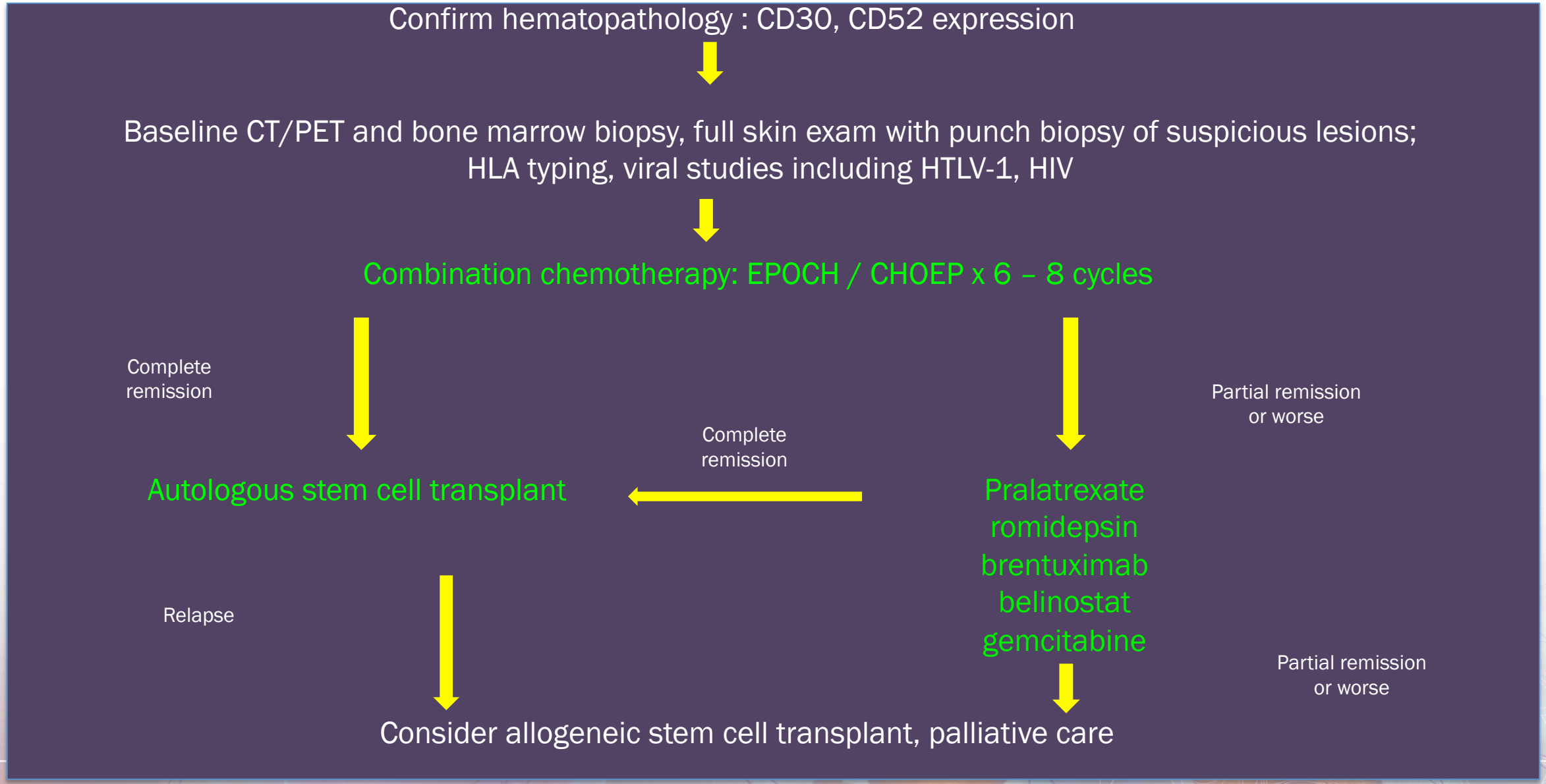
Single Agents for Relapsed or Refractory PTCL: < 100 Patients Accrued in 17 Years!

- Limited data for single-agent treatment of relapsed/refractory NHL
  - Most studies are small, uncontrolled, and single center
  - No central review of histology or response rate
  - Accrued PTCL patients across all studies (1991-2008) = 87

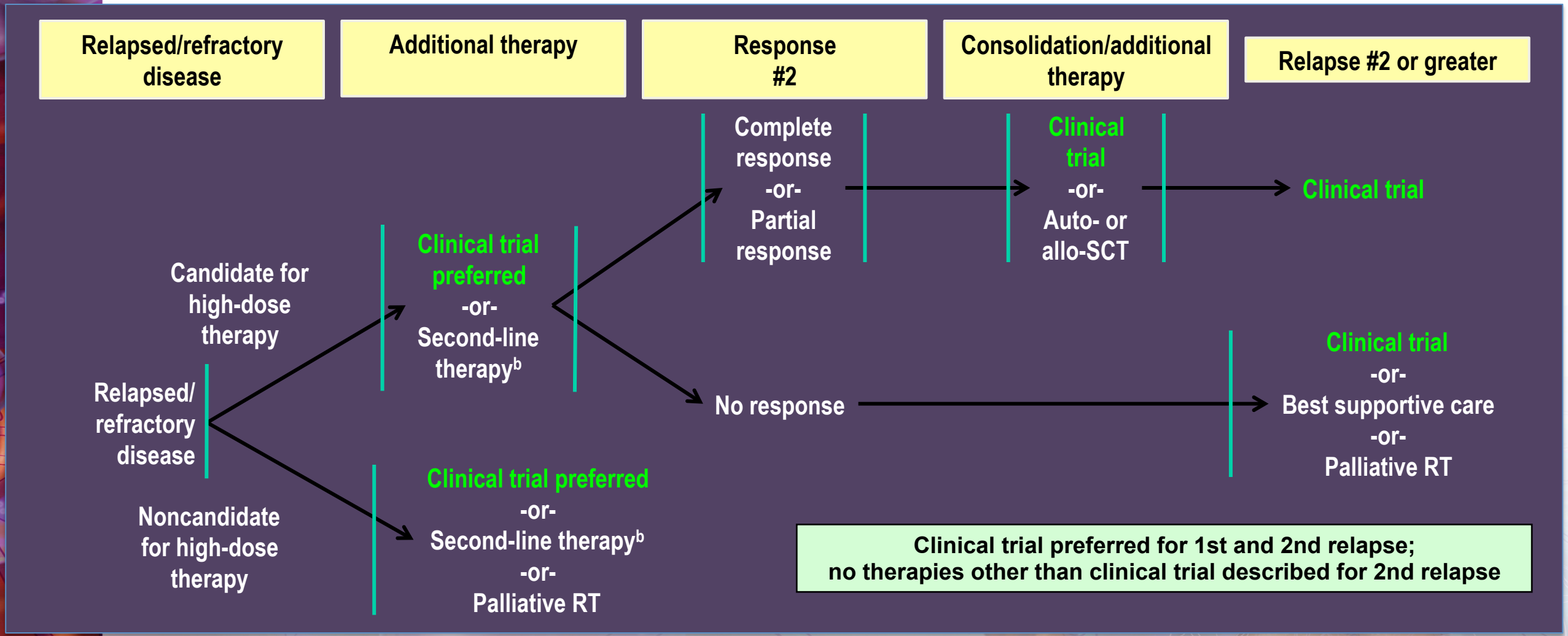
Off-label drugs used for single-agent treatment

Agent	Author, year	Total pts accrued	No. PTCL accrued	Response in PTCL	Single or multi-center
Pentostatin	Dearden, Br J Cancer 1991	68	6	0/6	single
Gemcitabine	Zinzani, Ann Oncol 1998	13	8	5/8	single
Gemcitabine	Sallah, Br J Haematol 2001	10	4	–	single
Alemtuzumab	Enblad, Blood 2004	14	14	5/14	multi-center
Pentostatin	Tsimberidou, Cancer 2004	42	8	–	single
Denileukin	Dang, Br J Haematol 2006	27	27	13/27	single
Bortezomib	Zinzani, JCO 2007	12	2	1/2	single
Lenalidomide	Reiman, Blood 2007	10	10	4/10	multi-center
Nelarabine	Czuczman, Leuk Lymphoma 2007	19	8	1/8	multi-center
Pralatrexate	O'Connor, JCO, 2009	57	30	14/26	single

Algorithm for the Management of PTCL-NOS Upfront



NCCN Guidelines for Relapsed or Refractory PTCL[a]: Clinical Trial Is Recommended First!



[a] Reproduced from NCCN Practice Guidelines in Oncology – v.4.2014.
[b] See suggested regimens (TCEL-B).

Conclusions for PTCL

- PTCL is a heterogeneous group of aggressive T- and NK-cell lymphomas
- Incidence of PTCL is growing
- TCL comprises 10%–15% of NHL cases
- PTCL has a poor prognosis
- PTCL is more challenging to diagnose than other types
- Appropriate treatments are needed to manage PTCL

Cutaneous T-Cell Lymphoma: Overview

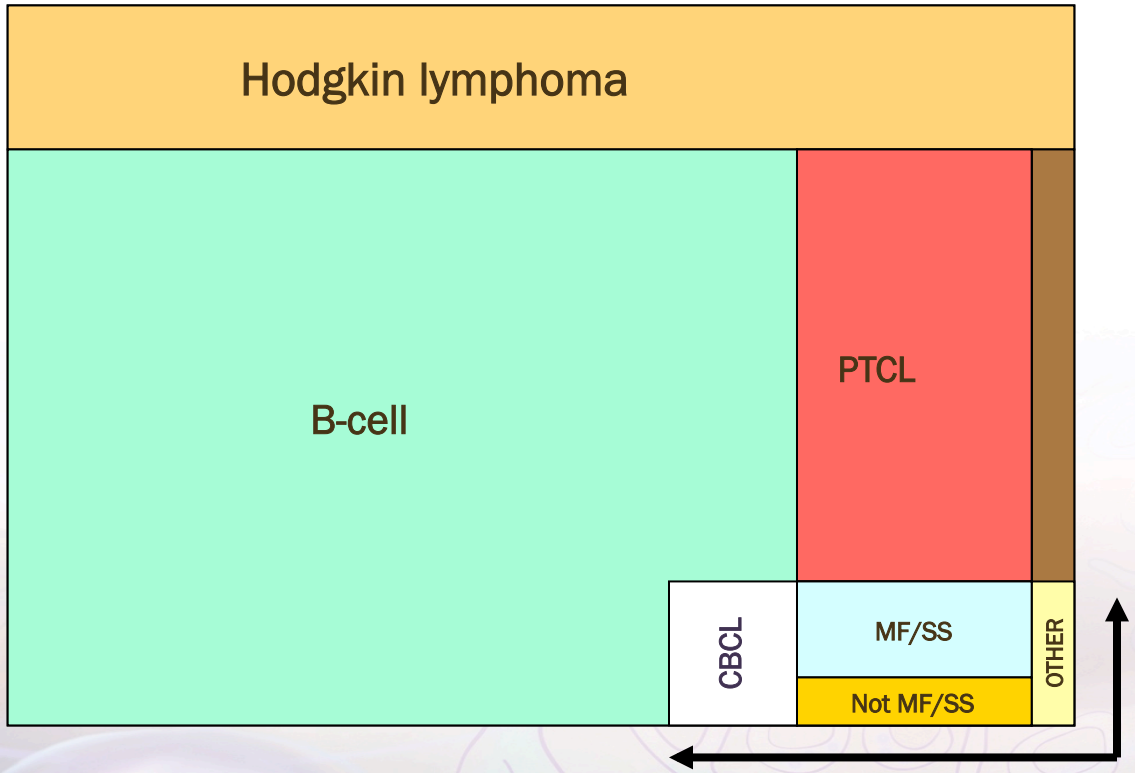
- Refer to group of T-cell lymphomas with primary manifestations in the skin
- Invasion of CD4+ T cells (lymphocytes) can occur in lymph nodes, blood, and visceral organs
- Mycosis fungoides (MF) and its leukemic variant Sézary syndrome (SS) are chronic disease states with considerable variation

CTCL Overview (Cont)

- Presentation: What is the appearance of the rash, symptoms, evolution over time?
- Histology: Characteristics of the atypical skin cells under the microscope
- Blood: Have the atypical cells migrated from the skin and populated the bloodstream? Use flow cytometry to assess
- Immunophenotyping: Proteins expressed on the surface of the cells
- Prognosis: Varies with stage, response to treatment, comorbidities, and luck

Breakdown of Lymphomas by Type

70,000 new cases each year



Hodgkin lymphoma

Non-Hodgkin lymphoma

Cutaneous lymphomas

Incidence of CTCL

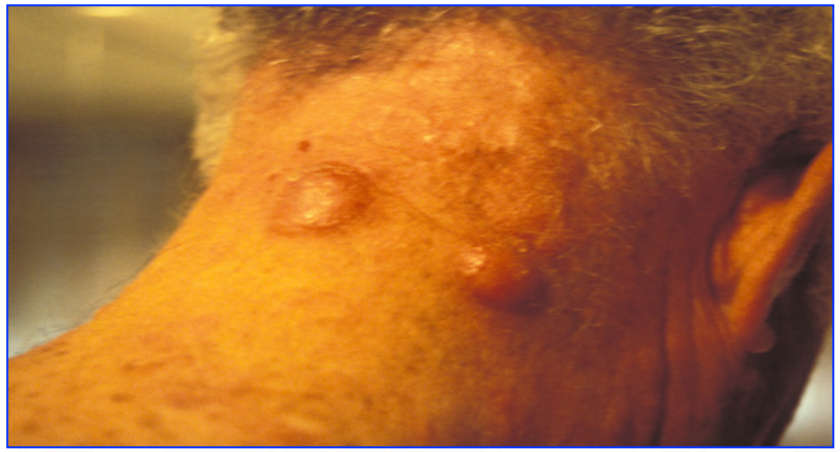
- Mycosis fungoides: 60%
- Sézary syndrome: 15%
- CD30+ lymphoproliferative disorders: 20%
  - Lymphomatoid papulosis (LyP)
  - Anaplastic large cell lymphoma (ALCL)
- Other rare types: 5%

Mycosis Fungoides

- Most common CTCL
- 1% of all NHL cases
- Median presentation at age 57
- Male-to-female ratio 2:1
- Incidence 0.36–0.90 per 100,000 person years or 1,000 cases per year
- More common in African Americans

Clinical Phases of CTCL

Patch



Tumor

Plaque

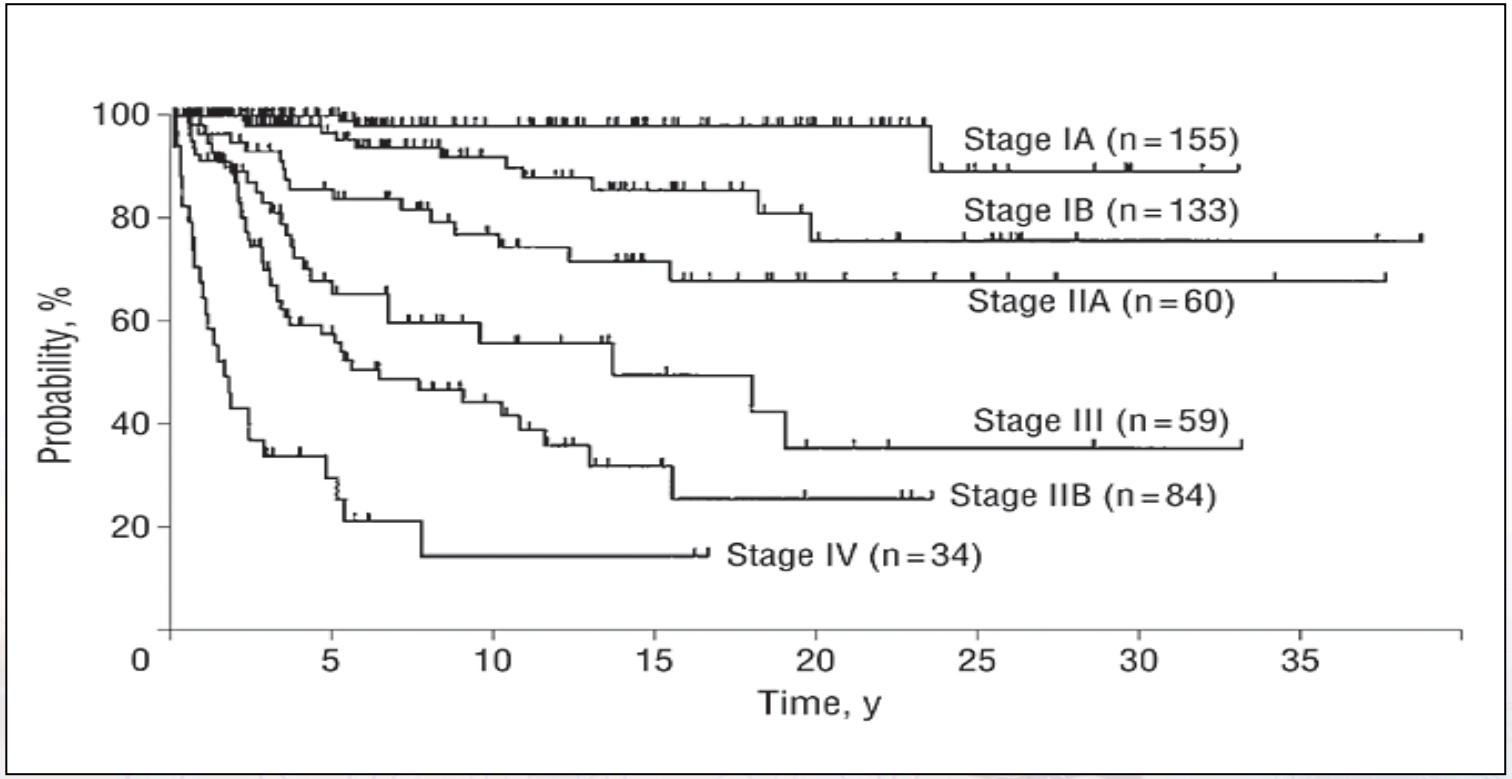
Erythroderma

Diagnosing CTCL

- It's not easy!
  - It can take 6–10 years for the rash to evolve
  - Not all skin lesions biopsied may show classic changes under the microscope
- Need both
  - The characteristic rash
  - The characteristic findings under the microscope

Prognostic Factors for CTCL

- Skin stage
- Blood involvement
- Large cell transformation
  - Mycosis fungoides or Sézary syndrome
  - De novo large cell transformation has better prognosis



Kim YH, et al. *Arch Dermatol*. 2003;139:857-866.

Classes of Systemic Therapies for CTCL

Immune Modulators

- Interferon alpha/gamma
- Bexarotene
- Toll-like receptor agonists (imiquimod)
- Lenalidomide
- Photopheresis
- Bone marrow transplantation

Cell killers

- **Biologicals**
  - Bexarotene
  - Interferons
  - Vorinostat
  - Romidepsin
  - Pralatrexate
- **Antibodies**
  - Alemtuzumab (anti-CD52)
  - Zanolimumab (anti-CD4)
  - Siplizumab (anti-CD2)
  - Brentuximab vedotin
- **Chemotherapy**
  - Gemcitabine
  - Liposomal doxorubicin
  - Methotrexate
  - Fludarabine and pentostatin
  - Alkylating agents

Classes of Histone Deacetylase (HDAC) Inhibitors

Class /potency	Select examples	Pharmacologic profile
Aliphatic acids	Valproic acid Phenylbutyric acid	Longest studied HDAC inhibitor. Although well tolerated, these drugs exhibit a short half-life due to rapid metabolism, are relatively less potent, and are nonspecific
Hydroxamic acids	Vorinostat LBH598 Belinostat LAQ-824 Trichostatin A	Pan-HDAC inhibitor with class 1 & 2 activity. Vorinostat first in class approved for CTCL (oral and IV)
Benzamides	MS-275 CI-994 MGCD-0103	Includes both pan- and isotype selective HDAC inhibitor (MGCD-0103; uM to nM potency)
Cyclic peptides	Depsipeptide Apicidin A CHAP	Structurally complex pan-HDAC inhibitor active in nM range. Depsipeptide metabolically converted to active metabolite

Which of the following is NOT a common toxicity associated with romidepsin used in the treatment of T-cell lymphoma?

A. Prolonged QT interval

B. Fatigue

C. Thromboembolism

D. Cytopenias

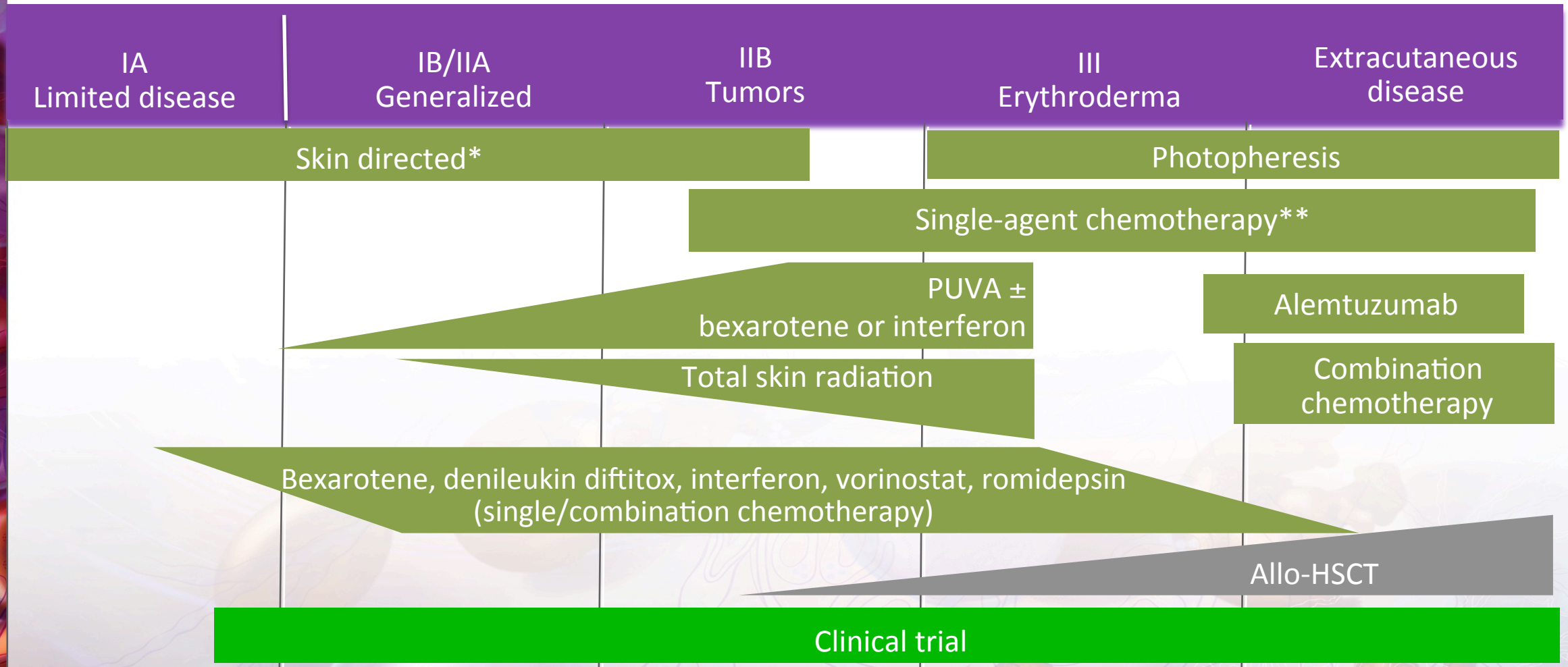
Closer Look at HDAC Inhibitors

- Vorinostat
  - Approved in 2006 for CTCL
  - Given orally
  - 200–400 mg daily
  - Response rate: ~30%
  - Common AEs: cytopenias, thrombosis, diarrhea, dehydration, hyperglycemia, fatigue
- Romidepsin
  - Approved in 2009 for CTCL (also for PTCL in 2011)
  - Given intravenously over 4 hours
  - 3 weeks on, 1 week off
  - Response rate: ~30%
  - Common AEs: cytopenias, asthenia, QT prolongation, headache, weight loss

FDA-Approved Therapies for CTCL

- Extracorporeal photophoresis (ECP): 1990
- Denileukin diftitox accelerated approval: 1999
  full approval: 2008
- Bexarotene capsules: 1999
- Bexarotene gel: 2000
- Vorinostat: 2006
- Romidepsin: 2009
- Valchlor (topical nitrogen mustard): 2013

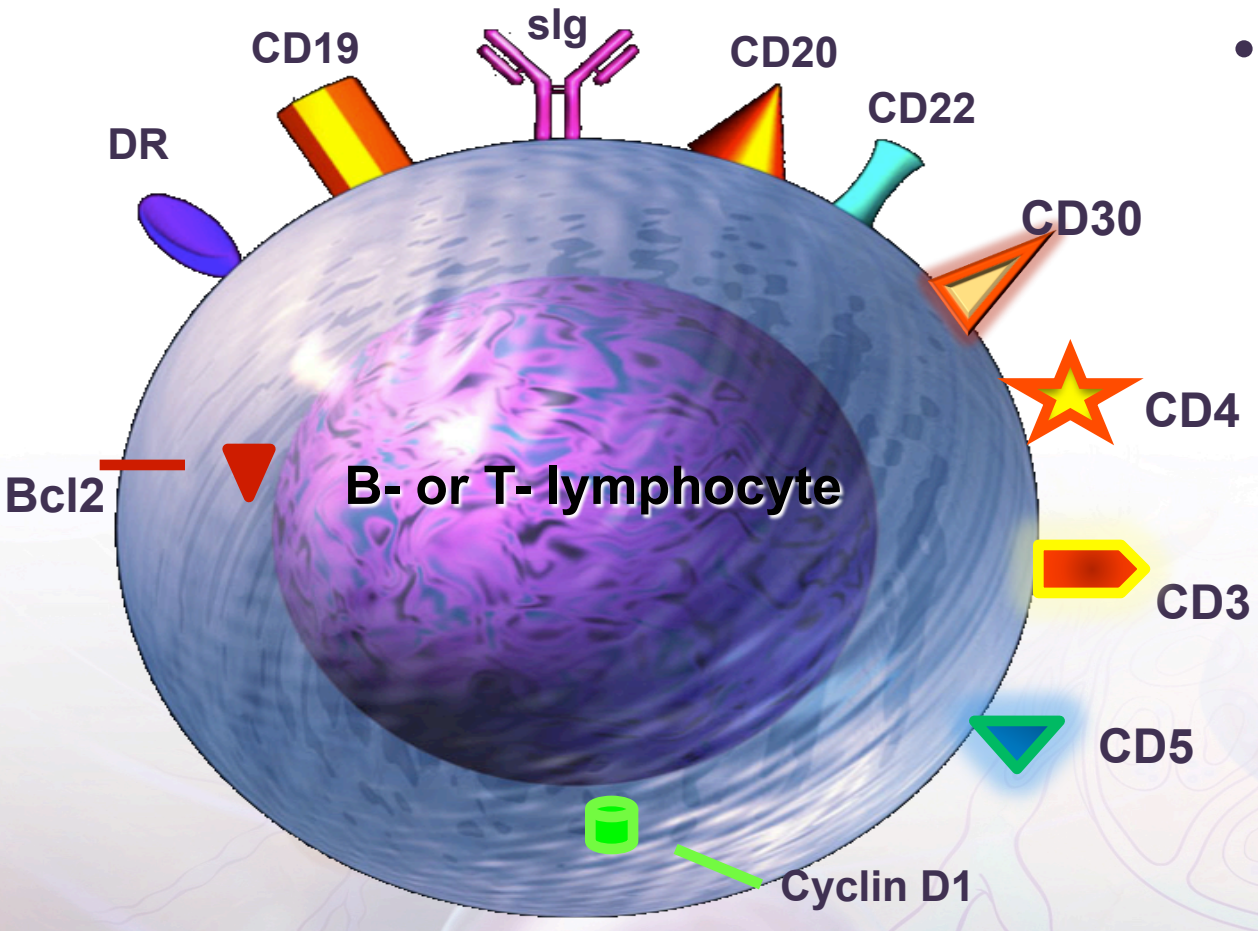
Management of CTCL



* Topical steroid, retinoid gel, nitrogen mustard, phototherapy

** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, temozolomide

Immunohistochemical Staining on B- and T- Cell Lymphocytes



- Surface and cytoplasmic proteins targeted by antibodies are:
  - Differentially expressed on different types of lymphoma
  - Can serve as targets for newer drugs (rituximab, brentuximab vedotin, ibritumomab tiuxetan)

Symptom Management in Rare Lymphomas

Sandra E. Kurtin, RN, MS, AOCN®, ANP-C
Nurse Practitioner
Clinical Assistant Professor of Medicine and Nursing
The University of Arizona Cancer Center
Tucson, Arizona

Management of Cytopenias

- Preventative use of growth factors in high-risk patients
  - Understand the risk and benefits of each
- Transfusion support based on target hemoglobin or platelet count
  - Familiarize yourself with the current transfusion guidelines from ASH, AABB, and other published guidelines
- Educating patients and caregivers for infection prevention
  - WASH YOUR HANDS!

Infection Prevention Strategies

- Recognize early signs and symptoms of infection
- Emphasize the importance of hand hygiene
- Assure appropriate immunizations administered
- Avoid food exposure (raw or undercooked meats/eggs, deli meats, cured meats in natural wrap, unpasteurized dairy products, cheeses with molds, raw honey/honey in the comb, unwashed raw fruits and vegetables, and raw vegetable sprouts)
- Monitor for fever, persistent cough, and urinary symptoms
- Immediate contact instructions for fever 100.4°F (38°C) or higher; cough or sore throat; any wound with swelling, warmth, or increasing redness
- Teaching/support related to prophylactic anti-infective compliance

Common Infectious Pathogens in Neutropenic or Lymphopenic Patients

- Initial infections are primarily bacteria; subsequent infections are primarily antibiotic-resistant bacteria, yeast, other fungi, and viruses
- Infection from Candida species occurs later in the course of neutropenia, often as a consequence of GI mucositis
- Aspergillus species and other filamentous fungi are causes of morbidity and mortality with severe, and prolonged neutropenia
- Many infectious complications in lymphoma patients are opportunistic and related to lymphopenia

Wood SK, et al. *J Adv Pract Oncol*. 2011;2:356-371.

Infection Prophylaxis

- Herpes zoster with bortezomib requires antiviral prophylaxis
- CMV reactivation risk with alemtuzumab, CMV PCR monitoring every 2 to 3 weeks, may prevent or treat when active
- Herpes virus and PCP prophylaxis for purine-analog and/or alemtuzumab therapy
- Vaccinations:
  - Influenza vaccine yearly
  - Pneumococcal vaccine every 5 years
  - No live vaccines, ie, zoster

© American Society of Hematology, 2014

Choosing Wisely®

An initiative of the ABIM Foundation

FIVE THINGS HEALTH CARE PROFESSIONALS AND PATIENTS SHOULD QUESTION

© American Society of Hematology, 2014

ASH Choosing Wisely Recommendations

1. Do not transfuse more than the minimum necessary units of red blood cells
2. Do not test for thrombophilia in patients with major transient risk factors for venous thromboembolism (VTE) and acute VTE
3. Do not use inferior vena cava filters routinely in the management of VTE
4. Do not use plasma or prothrombin concentrates for nonemergent reversal of vitamin K antagonists
5. Limit CT surveillance scans in asymptomatic people following curative-intent chemotherapy for aggressive lymphoma

© American Society of Hematology, 2014

ASH Choosing Wisely Recommendations (cont)

1

Don't transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, noncardiac inpatients).

- A large body of evidence demonstrates that liberal RBC transfusion strategies do not benefit patients.
- Thus, liberal RBC transfusion should be avoided in most clinical settings.
- Transfusion of RBC is expensive (approximately $200 to $300 per unit) and is associated with a risk of adverse events.

© American Society of Hematology, 2014

Overall Survival Is Not Reduced With Restrictive Transfusion

- Evidence from 14 studies in a 2012 meta-analysis showed that overall survival is not significantly reduced with restrictive vs. liberal transfusion (RR, 0.84; 95% CI, 0.69–1.01)

Carson JL, et al. *Cochrane Database Syst Rev*. 2012;4:CD002042.

Risks and Benefits of Packed RBC (PRBC) Transfusion

Benefits

- Rapid increase in Hgb may improve fatigue in some patients, but it may be temporary if underlying causes are not addressed

Risks

- Viral transmission: HIV: 3.1/100,000; hepatitis C: 5.1/100,000; hepatitis B: 3.41–3.43/100,000
- Transfusion-related acute lung injury (TRALI): 0.81/100,000
- Transfusion-associated circulatory overload (TACO): 1%–6%, higher in ICU and postoperative settings
- Fatal hemolysis: 1.3–1.7/million transfused units
- Febrile nonhemolytic reactions: 1.1%–2.15%

Kurtin S. *J Adv Pract Oncol*. 2012;3:209-224

Parameters for Transfusion of PRBCs

- Requires informed consent for potential risks and benefits
- Establish a target Hgb for each individual patient
- Asymptomatic patients: Transfuse to maintain Hgb 7–9 g/dL
- Symptomatic with hemorrhage: Transfuse to maintain hemodynamic stability
- Symptomatic with Hgb < 10 g/dL: Transfuse to maintain Hgb 8–10 g/dL
- Acute coronary syndromes with anemia: Transfuse to maintain Hgb > 10 g/dL
- Each unit of PRBCs should raise Hgb by 1 g/dL

Kurtin S. *J Adv Pract Oncol*. 2012;3:209-224

Assessment of Risk for Bleeding: WHO Bleeding Grades

1. Petechiae, ecchymosis, occult blood in body secretions, mild vaginal spotting
2. Evidence of gross hemorrhage not requiring RBC transfusion over routine needs: epistaxis, hematuria, hematemesis
3. Hemorrhage of one or more units of PRBCs/day
4. Life-threatening hemorrhage, defined as either massive bleeding causing hemodynamic compromise or bleeding into a vital organ (eg, intracranial, pericardial, or pulmonary hemorrhage)

Management

- Evaluate symptoms and underlying disease
- Know the status of the bone marrow
- Determine chronicity
- Consider individual patient characteristics, including proximity to treatment center, concomitant anticoagulation therapy or antiplatelet drugs, prior response to platelets, concurrent inflammatory process/infection, CNS disease
- Hold anticoagulation therapy for platelet count < 50,000/μL

Kurtin S. *J Adv Pract Oncol*. 2012;3:209-224

Parameters for Transfusion of Platelets Based on Platelet Levels and Patient Characteristics

- Platelets < 10,000/µL, threshold for therapeutic platelet transfusions
- Patients with a history of bleeding or an active infectious process may require higher threshold for transfusion
- Surgical or invasive procedure: Maintain platelets > 50,000/µL; more aggressive procedures for patients with complicating factors may require higher platelet count
- Neurosurgical procedures: Maintain platelets > 100,000/µL
- Contact the patient's provider if there are questions about transfusion
- Premedication for platelets may be required in patients with a history of urticaria or other symptoms of transfusion reactions
- Evaluate response to platelets by obtaining post platelet count 30–60 minutes after infusion

Kurtin S. *J Adv Pract Oncol*. 2012;3:209-224

Management of pruritus for patients with T-cell lymphoma may include which of the following?

A. Antihistamines

B. Aprepitant

C. Phototherapy

D. All of the above

Managing Pruritus

First step	Moisturizing therapy Avoidance of triggering factors Initial symptomatic therapy: Nonsedating H1 antihistamines (sometimes updosing needed) Topical corticosteroids	
Second step	Symptomatic therapy according to the cause of itch	
Third step	In case of unclear cause and nonresponse during the second step, symptomatic topical and/or systemic therapy including	
	Antidepressants Aprepitant Capsaicin Calcineurin inhibitors Cannabinoid agonists	Gabapentin Immunosuppressives (cyclosporine) Naltrexone UV therapy Clinical trials

Raap U, et al. *Curr Opin Allergy Clin Immunol*. 2011;11:420-427.

Management of Neurotoxicity Symptoms

- Baseline and ongoing evaluation
  - Include high-risk comorbidities
- Dose reduction, delay, or omission of drug
  - Agent-specific guidelines
- Use of various supplements
  - Avoid green tea or vitamin C with bortezomib administration
  - Daily doses of vitamin B_6 should not exceed 100 mg
- Emollient creams (e.g., cocoa butter, menthol, and eucalyptus-based)
- Physical therapy
- Stress reduction
- Cognitive behavioral therapy
- Acupuncture
- Gabapentin, tricyclic antidepressants, or other agents for neuropathic pain

Tariman JD, et al. *Clin J Oncol Nurs*. 2008;12(3 suppl);29-36; Palumbo A, et al. *J Clin Oncol*. 2014;32:587-600.

Common Supplements Used to Treat Peripheral Neuropathy

Vitamin/supplement	Dosing regimen
Multi-B complex vitamins (with B1, B6, B12, folic acid, and other)	B6: ~ 50 mg daily, not to exceed 100 mg daily Folic acid: 1 mg daily
Vitamin E	400 IU daily
Vitamin D	400–800 IU daily
Fish oils (omega-3 fatty acids [EPA and DHA])	1–2 capsules daily with food (1 capsule is usually 1 g)
Magnesium	Suggested doses include: 250 mg twice a day May cause diarrhea in larger doses
Potassium	Either as provided by the treating physician or foods rich in potassium (eg, bananas, oranges, potatoes)
Tonic water (seltzer water)	Drink 1 glass in evening and any other time cramping occurs
Acetyl-L-carnitine	500 mg twice a day with food Can take up to 2,000 mg a day
Alpha-lipoic acid	300–1,000 mg a day with food
Glutamine	1 g up to 3 times a day with food

Richardson PG et al. J Natl Compr Canc Netw. 2010;8(suppl 1):S4-S12.

Tools for Management of Fatigue

- Individualized assessment
  - Sleep, nutrition, depression, medications, activity, comorbidities
- Individualized interventions
  - Balance between activity and energy conservation
  - Psychosocial interventions
  - Nutrition consultation
  - Sleep evaluation
  - Pharmacologic interventions
    - Psychostimulants, sleep medications

Pachman DR, et al. *J Clin Oncol*. 2012;30:3687-3696.

Myelodysplastic Syndromes: Practical Tools for Management

Sandra E. Kurtin, RN, MS, AOCN®, ANP-C
Nurse Practitioner
Clinical Assistant Professor of Medicine and Nursing
The University of Arizona Cancer Center
Tucson, Arizona

The Diagnosis of MDS Can Be Difficult

Facts About MDS

- The average age at diagnosis is 73 years
- MDS remains an incurable malignancy for the majority of patients
- Allogeneic-hematopoietic cell transplantation is the only potential "cure"
- The leading cause of death is the disease itself (~80%)
- The MDS population is heterogeneous based on disease and individual characteristics
- Risk-stratified treatment strategies are key to optimal therapeutic outcomes
  - Revised International Prognostic Scoring System (IPSS-R)
  - Patient-specific characteristics

Dayyani F, et al. *Cancer*. 2010;116:2174-2179; Kurtin SE. *Clin J Oncol Nurs*. 2012;16(suppl):5-7.

MDS: Diagnostic Evaluation

- History and physical exam
  - Include comorbidity evaluation and performance status
- Peripheral blood counts and reticulocyte count
- Bone marrow biopsy and aspiration
  - Hematopathology
    - Bone marrow blasts (%)
    - Cellularity
    - Dysplastic features
  - Metaphase cytogenetics
  - Iron stain
  - Reticulin stain for fibrosis
- Additional tests
  - Iron saturation, ferritin
  - Vitamin B_{12}, folate levels
  - Serum erythropoietin level
  - Hemolysis screen
  - TSH, testosterone
  - Renal and hepatic profiles

Establish diagnosis of MDS

Determine subtype
FAB/WHO

Estimate prognosis
IPSS score

FAB = French-American-British; IPSS = International Prognostic Scoring System; TSH = thyroid stimulating hormone; WHO = World Health Organization

IPSS Risk Categories

Variable/score	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	< 5	5–10	–	11–20	21–30*
Karyotype	Good	Intermediate	Poor	–	–
Cytopenias	0/1	2/3	–	–	–

Risk category	Numeric score	Patient distribution	Median survival†	Evolution to AML
Low	0	31%	5.7 years	9.4
Int-1	0.5–1.0	39%	3.5 years	3.3
Int-2	1.5–2.0	22%	1.2 years	1.1
High	≥ 2.5	8%	0.4 years	0.2

Life expectancy at 75 years US	**11.2 years**
Life expectancy at 65 years US	**17.7 years**

† Data generated prior to active therapies

* >20% blasts denotes acute myeloid leukemia (AML)

US Social Security Administration, 2009; Greenberg P, et al. *Blood*. 1997;89:2079-2088 [published correction in *Blood*. 1998;91:1100].

IPSS-R Cytogenetic Risk Groups

Cytogenetic risk grouping	Cytogenetic types	Estimated survival
Very good	del(11q), -Y	60.8 mo
Good	Normal, del(20q), del(5q) alone and double, del(12p)	48.5 mo
Intermediate	+8, 7q-, i(17q), +19, +21, any other single or double, independent clones	24 mo
Poor	der(3)q21/q26, -7, double including 7q-, complex (3 abnormalities)	14 mo
Very poor	Complex (> 3 abnormalities)	5.7 mo

IPSS-R Risk Categories

Score/attribute	0	1	1.5	2.5	3.5	5
Cytogenetics	Very good		Good	Int	Poor	Very poor
Blasts	< 5%		5%–10%	11%–30%		
Hemoglobin	≥ 10 g/dL		< 10 g/dL			
Platelets	≥ 100,000		< 100,000			
Absolute neutrophil count	> 0.8	< 0.8				

IPSS-R: Variable Survival/Prognosis and Risk of Leukemic Transformation

Score	1 Very Low	2 Good	3 Intermediate	4 Poor	5 Very High
Mean overall survival	8.7 years	5.3 years	3.0 years	1.6 years	0.8 years
Mean risk of AML in 25% of patients	Not reached	10.7 years	4.0 years	1.4 years	0.8 years

Greenberg, PL et al. *Blood*. 2012;120:2454-2465.

IWG-PM
INTERNATIONAL WORKING GROUP FOR THE PROGNOSIS OF MDS

mds foundation
the myelodysplastic syndromes foundation, inc.
MDS - A bone marrow failure disorder

The manuscript describing the Revised IPSS (IPSS-R) for MDS is available at *Blood Online* (June 27, 2012;120:2454) *OR* on the MDSF website

http://www.mds-foundation.org/ipss-r-calculator/

http://www.ipss-r.com

An iPhone App for the IPSS-R calculator tool is also accessible through the Apple Store (enter MDS IPSS-R)

Comorbidities and MDS

- 600 consecutive patients evaluated at MD Anderson using Adult Comorbidity Evaluation-27 (ACE-27)
- Median overall survival
  - Overall: 18.6 months ($p < .001$ for all)
  - No comorbidities: 31.8 months
  - Mild: 16.8 months (HR, 1.3)
  - Moderate: 15.2 months (HR, 1.6)
  - Severe: 9.7 months (HR, 2.3)
- Patients with severe comorbidities have a 50% decrease in median survival independent of age or IPSS risk group
  - Low-risk: 43 months
  - Intermediate-risk: 23 months
  - High-risk: 9 months

Nagvi K, et al. *J Clin Oncol*. 2011;29:2240-2246.

MDS, Transfusions, and Survival

- 2,253 newly diagnosed MDS patients
  - Median age of 77
- Transfusion-dependent patients with MDS
  - Higher incidence of dyspnea, hepatic disease, and infections (all $p < .001$)
  - 82% experienced a cardiac event within 3 years of follow-up ($p < .001$)
  - Increased risk of death (age adjusted) compared with other MDS patients (HR, 2.41; 95% CI, $p < .001$)
- Transfusion dependence is a common trigger for disease-modifying therapies

Goldberg SL, et al. *J Clin Oncol*. 2010;28:2847-2852.

Functional Status, Frailty, and Comorbidities

- Functional Status: Measures by ECOG and KPS
  - Activities of daily living (ADLs)/instrumental ADLs
  - Limited by brief and episodic evaluation in the clinical setting
  - Need to enlist the “Truth Squad” – caregivers and friends
- Comorbidities
- Frailty
  - Weight loss, weakness, poor nutritional intake, cognitive impairment, and poor endurance (the “withering phenomenon”)
  - Cardiovascular Health Study (N = 5,317): Frailty associated with hospitalization, falls, declining ADLs including diminished mobility, and death ($p < .001$)

Pal SK, et al. *CA Cancer J Clin*. 2010;60:120-132; Balducci L, et al. *Oncologist*. 2000;5:224–237.

Key Principles of Therapy in MDS: Treatment Goals and Duration

- MDS is not curable without allogeneic hematopoietic cell transplantation
  - Not an option for the majority of patients
- Not every patient will have a complete response
  - Hematologic improvement, stable disease, and transfusion independence are good things
- Treatment should continue until disease progression or unacceptable toxicity
  - Methylation is a continuous process and is associated with leukemogenesis
  - Limited approved agents currently available

Kurtin SE, et al. *Clin J Oncol Nurs*. 2010;14:E29-E44; Kurtin S. *J Adv Pract Oncol*, 2011;2(suppl 2):7-18.

Additional Key Therapeutic Principles in MDS

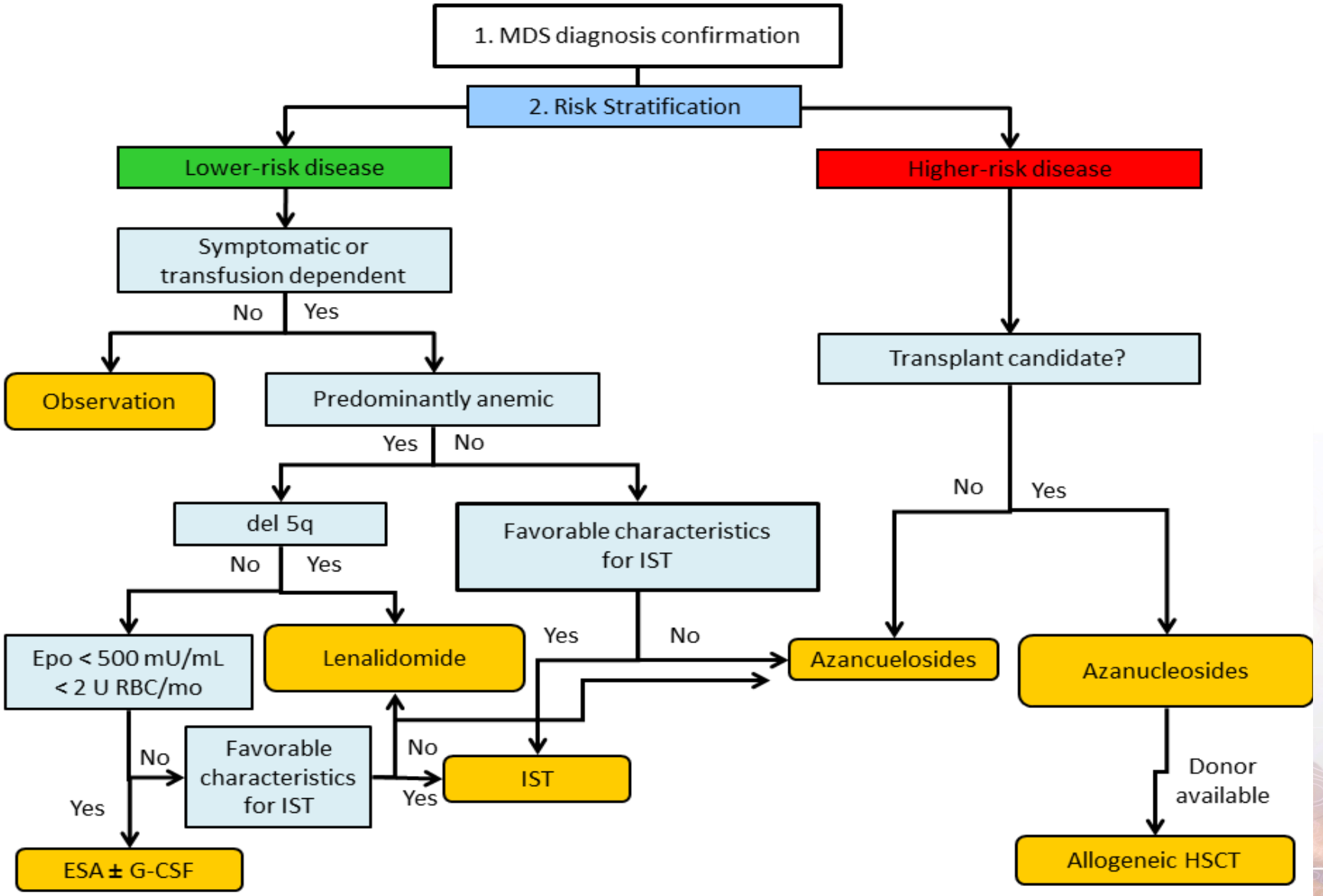
- Age alone should not exclude active therapies
  - Consider performance status and comorbidities
- Blood counts often get worse before they get better
- All active therapies for MDS require time to work (4–6 months of continued treatment)
- Strategies for proactive management of adverse events are key to obtaining the best response

What Are the Current Treatment Options?

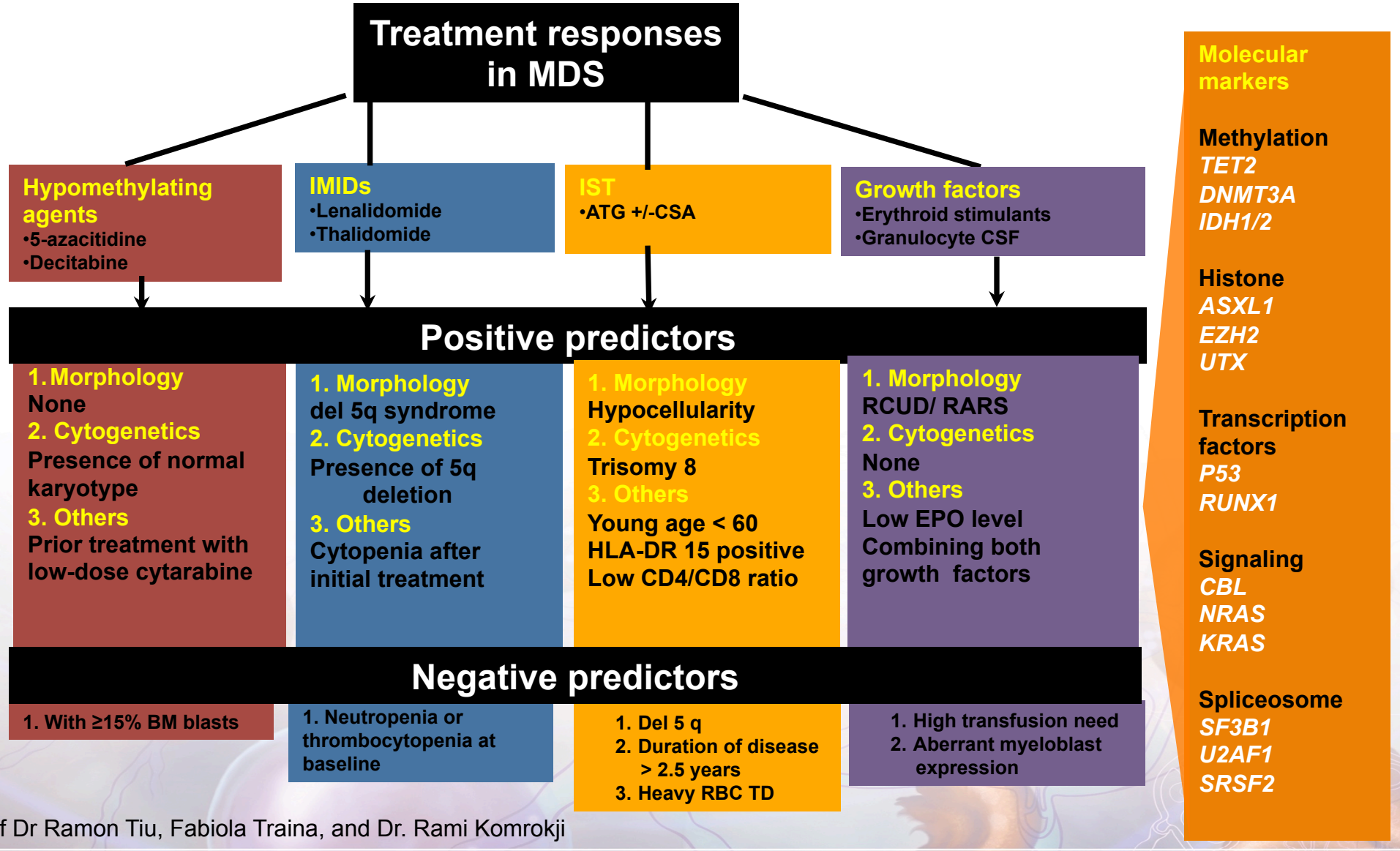
- Supportive care: Transfusions, growth factors
- Lenalidomide
- Azacitidine for injection
- Decitabine
- Chemotherapy: Cytarabine, clofarabine, etoposide
- Bone marrow transplant
- Investigational agents

Approved agents are limited
Maximizing each option to its full benefit is critical

MDS 2014 Management Algorithm



Summary of Predictive Factors of Treatment Response in MDS



Courtesy of Dr Ramon Tiu, Fabiola Traina, and Dr. Rami Komrokji

Strategies to Minimize Adverse Events

- Set expectations
- Plan supportive care strategies
- Engage and empower patients and caregivers

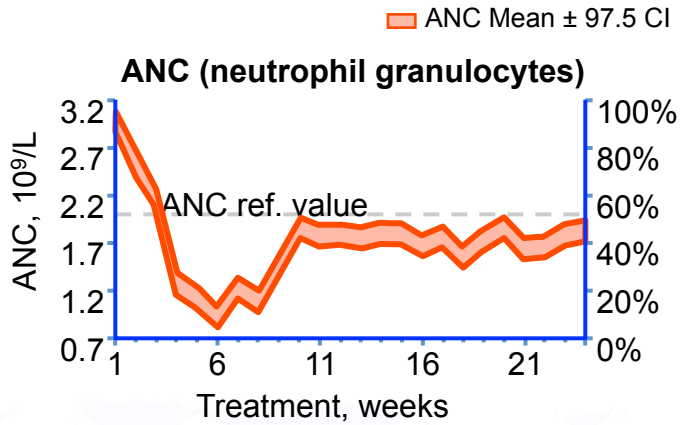
Kurtin SE, et al. *Clin J Oncol Nurs*. 2010;14:E29-E44; Kurtin S. *J Adv Pract Oncol*, 2011;2(suppl 2):7-18.

The Challenge: Getting Through the First Few Cycles of Treatment

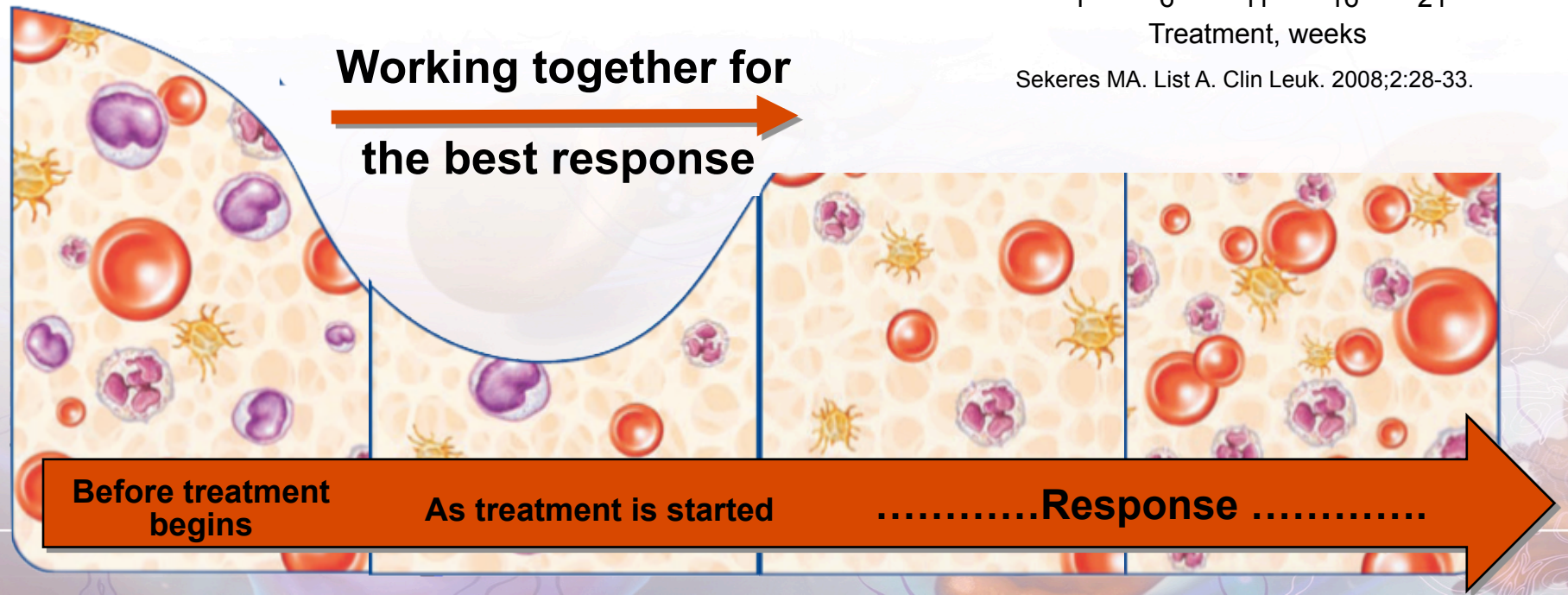
Time is required for the best response: a minimum of 4−6 months.

Cytopenias often get worse before they get better.

- Strategies for management
  - Dose modifications/delays
  - Supportive care
  - Set expectations and provide support



Sekeres MA. List A. Clin Leuk. 2008;2:28-33.

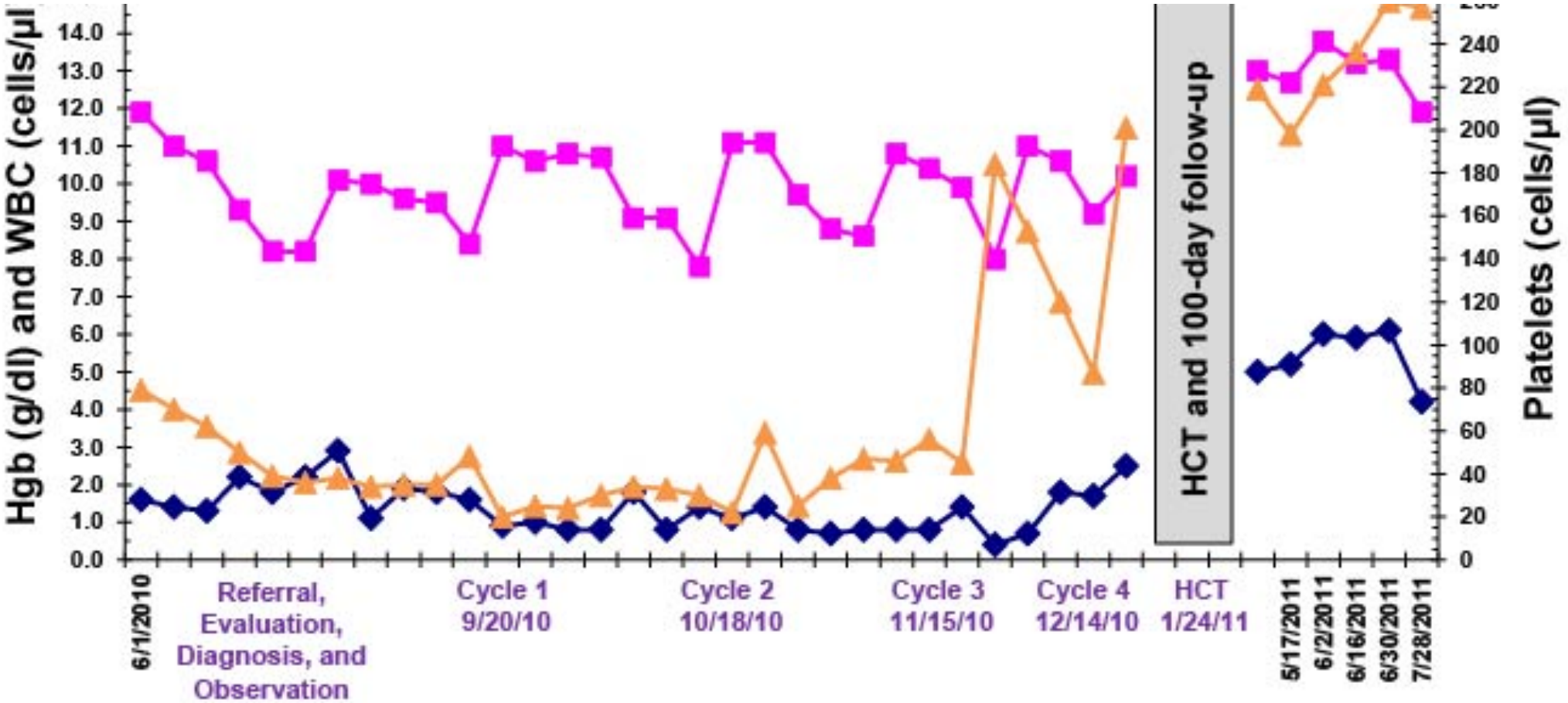


Setting Expectations and Empowering Patients and Family Members

- Setting expectations: Blueprints for treatment
  - Cytopenias are expected
  - Require close monitoring during the first 8–12 weeks of therapy
    - Create a plan for follow-up
  - Likely to improve with treatment response but may not return to normal – "new normal"
- Empower patients and family members to track, report, and manage
    - My MDS plan: Treatment tracker, transfusion records
    - Early identification of adverse events, how and when to report or manage

Kurtin SE, et al. *Clin J Oncol Nurs*. 2010;14:E29-E44; Kurtin S. *J Adv Pract Oncol*, 2011;2(suppl 2):7-18.

Trilineage Response to Azacitidine



Kurtin SE, et al. *Clin J Oncol Nurs*. 2012;16(suppl):23-25.

Subgroup Analysis of the AZA-001: Elderly Patients >75 Years With High-Risk Disease

- 87 elderly patients > 75 years
- High-risk disease: IPSS: Int-2 or high
- Azacitidine (AZA) significantly improved overall survival (OS) compared with best supportive care (BSC)
  - 2-year OS rates: 55% vs 15% ($p < .001$)
- AZA generally well tolerated
  - Adverse events (AEs) most common in the first 2 cycles

AE (grade 3/4)	Cycle 1–2		Cycle 3–4		Cycle 5–6	
	AZA	BSC	AZA	BSC	AZA	BSC
Anemia (%)	2	1	0	1	2	0
Neutropenia (%)	15	6	8	3	7	2
Thrombocytopenia (%)	14	10	8	2	5	0
Fatigue (%)	0	0	1	1	1	0
Pyrexia (%)	0	0	1	1	1	0

Seymour JF, et al. *Crit Rev Oncol Hematol*. 2010;76:218-227.

What is the average time to achieve transfusion independence in patients treated with lenalidomide for myelodysplastic syndromes with the del5q abnormality?

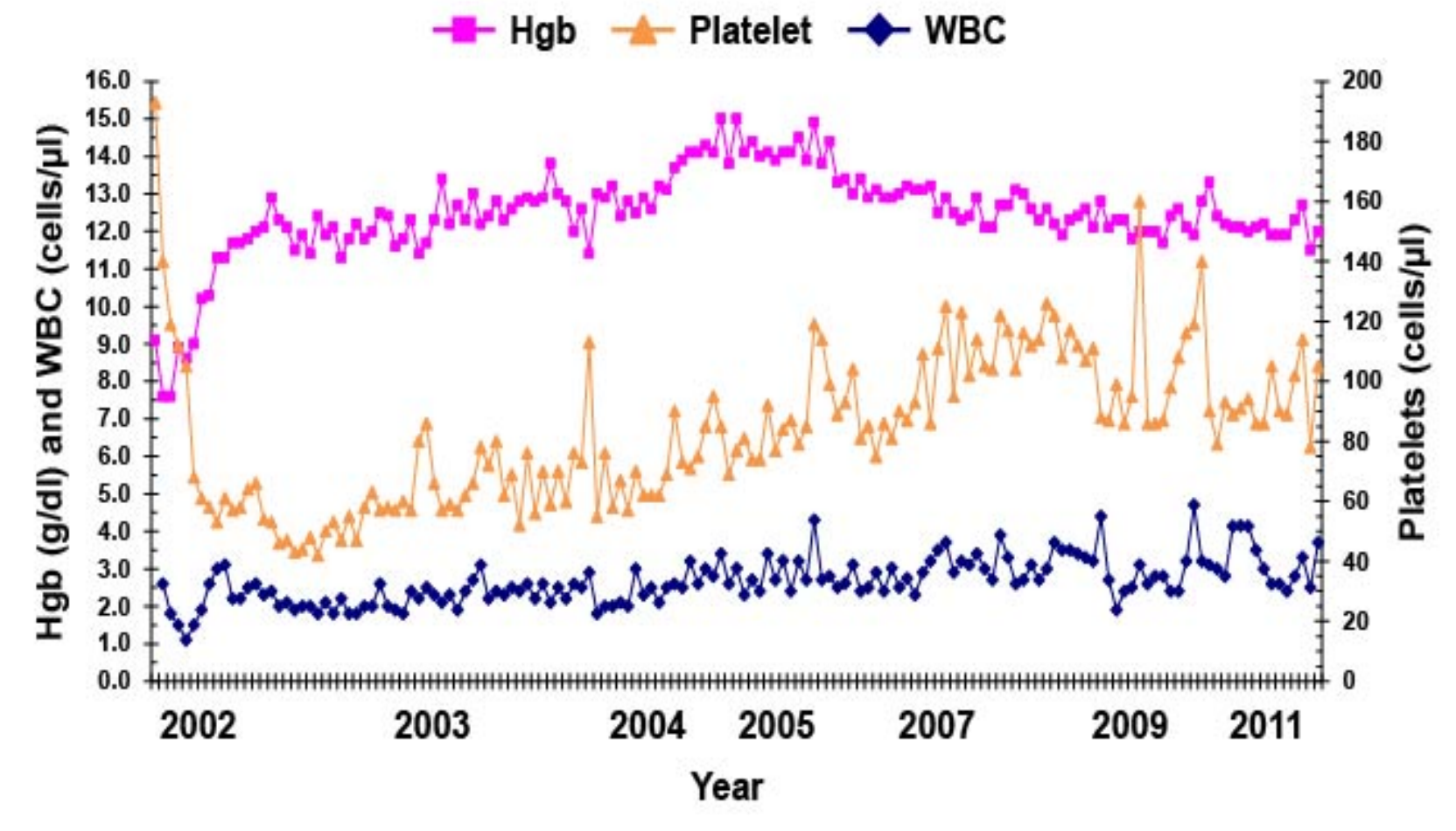
A. 20 weeks

B. 8 to 12 weeks

C. 2 to 3 weeks

D. 1 week

Sustained Response to Lenalidomide: 10 Years Transfusion Independent



Kurtin SE, et al. *Clin J Oncol Nurs*. 2012;16(suppl):23-25.

Common Adverse Events

- All agents
  - Myelosuppression (may also be disease related)
    - Anemia, neutropenia, thrombocytopenia
  - Nausea and vomiting
  - Constipation
  - Renal and hepatic toxicities
- Drug-specific adverse events
  - Azacitidine: Injection-site reactions
  - Lenalidomide: Rash, pruritus, diarrhea, safety program for lenalidomide
- Iron overload
  - Chelation therapy may be associated with cytopenias, renal and hepatic toxicities

Quick Tips

Patient and caregiver guidelines for monitoring symptoms including when and how to report them to the health care provider.

Practical strategies for preventing more severe symptoms

Dedicated chapter in the building blocks of hope

Kurtin SE, et al. *Clin J Oncol Nurs*. 2010;14:E29-E44; Scott BL, et al. *Annu Rev Med*. 2010;61:345-358; Kurtin SE. *Oncology* (Williston Park). 2007;21(11 suppl, nurse ed):41-48.

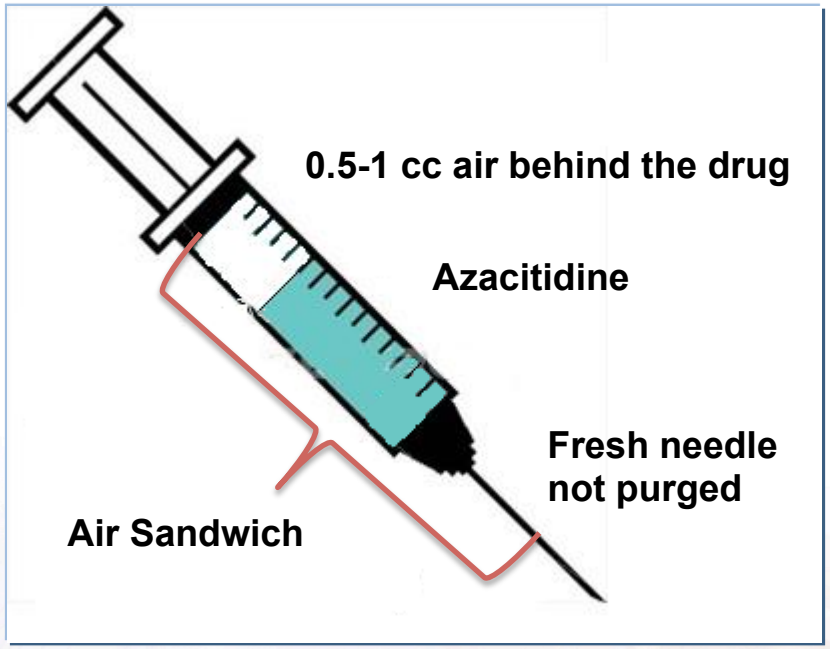
Injection-Site Reactions: Azacitidine

- Injection-site reactions are common
- May vary greatly from patient to patient
  - From small bruise to large tender, red welt
- Usually disappear after several days and normally do not scar
- Air sandwich technique can reduce irritation

Kurtin S, et al. *J Adv Pract Oncol.* 2012;3:406-410.
Millennium Pharmaceuticals, Inc. (2012). Velcade (bortezomib) package insert. http://www.velcade.com/files/PDFs/velcade_prescribing_information.pdf

Subcutaneous Injection: The Air Sandwich Technique

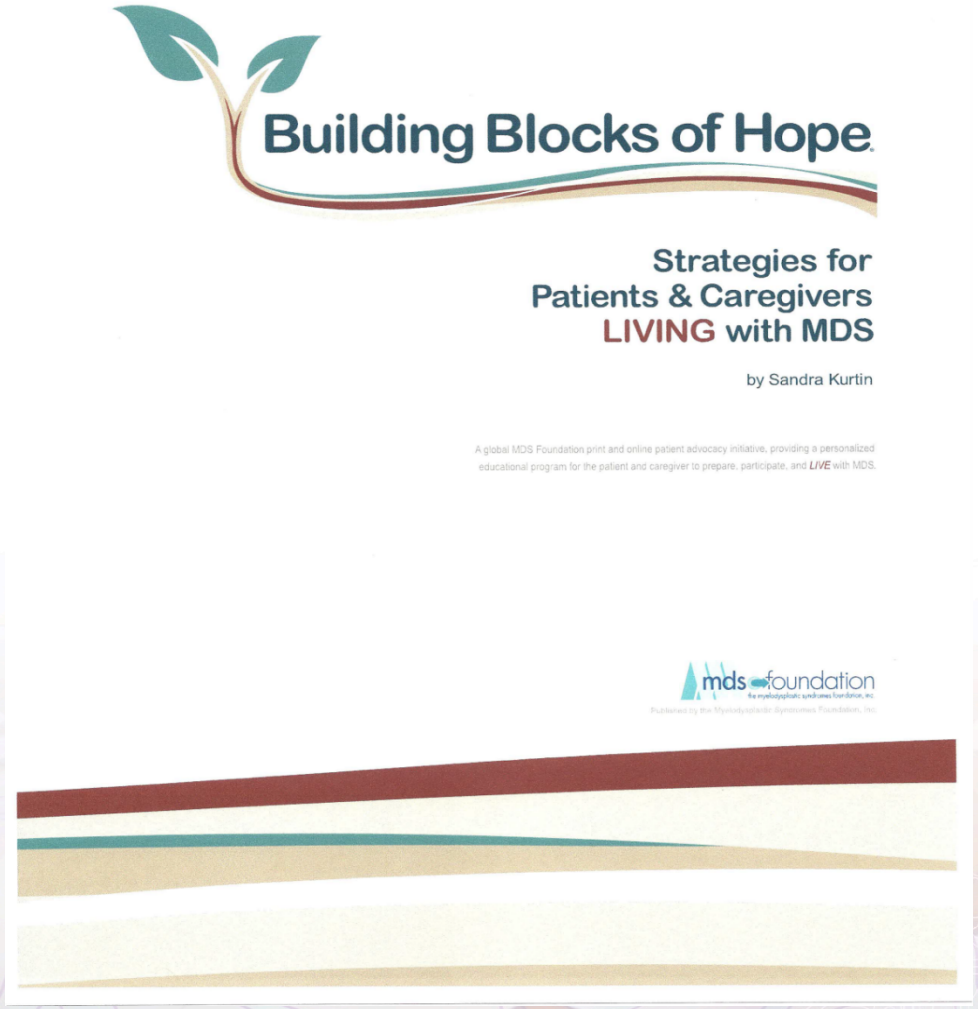
- "Air sandwich" technique
- Attach fresh needle (4–6 mm) to syringe with prepared medication
- Do not purge needle (air in needle)
- Maximum volume for SC injection is 2 mL per site
- Pull 0.5–1.0 mL air into syringe
- Use index finger and thumb to "pinch an inch"—avoid pinching the underlying muscle
- Invert syringe and inject including air behind the drug
  - 90° angle for 4-6 mm needles
  - 45° angle for ≥ 8 mm needle
- Remove needle promptly
- Apply gentle pressure to site



Use "air sandwich" technique to avoid seeding of irritating medication in the injection track

Kurtin S, et al. *J Adv Pract Oncol*. 2012;3:406-410.

The Building Blocks of Hope® is a global print and online patient advocacy initiative providing a personalized educational program for patients and caregivers to prepare, participate, and ***LIVE*** with MDS



http://www.mds-foundation.org/bboh2/

Building Blocks of Hope: Online Interactive Format for Patients

- Create a personalized MDS Plan (pages 92–98)
  - A working document that allows you to create an individualized profile:
    - About your MDS diagnosis
    - Your health profile
    - Members of your health-care team
- Tools for tracking your progress (pages 85–91)
  - Place these resources in a 3-ring binder and add additional pages, such as laboratory or radiology results, as needed, to take to your health-care provider visits. This will provide a great tool for taking an active part in your care.