T-Cell Lymphomas, Version 2.2022

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ABSTRACT

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoproliferative disorders arising from mature T cells, accounting for about 10% of non-Hodgkin lymphomas. PTCL-not otherwise specified is the most common subtype, followed by angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma, anaplastic lymphoma kinase–positive, anaplastic large cell lymphoma, anaplastic lymphoma kinase–negative, and enteropathy-associated T-cell lymphoma. This discussion section focuses on the diagnosis and treatment of PTCLs as outlined in the NCCN Guidelines for T-Cell Lymphomas.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for T-Cell Lymphomas are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

Disclosures for the NCCN T-Cell Lymphomas

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN T-Cell Lymphomas Panel members can be found on page 308. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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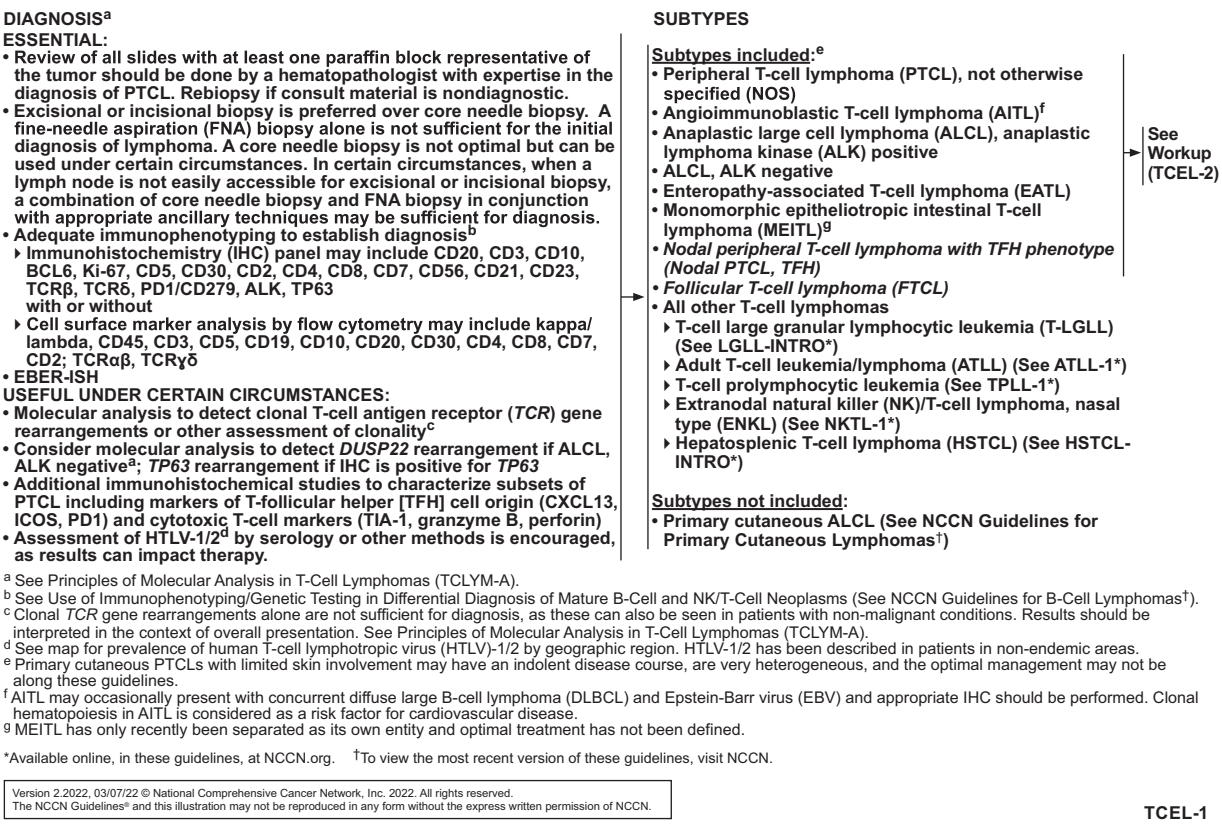


[a] See Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[b] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See NCCN Guidelines for B-Cell Lymphomas†).
[c] Clonal *TCR* gene rearrangements alone are not sufficient for diagnosis, as these can also be seen in patients with non-malignant conditions. Results should be interpreted in the context of overall presentation. See Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[d] See map for prevalence of human T-cell lymphotropic virus (HTLV)-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.
[e] Primary cutaneous PTCLs with limited skin involvement may have an indolent disease course, are very heterogeneous, and the optimal management may not be along these guidelines.
[f] AITL may occasionally present with concurrent diffuse large B-cell lymphoma (DLBCL) and Epstein-Barr virus (EBV) and appropriate IHC should be performed. Clonal hematopoiesis in AITL is considered as a risk factor for cardiovascular disease.
[g] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.

TCEL-1

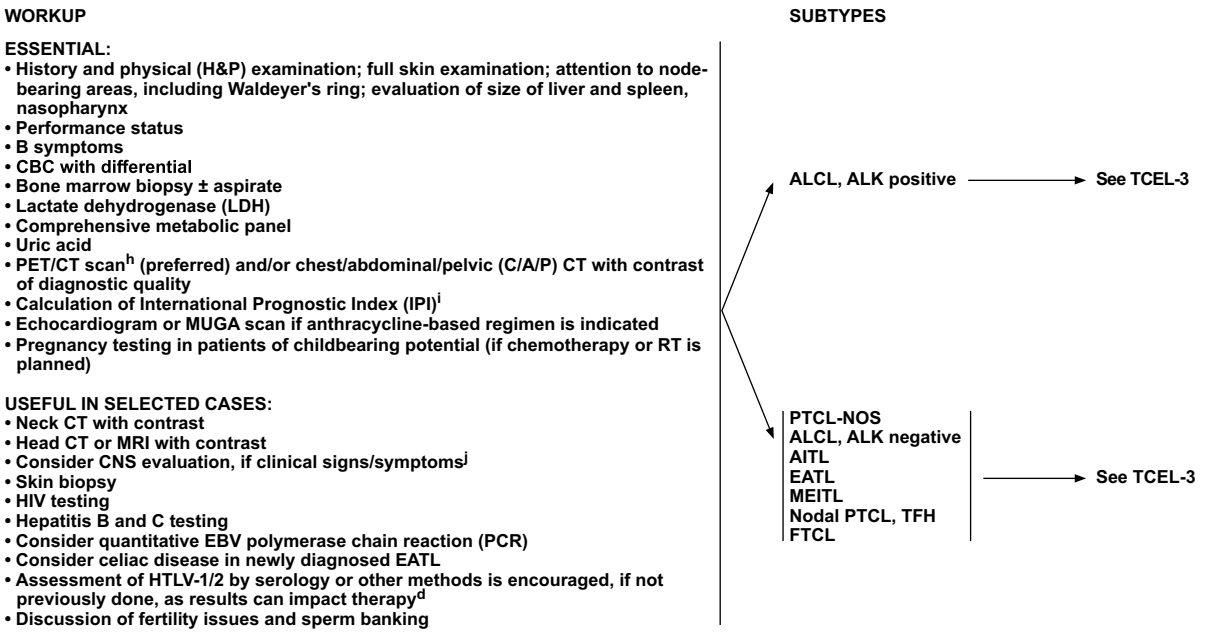
Overview

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoproliferative disorders arising from mature T-cells, accounting for about 10% of non-Hodgkin lymphomas (NHLs).[1] PTCL-not otherwise specified (PTCL-NOS; 26%) is the most common subtype, followed by angioimmunoblastic T-cell lymphoma (AITL; 19%), anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive (7%), ALCL, ALK-negative (6%), and enteropathy-associated T-cell lymphoma (EATL; <5%).[2] In the 2017 WHO classification, nodal PTCL with T-follicular helper (TFH) phenotype (PTCL,TFH) and follicular T-cell lymphoma (FTCL) are also included as provisional entities of TFH origin (which were previously classified as PTCL-NOS).[3]

PTCL-NOS most often involves nodal sites; however, many patients present with extranodal involvement, including the liver, bone marrow, gastrointestinal tract, and skin. PTCL-NOS is associated with poorer overall survival (OS) and event-free survival (EFS) rates compared with aggressive B-cell lymphomas.[4,5] Gene expression profiling studies and immunohistochemistry (IHC) algorithms have identified 2 major molecular subgroups of PTCL-NOS (characterized by high expression of either GATA3 or TBX21).[6–9] In a multivariate analysis, a high international prognostic index (IPI) score and PTCL-GATA3 subtype identified by IHC were independently associated with poor OS.[9] The 2017 WHO classification also recognizes the clinical significance of GATA3 and TBX21 expression in PTCL-NOS subtypes.[3]

AITL is the classic form of the TFH phenotype, usually presents with generalized lymphadenopathy, and is often with associated hypergammaglobulinemia, hepatomegaly or splenomegaly, eosinophilia, skin rash, and fever.[10] AITL is also characterized by the frequent presence of Epstein-Barr virus (EBV)-positive B cells and cases of coexistent EBV+ DLBCL are reported.[10–12] AITL occurs mainly in older patients, and the prognosis is similar to PTCL-NOS.[5,13]

ALCL is a CD30-expressing subtype that accounts for fewer than 5% of all cases of NHL. There are now 4 distinctly recognized subtypes of ALCL: systemic ALCL, ALK-positive; systemic ALCL, ALK-negative; breast implant-associated ALCL (BIA-ALCL), and primary cutaneous ALCL. ALCL, ALK-positive is most common in children and young adults and is characterized by the overexpression of ALK-1 protein, resulting from a chromosomal translocation [t(2;5)] in 40%–60% of patients.[14] Most patients with systemic ALCL present with advanced stage III or IV disease (65% for ALK-positive and 58% for ALK-negative) frequently associated with systemic



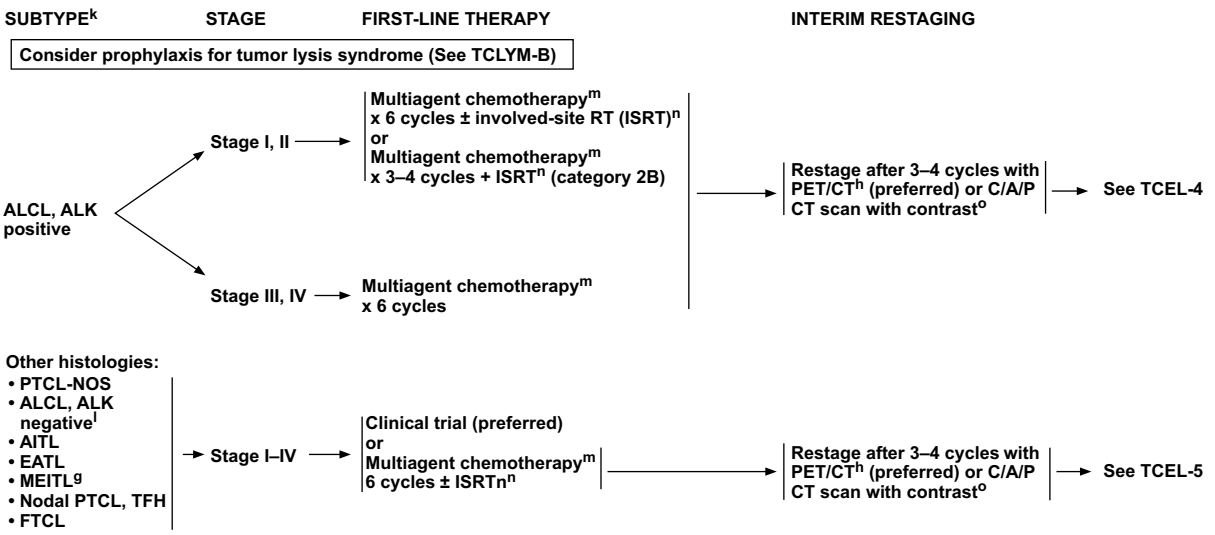
[d] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.
[h] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan is preferred.
[i] See International Prognostic Index (TCEL-A).
[j] The role of intrathecal prophylaxis in PTCL is largely unknown.

TCEL-2

symptoms and extranodal involvement.[15] In the 2017 WHO classification, ALCL, ALK-negative is listed as a definite entity.[3] BIA-ALCL represents a distinct entity from systemic ALCL and other forms of primary breast lymphoma (which are usually of B-cell origin). BIA-ALCL is included as a provisional entity in the 2017 WHO classification.[3] See the full NCCN Guidelines for T-Cell Lymphomas (available at NCCN.org) for the diagnosis and management of BIA-ALCL.

IHC, FISH, and gene expression profiling studies have identified molecular subtypes of ALCL, ALK-negative characterized by the presence of dual-specificity phosphatase 22 (*DUSP22*) and *TP63* rearrangements.[16–19] In earlier reports, the presence of *DUSP22* rearrangement (identified in 30% of all ALCL, ALK-negative cases) was associated with a favorable prognosis (5-year OS rate 80%–90%), whereas the presence of *TP63* rearrangement (occurring in about 8% of cases) was associated with a worse prognosis (5-year OS rate of 17%).[16,17] In a more recent report, the outcome of ALCL, ALK-negative with a *DUSP22* rearrangement was inferior to that observed in earlier studies (5-year progression-free survival [PFS] and OS rates of 40%), and cases with *DUSP22*-rearrangement were also associated with some high-risk features (probably contributing to lower survival outcome).[19] Nevertheless, outcomes in the presence of *DUSP22*-rearrangement were significantly better than both ALCL, ALK-negative with *TP63* rearrangements (5-year OS rate of 17% as reported in the earlier studies) and triple negative ALCL lacking all 3 rearrangements of *ALK, DUSP22*, and *TP63* (5-year PFS and OS rates were 19% and 28%, respectively).

EATL is a rare T-cell lymphoma of the small intestine, accounting for less than 1% of all NHLs, and is associated with a very poor prognosis.[20–23] The median age of diagnosis is 60 years. In the previous WHO classifications, EATLs were classified as EATL type I and EATL type II, but only EATL type I was truly associated with enteropathy (celiac disease). In the 2017 WHO classification, the 2 diseases are redefined as separate entities. EATL type 1 (associated with celiac disease) is now listed as EATL whereas EATL type II has been renamed as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).[3] In the analysis from the International T-Cell Lymphoma Project, EATL comprised 5% of all PTCL and natural killer (NK)-cell lymphomas included in the study.[23] EATL was more common (66%) than MEITL (34%). With a median follow-up of 11 months, the median OS and failure-free survival (FFS) were 10 months and 6 months for EATL and MEITL, respectively. The 5-year



[g] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[h] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan is preferred.
[k] For selected patients, palliative therapy for symptom management may be considered. See TCEL-B 2 of 7 for palliative treatment options.
[l] ALCL, ALK-negative with a *DUSP22* rearrangement has been variably associated with a prognosis more similar to ALK-positive disease and treatment according to the ALCL, ALK-positive algorithm may be considered for ALK-negative ALCL with *DUSP22* rearrangement (Parrilla Castellar ER, et al. Blood 2014;124:1473-1480; Pedersen MB, et al. Blood 2017;130:554-557; Hapgood G, et al. Br J Haematol 2019;186:e28-e31).
[m] See Suggested Treatment Regimens (TCEL-B).
[n] See Principles of Radiation Therapy (TCLYM-D).
[o] Other baseline imaging studies relevant for response assessment should be repeated as well.

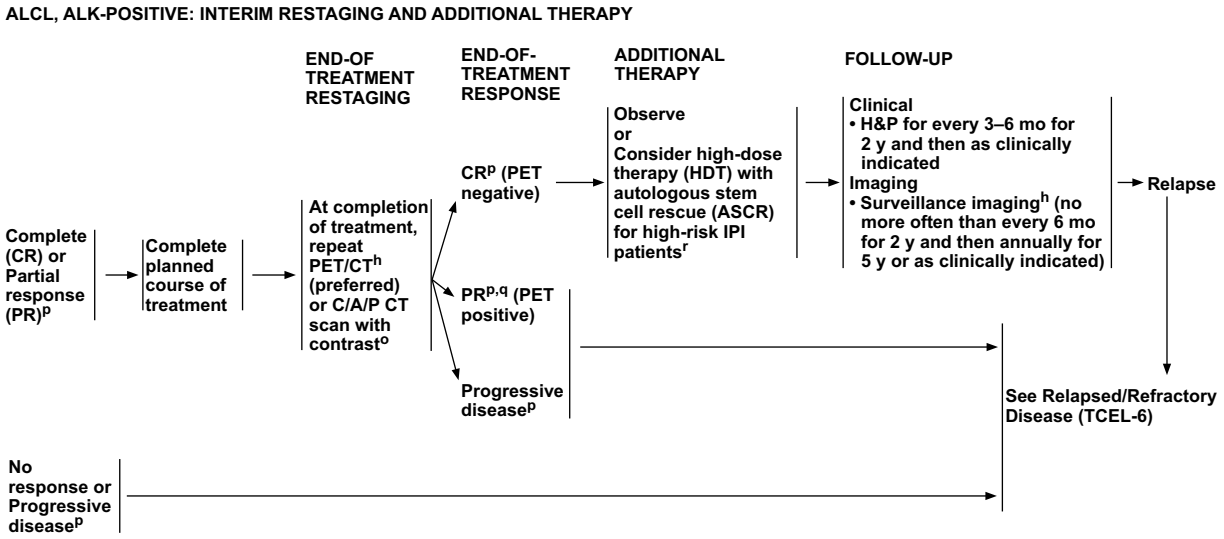
OS and FFS rates were 20% and 4%, respectively. The optimal treatment for MEITL has not yet been defined.

Prognosis

PTCLs carry a poorer prognosis than aggressive B-cell lymphomas because they are less responsive to and have less frequent durable remissions with standard anthracycline-based chemotherapy regimens. Progress has been further hampered by the relative rarity and the biologic heterogeneity. In general, ALCL, ALK-positive is associated with better clinical outcomes than ALCL, ALK-negative, PTCL-NOS, or AITL. The favorable prognosis of ALK-1 positivity, however, is diminished with older age and higher prognostic risk scores.[24–28] In an analysis of 341 patients with newly diagnosed PTCL treated with anthracycline-based chemotherapy, the 3-year PFS and OS rates (32% and 52%, respectively) were significantly inferior to the matched cohort of patients with diffuse large B-cell lymphoma (DLBCL) and there was no clear benefit for patients undergoing consolidative hematopoietic cell transplant (HCT).[27] Stage I–II disease was the only significant pretreatment prognostic factor in the multivariate analysis. ALK positivity was a prognostic factor on univariate analysis but lost its significance on multivariate analysis.

In the survival analysis from the International T-Cell Lymphoma Project, ALCL, ALK-positive was associated with significantly better prognosis with anthracycline-containing regimens compared with ALCL, ALK-negative, both in terms of the 5-year FFS rate (60% vs 36%; P=.015) and OS rate (70% vs 49%; P=.016). ALK-negative was associated with superior survival rates when compared with PTCL-NOS (5-year FFS and OS rates were 20% and 32%, respectively).[25]

In a report from the GELA study, which included the largest series of patients with AITL (n=157), 5- and 7-year OS rates were 33% and 29%, respectively, reaching an apparent plateau around 6 years.[13] The corresponding EFS rates were 29% and 23%, respectively. In the recently published survival analyses from the International T-Cell Lymphoma Project, 5-year PFS and OS rates were 43% and 49%, respectively, for patients with ALCL, ALK-negative treated with multiagent chemotherapy regimens and the estimated 5-year PFS and OS rates were 32% and 44%, respectively, for patients with AITL.[29,30] A novel prognostic score (AITL score) based on age (age ≥60 years; ECOG performance score >2; elevated C-reactive protein and elevated β2 microglobulin) stratified patients into 3 risk groups (low-, intermediate-, and high-risk) with estimated 5-year OS rates of 63%, 54%, and 21%, respectively.[30]



[h] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan is preferred.
[o] Other baseline imaging studies relevant for response assessment should be repeated as well.
[p] See Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYM-C*).
[q] Repeat biopsy should be considered (strongly consider for AITL since it may occasionally present with concurrent DLBCL) for persistent or new PET-positive lesions prior to additional therapy.
[r] Localized areas can be irradiated before or after HDT. See Principles of Radiation Therapy (TCLYM-D).

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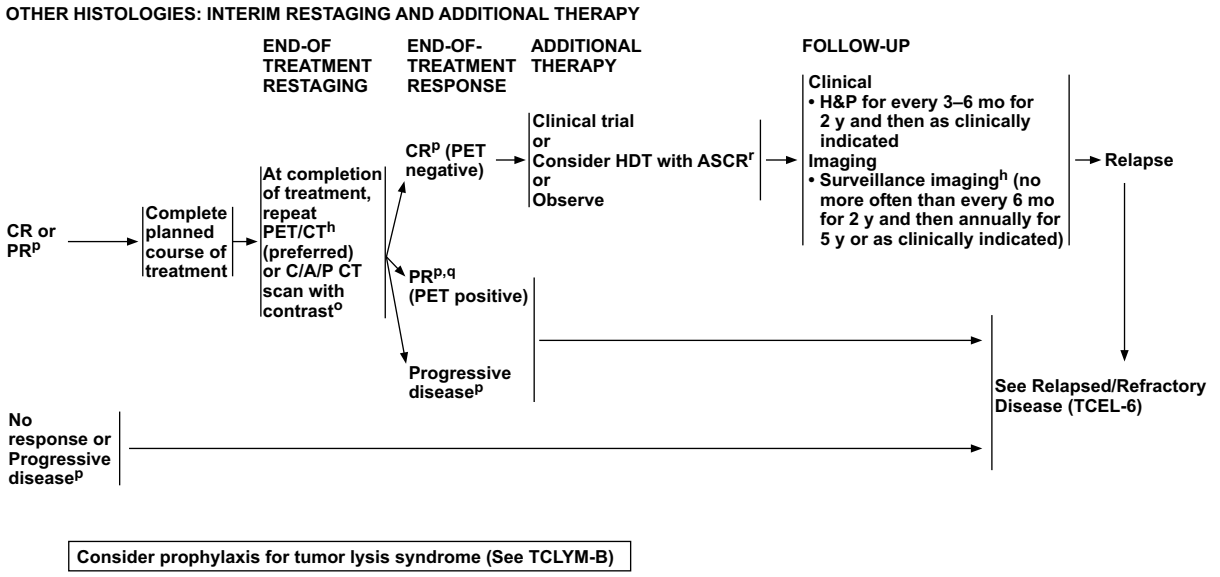
Historically, the IPI and NCCN-IPI developed for DLBCL have been used for the risk stratification of patients with PTCL.[4,15,31] Prognostic Index for PTCL-U (PIT) and T-cell score are the new prognostic models that have been developed for the risk stratification of patients with PTCL-NOS.[32,33] PIT is based on the following risk factors: age >60 years, elevated lactate dehydrogenase levels, performance status of 2 or more, and bone marrow involvement.[32] The 5-year OS rate was 33% for patients with 2 risk factors and 18% for those with 3 or 4 risk factors. This prognostic index also identified a subset of patients with relatively favorable prognosis who had no adverse risk factors.[32] This group represented 20% of patients and had a 5-year OS rate of 62%. T-cell score (developed by the International T-cell Project Network) is based on 4 clinical variables: serum albumin, performance status, stage, and absolute neutrophil count. T-cell score stratified patients into 3 risk groups (low-, intermediate-, and high-risk) with estimated 3-year OS rates of 76%, 43%, and 11%, respectively.[33]

In a pooled analysis of 3 international cohorts of nodal PTCL, all 3 indices (IPI, NCCN-IPI, and PIT) demonstrated better risk stratification for ALK-ALCL and PTCL-NOS.[34] However, none of the indices were useful for prognostication or stratification in AITL. IPI, NCCN-IPI, and PIT can be used to stratify for prognosis and under certain circumstances may aid in guiding treatment decisions for patients with PTCL.

Progression of disease within 24 months (POD24) after primary treatment has been identified as a predictor of survival in patients with newly diagnosed PTCL. In a large multinational cohort study of 775 patients with newly diagnosed PTCL, the median OS was 5 months versus not reached for those without POD24.[35] The corresponding 5-year OS rates were 11% and 78%, respectively. The prognostic significance of POD24 in patients with newly diagnosed PTCL was also demonstrated in subsequent studies.[30,36–38] These results suggest that patients with primary refractory disease or early relapse have extremely poor survival and that POD24 could be used for risk stratification of patients with PTCL.

Diagnosis

Excisional or incisional biopsy is preferred over core needle biopsy if possible for initial diagnosis (see TCEL-1, page 286). If only core needle biopsy is feasible due to the sites of disease, a combination of core needle biopsy and fine-needle aspiration biopsy in conjunction with appropriate ancillary techniques may be sufficient for diagnosis (multiple cores should be obtained to allow for adequate workup).



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[p] See Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYM-C*).
[q] Repeat biopsy should be considered (strongly consider for AITL since it may occasionally present with concurrent DLBCL) for persistent or new PET-positive lesions prior to additional therapy.
[r] Localized areas can be irradiated before or after HDT. See Principles of Radiation Therapy (TCLYM-D).

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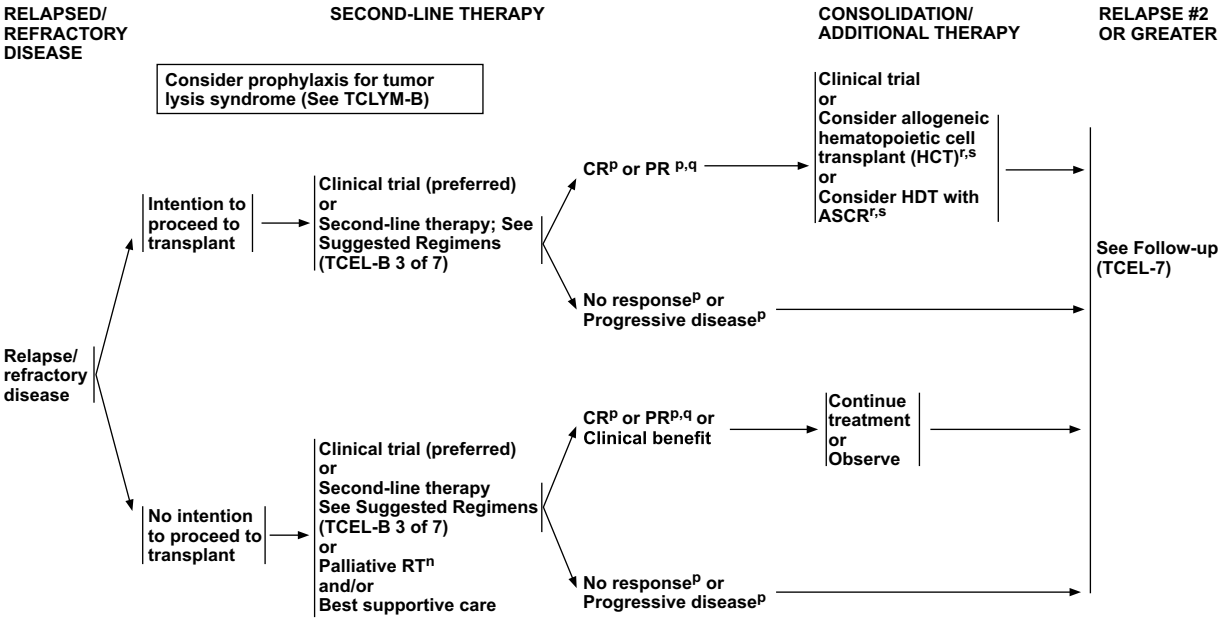
PTCL-NOS has variable T-cell–associated antigens and usually lacks B-cell–associated antigens (although aberrant CD20 expression in T-cell lymphomas is infrequently encountered). Although CD30 expression can be found at times in many T-cell lymphomas, with the exception of systemic ALCL (which has a uniform strong expression of CD30), CD30 expression by IHC (score ≥2) is variable across other subtypes of PTCL (52% in PTCL-NOS and 21% in AITL).[39] Most of the nodal cases express CD4 and lack CD8; however, CD4-/CD8+, CD4-/CD8-, and CD4+/CD8+ cases are seen.[40] In ALCL cases only, evaluation of ALK-1 status, either based on immunophenotyping or genetic analysis of the t(2;5) or variant chromosomal rearrangements, is important to identify the ALK-1–positive tumors that have a better prognosis. AITL cells express T-cell–associated antigens and are usually CD4+. Expression of CXCL13 has been identified as a useful marker that may help distinguish AITL from PTCL-NOS.[41,42]

Adequate immunophenotyping is essential to distinguish PTCL subtypes from B-cell lymphomas. The initial paraffin panel for IHC studies may only include pan–T-cell markers and can be expanded to include antibodies of T-cell lymphoma, if suspected. The IHC panel may include the following markers: CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD21, CD23, TCRbeta, TCRdelta, PD1/CD279, ALK, and TP63. Alternatively, the following markers can be analyzed by flow cytometry: CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, and CD2; and TCRalpha, TCRbeta, and TCRgamma. Additional immunohistochemical studies to evaluate for markers of TFH cell origin (CXCL13, ICOS, PD1) and cytotoxic T-cell markers (TIA-1, granzyme B, perforin) may be useful to characterize subsets of PTCL.[41–43] As noted earlier, AITL may occasionally present with concurrent EBV+ DLBCL and EBV evaluation by EBER-ISH should be performed.[10–12]

PTCL is often associated with clonal T-cell antigen receptor (*TCR*) gene rearrangements that are less frequently seen in noncancer T-cell diseases, although false-positive results or nonmalignant clones can at times be identified. Under certain circumstances, molecular analysis to detect clonal *TCR* gene rearrangements and translocations involving the *ALK* gene [ie, t(2;5) or variant] may be useful. Molecular analysis to detect *DUSP22* rearrangement and *TP63* rearrangement (if IHC is positive for TP63) may be useful for patients with ALCL, ALK-negative. As discussed previously, ALCL, ALK-negative with *DUSP22* rearrangement has been associated with a favorable prognosis more similar to ALK-positive ALCL, although the



[n] See Principles of Radiation Therapy (TCLYM-D).
[p] See Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYM-C*).
[q] Repeat biopsy should be considered (strongly consider for AITL since it may occasionally present with concurrent DLBCL) for persistent or new PET-positive lesions prior to additional therapy.
[r] Localized areas can be irradiated before or after HDT. See Principles of Radiation Therapy (TCLYM-D).
[s] Many NCCN Member Institutions would recommend allogeneic HCT in this setting.

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TCEL-6

data supporting a truly favorable prognosis is inconsistent, whereas ALCL, ALK-negative with *TP63* rearrangements and triple negative ALCL (lacking all 3 rearrangements of *ALK, DUSP22*, and *TP63)* are associated with an unfavorable prognosis (inferior survival outcomes compared with ALCL, ALK-negative with *DUSP22* rearrangement).[16–19]

Workup

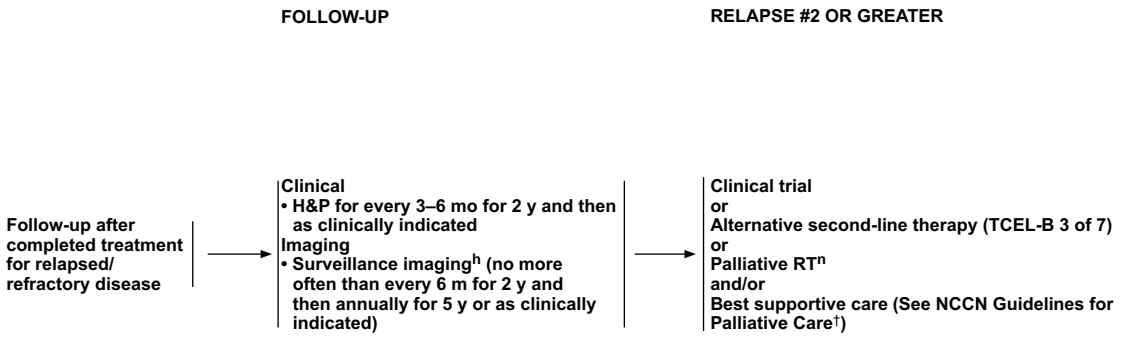
The workup for PTCL is similar to the workup for other lymphoid neoplasms, focusing on the determination of stage, routine laboratory studies (bone marrow biopsy ± aspirate, complete blood count with differential, comprehensive metabolic panel), physical examination including a full skin examination, and imaging studies, as indicated (see TCEL-2, page 287). PET/CT scan and/or chest/abdominal/pelvic CT with contrast of diagnostic quality are essential during workup. In some cases, CT scan of the neck and CT or MRI of the head may be useful. Multigated acquisition scan or echocardiogram is also recommended, since chemotherapy is usually anthracycline based. In selected cases, serology testing for HIV and human T-cell lymphotropic virus (HTLV-1) may be useful. HTLV-1 positivity, in particular, can lead to the alternate diagnosis and alternate management of adult T-cell leukemia/lymphoma for cases that would otherwise be classified as PTCL-NOS by the pathologist if positive HTLV-1 serology was not known.

First-Line Therapy

In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas and assessing the impact of chemotherapy has not been possible in this subgroup of patients with PTCLs due to small sample size. Data to support the use of multiagent combination chemotherapy for the treatment of previously untreated PTCL are available mainly from retrospective analyses and small prospective studies (as discussed subsequently).

Anthracycline-based chemotherapy regimens (eg, CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] or CHOP + etoposide [CHOEP] or dose-adjusted EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin]) are the most commonly used first-line therapy regimens because these are associated with a trend toward significance in mortality reduction.[44] However, with the exception of ALCL, ALK-positive, outcomes are not optimal in other subtypes.[5,45–49]

In a retrospective analysis of 289 patients with PTCL treated within the DSHNHL trials, CHOEP was associated with an EFS benefit in ALCL, ALK-positive in patients younger than 60 to 65 years and also in patients with



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subtypes other than ALCL, ALK-positive with low-risk IPI (IPI <1).[46] The Nordic Lymphoma Group also reported similar findings among 122 patients with ALCL, ALK-positive treated with the CHOEP regimen (5-year OS and PFS rates were 78% and 64%, respectively).[47] CHOEP regimen was associated with an improved OS in patients aged 41 to 65 years, even after adjusting for risk factors (*P*=.05). Bone marrow involvement was independently associated with poorer PFS in a multivariate analysis.

In a prospective study of 24 patients with previously untreated ALCL with a median follow-up of 14 years, dose-adjusted EPOCH resulted in EFS rates of 72% and 63% (*P*=.54), respectively, for patients with ALCL, ALK-positive and ALCL, ALK-negative, and OS rates were 78.0% and 88% (*P*=.83), respectively.[48] However, definitive conclusions from these findings are limited by the small number of patients and possible selection bias (24 patients recruited over 16 years; median patient age was 36 years for ALCL, ALK-positive and 43 years for ALCL, ALK-negative). In another prospective study from Japan that evaluated dose-adjusted EPOCH as initial therapy in 41 patients with PTCL (PTCL-NOS was the predominant subtype [n=21, 51%] followed by AITL [n=17, 42%]), the overall response rate (ORR) and complete response (CR) rate were 78% and 61%, respectively.[49] At a median follow-up of 24 months, the 2-year PFS and OS rates were 53% and 73%, respectively. The ORR, CR, PFS, and OS rates were higher among patients ≤60 years (94%, 71%, 63%, and 82%, respectively).

The use of more intensive chemotherapy regimens also has not resulted in favorable outcomes in patients with PTCL, with the exception of ALCL. In a retrospective analysis that compared CHOP with more intensive chemotherapy regimens, including hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and prednisone) in 135 patients with T-cell malignancies (PTCL-NOS, n=50; ALCL, n=40; AITL, n=14), there was a trend toward higher 3-year OS rates for patients with ALK-positive ALCL treated with hyper-CVAD regimen compared with those with ALCL, ALK-negative (100% vs 70%, respectively).[50] When the subgroup with ALCL was excluded from the analysis, the 3-year OS rate with CHOP and intensive regimen were 43% and 49%, respectively.

Results from more recent studies also suggest that the addition of anti-CD52 monoclonal antibody (alemtuzumab) or histone deacetylase (HDAC) inhibitor to CHOP did not improve survival, at least in part due to increased toxicity.[51,52] The phase III trial comparing romidepsin + CHOP versus CHOP excluded patients with ALK-positive, ALCL and did not show a statistically significant PFS benefit for romidepsin + CHOP in the entire study population (hazard ratio [HR], 0.81; 95% CI, 0.63–1.04; *P*=.096). However,

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:	INTERNATIONAL INDEX, ALL PATIENTS:	
• Age >60 years	• Low	0 or 1
• Serum LDH > normal	• Low-intermediate	2
• ECOG Performance Status 2–4	• High-intermediate	3
• Stage III or IV	• High	4 or 5
• Extranodal involvement >1 site		

PROGNOSTIC INDEX FOR PTCL-U (PIT)[b]

RISK FACTORS:	PROGNOSTIC RISK:	
• Age >60 years	• Group 1	0
• Serum LDH > normal	• Group 2	1
• ECOG Performance Status 2–4	• Group 3	2
• Bone marrow involvement	• Group 4	3 or 4

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:	INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:	
• Stage III or IV	• Low	0
• Serum LDH > normal	• Low-intermediate	1
• ECOG Performance Status 2–4	• High-intermediate	2
	• High	3

PROGNOSTIC INDEX FOR PTCL-U (modified-PIT)[c]

RISK FACTORS:	PROGNOSTIC RISK:	
• Age >60 years	• Group 1	0 or 1
• Serum LDH > normal	• Group 2	2
• ECOG Performance Status 2–4	• Group 3	3 or 4
• Ki-67 ≥80%		

INTERNATIONAL T-CELL LYMPHOMA PROJECT[d]

RISK FACTORS:		
• Age >60 years	• Group 1	0
• ECOG Performance Status 2–4	• Group 2	1
• Platelet count (<150 x 10^9/L)	• Group 3	2
	• Group 4	3

[a] International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987-994.
[b] Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-2479.
[c] Went P, Agostinelli C, Gallamini A, et al. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol 2006;24:2472-2479.
[d] Vose JM. International peripheral T-cell lymphoma (PTCL) clinical and pathologic review project: poor outcome by prognostic indices and lack of efficacy with anthracyclines [abstract]. Blood 2005;106:Abstract 811a.

TCEL-A

an exploratory analysis suggests a PFS benefit for romidepsin + CHOP in a subgroup of patients with histologically confirmed PTCL-TFH subtype (20 vs 11 months for CHOP).[52] Although statistical considerations preclude any firm conclusion, these findings are consistent with other reports that have suggested HDAC inhibitors may have superior activity in PTCL with TFH phenotype compared with non-TFH PTCL.[53,54] The addition of azacitidine to CHOP has also been shown to induce high CR rate in PTCL-TFH subtype, and this combination will be further evaluated in a randomized study.[55]

The phase III randomized trial (ECHELON-2) showed that brentuximab vedotin in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) was superior to CHOP for the treatment of patients with previously untreated CD30-positive PTCL (defined in ECHELON-2 as CD30 expression on ≥10% of cells), resulting in significantly improved PFS and OS.[56,57] In this trial, 452 patients were randomly assigned to either brentuximab vedotin + CHP or CHOP, and most (70%) patients had ALCL (48% ALCL, ALK-negative and 22% ALCL, ALK-positive). After a median follow-up of 5 years, the median PFS was 63 months versus 24 months for brentuximab vedotin + CHP and CHOP, respectively. The estimated 5-year PFS rates were 51% and 43%, respectively.[57] The median OS was not reached for either arm, and the estimated 5-year OS rates were 69% and 60% for brentuximab vedotin + CHP and CHOP, respectively. The ORR (83% vs 72%) and CR rate (68% vs 56%) were also higher for brentuximab vedotin + CHP compared with CHOP. The estimated 5-year PFS rates were 60% for brentuximab vedotin + CHP vs 48% for CHOP in the subset of patients with ALCL (HR, 0.55). The survival benefit (clearly established for the subset of patients with ALCL) was less clear across other histologic subtypes (the HR for PFS and OS were 0.75 and 0.83, respectively, for PTCL-NOS, and the corresponding HRs were 1.4 and 0.87, respectively, for AITL), all with wide confidence intervals.[56] However, this study was not powered to compare efficacy of brentuximab vedotin + CHP within individual histologic subtypes due to small subgroup sizes. Neutropenia (35%), anemia (13%), diarrhea (6%), peripheral neuropathy (4%), and nausea (2%) were the most common grade ≥3 adverse events with brentuximab vedotin + CHP. Peripheral neuropathy associated with brentuximab vedotin continued to improve or resolve with long-term follow-up. Based on the results of the ECHELON-2 trial, brentuximab vedotin in combination with CHP was approved by the FDA as a first-line therapy for patients with untreated systemic ALCL or other CD30-

SUGGESTED TREATMENT REGIMENS[a]

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

FIRST-LINE CONSOLIDATION

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

See Initial Palliative Intent Therapy (TCEL-B 2 of 7)

See Second-line and Subsequent Therapy:
• PTCL-NOS; EATL; MEITL; FTCL (TCEL-B 3 of 7)
• AITL, including nodal PTCL, TFH (TCEL-B 4 of 7)
• ALCL (TCEL-B 5 of 7)

[a] See references for regimens on TCEL-B 6 of 7* and TCEL-B 7 of 7*.
[b] While anthracycline-based regimens confer a favorable prognosis in ALCL, ALK-positive, these regimens have not provided the same favorable results for other PTCL histologies; clinical trial is therefore preferred for the management of these other histologies.
[c] ALCL, ALK-negative with a *DUSP22* rearrangement has been variably associated with a prognosis more similar to ALK-positive disease and treatment according to the ALCL, ALK-positive algorithm may be considered (Parrilla Castellar ER, et al. Blood 2014;124:1473-1480; Hapgood G, et al. Br J Haematol 2019;186:e28-e31; Pedersen MB, et al. Blood 2017;130:554-557).
[d] See Supportive Care (TCLYM-B).
[e] Oral etoposide dose of 200 mg/m^2 (PO dosing of etoposide is 2x the IV dose) may be substituted on day 2 and 3 for IV etoposide. Consider splitting the daily doses of oral etoposide over 200 mg.
[f] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[g] Interpretation of CD30 expression is not universally standardized. Responses have been seen in patients with a low level of CD30-positivity.
[h] CHOP followed by IVE regimen includes HCT.

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expressing subtypes (≥1% CD30 expression) including PTCL-NOS and AITL.

Multiagent chemotherapy (6 cycles with or without involved-site radiation therapy [ISRT] or for 3 to 4 cycles with ISRT) is recommended for patients with stage I–II ALCL, ALK-positive, whereas multiagent chemotherapy alone for 6 cycles is recommended for patients with stage III–IV ALCL, ALK-positive (see TCEL-3, page 288).

Participation in clinical trials is the preferred management approach for patients with other subtypes (PTCL-NOS, ALCL, ALK-negative, AITL, EATL, MEITL, nodal PTCL, TFH, and follicular T-cell lymphoma). In the absence of suitable clinical trials, multiagent chemotherapy (6 cycles) with or without ISRT is recommended for all patients (stage I–IV disease; see TCEL-3, page 288). ALK-negative with a *DUSP22* rearrangement has been variably associated with a prognosis more similar to ALK-positive ALCL and could be treated according to the algorithm for ALCL, ALK-positive.[16–19]

Based on results of the ECHELON-2 trial and FDA approval, brentuximab vedotin + CHP is included as a preferred first-line therapy option for patients with ALCL (category 1) or other CD30-positive histologies (category 2A; see TCEL-B 1 of 7, above). As noted earlier, CD30 expression is variable across the PTCL subtypes other than ALCL.[39] Interpretation of CD30 expression is not universally standardized, and responses with brentuximab vedotin have been observed at all levels of CD30 expression, including in patients with very low or absent CD30 expression.[58] CHOP, CHOEP, dose-adjusted EPOCH, or hyper-CVAD are included as other options for multiagent chemotherapy.

CHOP followed by IVE (ifosfamide, etoposide, and epirubicin) alternating with intermediate-dose methotrexate (MTX) as initial therapy resulted in a median PFS and OS of 3 months and 7 months, respectively, in patients with EATL.[59] The 5-year PFS and OS rates (52% and 60%, respectively) were significantly higher in historical comparison with the corresponding survival rates (5-year PFS and OS rates were 22%) reported with conventional anthracycline-based chemotherapy regimens. CHOP followed by IVE alternating with MTX may be an appropriate first-line therapy option for patients with EATL.

First-Line Consolidation Therapy

Several nonrandomized prospective studies[59–70] and retrospective analyses[28,71–74] have reported favorable outcomes in patients with PTCL undergoing first-line consolidation with high-dose therapy followed by autologous stem cell rescue (HDT/ASCR). Some studies have reported that the

SUGGESTED TREATMENT REGIMENS[a]

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

See First-line Therapy on TCEL-B 1 of 7.

See Second-line and Subsequent Therapy:
PTCL-NOS; EATL; MEITL (TCEL-B 3 of 7)
AITL, including nodal PTCL, TFH and FTCL (TCEL-B 4 of 7)
ALCL (TCEL-B 5 of 7)

[a] See references for regimens on TCEL-B 6 of 7* and TCEL-B 7 of 7*.
[d] See Supportive Care (TCLYM-B).
[f] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[g] Interpretation of CD30 expression is not universally standardized. Responses have been seen in patients with a low level of CD30-positivity.
[i] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. Recommend cytomegalovirus (CMV) monitoring or prophylaxis. (See TCLYM-B).
[j] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[k] In the phase II study, the preferred dosing regimen of duvelisib was 75 mg for 2 cycles followed by 25 mg BID for long-term disease control.
[l] See Principles of Radiation Therapy (TCLYM-D).
[m] With close follow-up of renal function.
[n] In AITL, pralatrexate has limited activity.
[o] Alectinib has shown activity in patients with CNS involvement.

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achievement of CR before HDT/ASCR is an independent predictor of improved survival in patients receiving first-line consolidation with ASCR.[61,65,74,75]

A recent report from Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE), a prospective multicenter cohort study, suggests that consolidation of first complete remission (CR1) with HDT/ASCR may provide a survival benefit in selected patients with PTCL (eg, patients with advanced-stage disease or intermediate-to-high IPI scores).[76] Consolidation with HDT/ASCR significantly improved OS and PFS for patients with AITL but not for patients with other PTCL subtypes. In a randomized phase III study that evaluated the role of autologous versus allogeneic HCT following an anthracycline-based induction therapy in patients with high-risk nodal PTCL, the EFS and OS outcomes were similar for patients in both treatment arms.[77] With a median follow-up of 42 months, the 3-year EFS rates were 43% and 38%, respectively, for patients randomized to allogenic HCT and autologous HCT. The corresponding 3-year OS rates were 57% and 70%, respectively. However, autologous HCT was associated with a much higher relapse rate (36% vs 0%), and allogeneic HCT resulted in much higher transplant-related mortality (31% vs 0%).

In the ECHELON-2 trial, first-line consolidation with HCT was permitted (at investigator's discretion) and althouogh those who received HCT in CR1 appeared to have superior PFS, the benefits of brentuximab vedotin + CHP was retained in both groups of patients (with and without HCT).[56] In the aforementioned analysis from the International T-Cell Lymphoma Project, consolidation with autologous HCT after CR to first-line therapy was associated with improved outcomes in patients with AITL.[30] There is, however, no definitive study on the benefits of HCT as consolidation of first remission, with other retrospective studies showing no survival advantage for patients with PTCL-NOS, AITL, or ALCL, ALK-negative.[78–80]

In the absence of data from randomized controlled trials, available evidence (as discussed previously) suggests that HDT/ASCR is a reasonable treatment option only in patients with disease responding to induction therapy (although it is associated with a high relapse rate).[76,77] Longer follow-up and preferably data from a prospective randomized trial are necessary to evaluate the impact of first-line consolidation therapy with HDT/ASCR on time-to-treatment failure and OS outcomes.

SUGGESTED TREATMENT REGIMENS[a]
PTCL-NOS; EATL; MEITL[f]

SECOND-LINE THERAPY AND SUBSEQUENT THERAPY (WITH INTENTION TO PROCEED TO TRANSPLANT)

- Clinical trial preferred

Preferred regimens

- Single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ PTCL[d,g]
  - Pralatrexate
  - Romidepsin
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Other recommended regimens

- Single agents (alphabetical order)
  - Bendamustine[d]
  - Duvelisib[k]
  - Gemcitabine
  - Lenalidomide[d]
- Combination regimen
  - GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[p]

SECOND-LINE AND SUBSEQUENT THERAPY (NO INTENTION TO TRANSPLANT)

- Clinical trial preferred

Preferred regimens (alphabetical order)

- Belinostat
- Brentuximab vedotin for CD30+ PTCL[d,g]
- Pralatrexate
- Romidepsin

Other recommended regimens (alphabetical order)

- Alemtuzumab[i]
- Bendamustine[d]
- Bortezomib[j] (category 2B)
- Cyclophosphamide and/or etoposide (IV or PO)
- Duvelisib[k]
- Gemcitabine
- Lenalidomide[d]
- RT[l]

See First-line Therapy on TCEL-B 1 of 7.
See Second-line and Subsequent Therapy:
AITL, including nodal PTCL, TFH and FTCL (TCEL-B 4 of 7)
ALCL (TCEL-B 5 of 7)

[a] See references for regimens on TCEL-B 6 of 7* and TCEL-B 7 of 7*.
[d] See Supportive Care (TCLYM-B).
[f] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[g] Interpretation of CD30 expression is not universally standardized. Responses have been seen in patients with a low level of CD30-positivity.
[i] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. CMV monitoring or prophylaxis is recommended. (See TCLYM-B).
[j] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[k] In the phase II study, the preferred dosing regimen of duvelisib was 75 mg for 2 cycles followed by 25 mg BID for long-term disease control.
[l] See Principles of Radiation Therapy (TCLYM-D).
[p] Data suggest there may be excessive pulmonary toxicity with GVD (gemcitabine, vinorelbine, liposomal doxorubicin) regimen when used in combination with unconjugated anti-CD30 monoclonal antibodies for the treatment of Hodgkin lymphoma (Blum KA, et al. Ann Oncol 2010;21:2246-2254). A similar regimen, gemcitabine and liposomal doxorubicin, may be used for mature T-cell lymphoma; however, it is recommended to wait 3 to 4 weeks following treatment with brentuximab vedotin before initiation.

*Available online, in these guidelines, at NCCN.org.

Response Assessment and Additional Therapy

Recent studies that have evaluated the utility of PET scans for assessment of response to therapy suggest that a positive interim PET scan after first- or second-line therapy for relapsed/refractory disease is an independent predictor of survival outcomes, thus suggesting that the use of interim PET scans may be helpful for risk stratification and could be used for risk-adapted treatment approach in patients with PTCL.[81–87] However, the optimal use of interim PET scans for the evaluation of response to treatment has not yet been established in a prospective study.

The use of a 5-point scale (5-PS) is recommended for the interpretation and reporting of PET/CT scans. The 5-PS is based on the visual assessment of FDG uptake in the involved sites relative to that of the mediastinum and the liver.[88–90] Different clinical trials have considered scores of either 1 to 2 or 1 to 3 to be PET negative, while scores of 4 to 5 are universally considered PET-positive. A score of 4 on an interim or end-of-treatment restaging scan may be consistent with a partial response (PR) if the FDG avidity has declined from initial staging, while a score of 5 denotes progression of disease.

The guidelines recommend interim restaging with PET/CT (preferred) or CT after 3 to 4 cycles of chemotherapy. Completion of planned course of treatment followed by end-of treatment restaging is recommended for all patients achieving CR or partial response PR to first-line therapy. Patients with no response or progressive disease after initial therapy should be managed as outlined for relapsed or refractory disease.

Patients with a CR at end of treatment can either be observed or treated with first-line consolidation with HDT/ASCR. First-line consolidation should be considered for all patients with subtypes other than ALCL, ALK-positive (see TCEL-5, page 290). Among patients with ALCL, ALK-positive, first-line consolidation should be considered only for patients with high-risk IPI (see TCEL-4, page 289). Localized areas can be treated with radiation therapy before or after HDT. Rebiopsy should be considered (especially for patients with AITL because it may occasionally present with concurrent DLBCL) before addition therapy for patients with PR (persistent or new PET-positive lesions) at end-of-treatment restaging.

Treatment of Relapsed or Refractory Disease

HDT/ASCR[91–97] and allogeneic HCT[95,96,98–103] have only been evaluated in retrospective studies in patients with relapsed or refractory PTCL-NOS. The general conclusion from these studies is that HDT/ASCR less frequently results

SUGGESTED TREATMENT REGIMENS[a]
AITL, INCLUDING NODAL PTCL, TFH AND FTCL

SECOND-LINE THERAPY AND SUBSEQUENT THERAPY (WITH INTENTION TO PROCEED TO TRANSPLANT)

- Clinical trial preferred

Preferred regimens

- Single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ AITL[d,g]
  - Romidepsin
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Other recommended regimens

- Single agents (alphabetical order)
  - Bendamustine[d]
  - Duvelisib[k]
  - Gemcitabine
  - Lenalidomide[d]
  - Pralatrexate[n]

SECOND-LINE AND SUBSEQUENT THERAPY (NO INTENTION TO TRANSPLANT)

- Clinical trial preferred

Preferred regimens (alphabetical order)

- Belinostat
- Brentuximab vedotin for CD30+ AITL[d,g]
- Romidepsin

Other recommended regimens (alphabetical order)

- Alemtuzumab[i]
- Bendamustine[d]
- Bortezomib[j] (category 2B)
- Cyclophosphamide and/or etoposide (IV or PO)
- Cyclosporine[l]
- Duvelisib[k]
- Gemcitabine
- Lenalidomide[d]
- Pralatrexate[n]
- RT[l]

See First-line Therapy on TCEL-B 1 of 7.
See Second-line and Subsequent Therapy:
PTCL-NOS; EATL; MEITL (TCEL-B 3 of 7)
ALCL (TCEL-B 5 of 7)

[a] See references for regimens on TCEL-B 6 of 7* and TCEL-B 7 of 7*.
[d] See Supportive Care (LYMP-B*).
[g] Interpretation of CD30 expression is not universally standardized. Responses have been seen in patients with a low level of CD30-positivity.
[i] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. Recommend CMV monitoring or prophylaxis. (See TCLYM-B).
[j] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[k] In the phase II study, the preferred dosing regimen of duvelisib was 75 mg for 2 cycles followed by 25 mg BID for long-term disease control.
[l] See Principles of Radiation Therapy (TCLYM-D).
[m] With close follow-up of renal function.
[n] In AITL, pralatrexate has limited activity.

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in durable benefit in patients with relapsed or refractory disease as compared with allogeneic HCT. However, this conclusion is not universal in the literature and HDT/ASCR has been associated with a survival benefit more often in patients with ALCL subtype and chemosensitive disease than in those with non-ALCL subtypes and less chemosensitive disease.[91,93,95] The cumulative incidence of nonrelapse mortality was also higher with allogeneic HCT compared with HDT/ASCR.[95] Allogeneic HCT using reduced-intensity conditioning may provide a more reliably curative option for the majority of patients with relapsed or refractory PTCL, based on the patient's eligibility for transplant.[98–101] Further data from prospective studies are needed to determine the role of HDT/ASCR and allogeneic HCT in patients with relapsed/refractory PTCL.

Second-line therapy for relapsed/refractory disease remains suboptimal, even with the incorporation of HDT/ASCR or allogeneic HCT. Among the 420 evaluable patients with relapsed and refractory PTCL from the COMPLETE registry, outcomes were inferior for patients with refractory disease compared with those with relapsed disease.[104] The median OS was 29 months and 12 months, respectively, for patients with relapsed and refractory disease. Participation in a clinical trial is strongly preferred for patients with relapsed/refractory disease. In the absence of a suitable clinical trial, the initial treatment of relapsed/refractory disease depends largely on the patient's eligibility for transplant.

Second-line systemic therapy followed by consolidation with HDT/ASCR or allogeneic HCT for those with a CR or PR is recommended for patients who are candidates for transplant (see TCEL-6, page 291). Localized relapse (limited to 1 or 2 sites) may be treated with ISRT before or after HDT/ASCR. Allogeneic HCT, when feasible, should be considered for the majority of patients with relapsed/refractory disease. HDT/ASCR may be an appropriate option, particularly those with ALCL and for selected patients with other subtypes with chemosensitive relapsed disease. Patients who are not candidates for transplant should be treated with second-line systemic therapy or palliative radiation therapy.

Data from clinical trials supporting the use of second-line systemic therapy options recommended in the guidelines (TCEL-B 3 through 6) are discussed subsequently.

Brentuximab Vedotin

The safety and efficacy of brentuximab vedotin (an antibody-drug conjugate that targets CD30-expressing malignant cells) in patients with relapsed or refractory systemic

SUGGESTED TREATMENT REGIMENS[a]
ALCL

SECOND-LINE THERAPY AND SUBSEQUENT THERAPY (WITH INTENTION TO PROCEED TO TRANSPLANT)

- Clinical trial preferred

Preferred regimen
- Brentuximab vedotin[d]

Other recommended regimens
- Single agents (alphabetical order)
  - Alectinib (ALK+ ALCL only)[o]
  - Belinostat
  - Bendamustine[d]
  - Crizotinib (ALK+ ALCL only)
  - Duvelisib[k]
  - Gemcitabine
  - Pralatrexate
  - Romidepsin
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

SECOND-LINE AND SUBSEQUENT THERAPY (NO INTENTION TO TRANSPLANT)

- Clinical trial preferred

Preferred regimens
- Brentuximab vedotin[d]

Other recommended regimens (alphabetical order)
- Alectinib (ALK+ ALCL only)[o]
- Belinostat
- Bendamustine[d]
- Bortezomib[l] (category 2B)
- Crizotinib (ALK+ ALCL only)
- Cyclophosphamide and/or etoposide (IV or PO)
- Duvelisib[k]
- Gemcitabine
- Pralatrexate
- RT[l]
- Romidepsin

See First-line Therapy on TCEL-B 1 of 7.
See Second-line and Subsequent Therapy:
PTCL-NOS; EATL; MEITL (TCEL-B 3 of 7)
AITL, including nodal PTCL, TFH and FTCL (TCEL-B 4 of 7)

[a] See references for regimens on TCEL-B 6 of 7* and TCEL-B 7 of 7*.
[d] See Supportive Care (TCLYM-B).
[j] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[k] In the phase II study, the preferred dosing regimen of duvelisib was 75 mg for 2 cycles followed by 25 mg BID for long-term disease control.
[l] See Principles of Radiation Therapy (TCLYM-D).
[o] Alectinib has shown activity in patients with CNS involvement.

*Available online, in these guidelines, at NCCN.org.

ALCL was initially established in a multicenter phase II study.[105] Long-term follow-up results confirmed the durability of clinical benefit of brentuximab vedotin in patients with relapsed or refractory systemic ALCL.[106] After a median follow-up of approximately 6 years, the ORR of 86% (66% CR and 21% PR) was similar to the previously reported ORR of 86% (59% CR) evaluated by an independent review committee. The estimated 5-year OS and PFS rates were 60% and 39%, respectively. The 5-year OS rate was higher for patients who experienced a CR (79% compared with 25% for those who did not experience CR). The median duration of objective response for all patients was 26 months (the median duration of response was not reached for patients with a CR). The ORRs were similar for patients with ALK-negative ALCL (88%; 52% CR) and those with ALK-positive ALCL (81%; 69% CR). The estimated 5-year OS and PFS rates were 61% and 39%, respectively, for patients with ALK-negative ALCL. The corresponding survival rates were 56% and 37%, respectively, for those with ALK-positive ALCL. Among patients who experienced a CR, the 5-year PFS rate was 60% for patients with ALK-negative ALCL and 50% for those with ALK-positive ALCL. Peripheral neuropathy was the most common adverse event reported in 57% of patients, with resolution or improvement reported in most patients with long-term follow-up.[106] In August 2011, based on the results from this study, brentuximab vedotin was approved by the FDA for the treatment of patients with systemic ALCL after failure of at least one prior multiagent chemotherapy regimen.

The planned subset analysis of a phase II multicenter study that evaluated the efficacy and safety of brentuximab vedotin in relapsed/refractory CD30-positive NHL showed that it was also effective in other subtypes of relapsed PTCL, particularly AITL.[107] This analysis included 35 patients with PTCL (22 patients with PTCL-NOS and 13 patients with AITL); the ORR, median duration of response, and median PFS for all T-cell lymphoma patients were 41%, 8 months, and 3 months, respectively. The ORR (54% vs 33%) and the median PFS (7 vs 2 months) were better for patients with AITL than those with PTCL-NOS.

Histone Deacetylase Inhibitors

HDAC inhibitors (eg, romidepsin and belinostat) have shown single-agent activity in patients with relapsed or refractory PTCL.[108–110] Romidepsin received accelerated FDA approval in June 2011 for the treatment of relapsed/refractory PTCL based on the results of the pivotal multicenter phase II study that evaluated the impact of romidepsin on the surrogate endpoint of ORR (130 patients with relapsed/refractory PTCL; PTCL-NOS, n=69 [53%]; AITL, n=27 [21%]; ALCL, ALK-negative, n=21 [16%]).[108]

PRINCIPLES OF MOLECULAR ANALYSIS IN T-CELL LYMPHOMAS[a]

- **Genetic testing, including high-throughput sequencing (HTS), array-based comparative genomic hybridization (CGH), NGS, karyotype, or FISH to detect somatic mutations or genetic abnormalities are often informative and in some cases essential for an accurate and precise diagnostic and prognostic assessment of T-cell lymphomas.**

***TCR* Gene Rearrangements**
- ***TCR* gene rearrangement testing is recommended to support a diagnosis of T-cell lymphoma.**
- **Diseases:**
  - **PTCLs; mycosis fungoides/Sézary syndrome; primary cutaneous CD30+ T-cell LPD; T-LGLL; T-PLL; ENKL; and HSTCL.**
- **Description:**
  - ***TCR* gene rearrangement is indicative of T-cell clonal expansion. The test targets the gamma and/or beta *TCR* genes using PCR methods with capillary or gel electrophoresis detection methods. Alternatively, HTS methods are increasingly used. HTS methods are more sensitive, precise, and capable of providing a unique sequence of the T-cell clone, which allows for comparison and confirmation of disease evolution and monitoring during remission. Clonal T-cell expansions can also be detected using V beta families in blood or tissue with flow cytometry methods.**
- **Diagnostic value:**
  - **Clonal *TCR* gene rearrangements without histopathologic and immunophenotypic evidence of abnormal T-cell population does not constitute a diagnosis of T-cell lymphoma since it can be identified in patients with non-malignant conditions. Conversely, a negative result does not exclude the diagnosis of T-cell lymphoma, which occasionally may fail *TCR* amplification. Nonetheless, it often provides essential information and increased precision for many of these complex diagnoses.**
- **Prognostic value:**
  - **Identification of clonal *TCR* gene rearrangement has no definitive established prognostic value; however, it could be helpful when used to determine clinical staging or assess relapsed or residual disease.**

***ALK* Gene Rearrangement**
- **A subset of CD30-positive ALCLs expresses ALK by IHC. ALK expression is often associated with t(2;5)(p23;q35), leading to the fusion of nucleophosmin (NPM1) to ALK and resulting in a chimeric protein.**
- **Detection:**
  - **FISH using probes to ALK (2p23)**
  - **Targeted messenger RNA (mRNA) sequencing**
- **Diagnostic value:**
  - **The current WHO classification of ALCLs includes two entities distinguishing ALK-positive and ALK-negative variants.**
- **Prognostic value:**
  - **Systemic ALK-positive ALCL with t(2;5) and ALK-negative ALCL with *DUSP22* rearrangement (to a lesser extent) have been associated with a favorable prognosis. ALK inhibition can be an effective therapeutic strategy.**

[a] See References on TCLYM-A 4 of 4*.

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Updated results from this study confirmed that responses were durable across all 3 subtypes of PTCL.[109] At a median follow-up of 22 months, no significant differences were seen in ORR or rates of CR between the 3 most common subtypes of PTCL. The ORRs were 29%, 30%, and 24%, respectively, for patients with PTCL-NOS, AITL, and ALCL, ALK-negative. The corresponding CR rates were 14%, 19%, and 19%, respectively. The median PFS was 20 months for all responders and it was significantly longer for patients who experienced CR for ≥12 months compared with those who experienced CR for <12 months or PR (29 months, 13 months, and 7 months, respectively). The median OS was not reached for patients who experienced CR and 18 months for those who experienced PR.[109] The most common grade ≥3 adverse events included thrombocytopenia (24%), neutropenia (20%), and infections (19%).[108]

In August 2021, the accelerated approval status for romidepsin for the treatment of relapsed/refractory PTCL was withdrawn after the results of the confirmatory phase III trial, which failed to meet the primary endpoint of improved PFS for romidepsin + CHOP in patients with previously untreated PTCL (421 patients randomized to receive romidepsin + CHOP or CHOP).[52] After a median follow-up of 28 months, the addition of romidepsin to CHOP did not result in any statistically significant improvement in ORR, PFS, or OS but increased the frequency of grade ≥3 adverse events.[52] Although the panel acknowledged the change in the regulatory status of romidepsin, the consensus of the panel was to continue the listing of romidepsin as an important option for relapsed or refractory PTCL based on the results of the earlier phase II study and subsequent studies in which romidepsin resulted in durable responses across all 3 subtypes of PTCL (ALCL, ALK-negative, PTCL-NOS, and AITL).[53,109]

The BELIEF trial evaluated belinostat in 129 patients with relapsed or refractory PTCL (pretreated with more than one prior systemic therapy).[110] The ORR in 120 evaluable patients was 26% (CR rate of 11% and PR rate of 15%). The median duration of response, median PFS, and median OS were 14 months, 2 months, and 8 months, respectively. The 1-year PFS rate was 19%.[110] The ORR was higher for AITL compared with other subtypes (45% compared with 23% and 15%, respectively, for patients with PTCL-NOS and ALCL, ALK-negative). Anemia (11%), thrombocytopenia (7%), dyspnea (6%), and neutropenia (6%) were the most common grade 3 or 4 adverse events. Belinostat was approved by the FDA in July 2014 for the treatment of relapsed or refractory

PRINCIPLES OF MOLECULAR ANALYSIS IN T-CELL LYMPHOMAS[a]

***DUSP22-IRF4* Gene Rearrangement**

- Testing for *DUSP22* rearrangement is considered if CD30-positive ALCL, ALK negative is diagnosed, and considered useful under certain circumstances for the diagnosis of primary cutaneous CD30+ T-cell LPDs.
- Diseases:
  - PTCLs, primary cutaneous CD30+ T-cell LPDs.
- Description:
  - *DUSP22* (dual-specificity phosphatase 22) is a tyrosine/threonine/serine phosphatase that may function as a tumor suppressor. *DUSP22* inactivation contributes to the development of PTCLs.
- Detection:
  - FISH using probes to *DUPS22-IRF4* gene region at 6p25.3.
- Diagnostic value:
- *DUSP22* rearrangements are associated with a newly recognized variant of ALK-negative ALCL and a newly reported subtype of lymphomatoid papulosis.
- Prognostic value:
  - ALCL, ALK negative with *DUSP22* rearrangement has preliminarily been associated with a favorable prognosis; however, the impact of this on choice of therapy is not currently known.

***TP63* Rearrangement**

- *TP63* gene rearrangements encoding p63 fusion proteins define a subset of ALK-negative ALCL cases and are associated with aggressive course.
- Detection:
  - FISH using probes to *TP63* (3q28) and *TBL1XR1*/*TP63*
  - Targeted mRNA sequencing
- Disease:
  - ALK-negative ALCL
- Diagnostic value:
  - To identify ALK-negative ALCL cases associated with aggressive course

[a] See References on TCLYM-A 4 of 4*.

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PTCL. Belinostat induced responses across all types of PTCL (with the exception of ALCL, ALK-positive) and response rates were significantly higher for AITL than other subtypes.[110]

Bendamustine

In a multicenter phase II study (BENTLEY trial) of heavily pretreated patients with relapsed or refractory PTCL (n=60; AITL, 53%; PTCL-NOS, 38%), bendamustine resulted in an ORR of 50% (28% CR) and the median duration of response was only 3.5 months.[111] Response rates were higher in patients with AITL compared with those with other subtypes. The ORR for AITL and PTCL-NOS was 69% and 41%, respectively (P=.47). However, this study was not powered to show differences in response rates between the different histologic subtypes. The median PFS and OS for all patients were 4 months and 6 months, respectively. The most common grade 3 or 4 toxicity included neutropenia (30%), thrombocytopenia (24%), and infectious events (20%).

Pralatrexate

In the pivotal, international phase II study (PROPEL) of heavily pretreated patients with relapsed or refractory PTCL (n=109; 59 patients with PTCL-NOS; 13 patients with AITL, and 17 patients with ALCL), pralatrexate resulted in an ORR of 29% (CR 11%; response assessed by an independent central review). Although the study was not statistically designed to analyze the ORR in specific subsets, response analyses by key subsets indicated that the ORR was lower in AITL (8%) than in the other 2 subtypes (32% and 35%, respectively, for PTCL-NOS and ALCL).[112] The median duration of response was 10 months. For all patients, the median PFS and OS were 4 months and 15 months, respectively. The most common grade 3–4 adverse events included thrombocytopenia (32%), neutropenia (22%), anemia (18%), and mucositis (22%).

Duvelisib

Preliminary findings from a dose optimization study confirmed that duvelisib (phosphatidylinositol 3-kinase [PI3K]-γ/δ inhibitor) monotherapy at 25 or 75 mg twice a day has clinical activity in patients with relapsed/refractory PTCL.[113] Early progression was seen more frequently in the 25 mg cohort, suggesting that higher initial doses may be required to achieve a more rapid tumor response. In the multicenter phase II trial (PRIMO), duvelisib was given at 75 mg twice daily for 2 cycles followed by 25 mg twice daily to maintain long-term disease control for patients with relapsed/

PRINCIPLES OF MOLECULAR ANALYSIS IN T-CELL LYMPHOMAS[a]

***TET2/IDH1/IDH2/RHOA/DNMT3A* Mutations**

- **High incidence of somatic mutations in *IDH2* and *TET2* genes has been identified in AITLs. *IDH2* and *TET2* encode for proteins involved in epigenetic regulation, suggesting that disruption of gene expression regulation by methylation and acetylation may be involved in AITL development and/or progression. Additional genetic findings include the presence of mutations affecting RHOA small GTPase gene (*RHOA G17V*) and *DNMT3A*.**
- **Disease:**
  - **Suspected AITL versus other PTCL.**
- **Detection method:**
  - **Bidirectional sequencing of the entire coding or selected exons in the genes *IDH1, IDH2, DNMT3A, TET2,* and *RHOA*.**
- **Diagnostic value:**
  - **Diagnosis of AITL versus other PTCLs. This pathway has been preliminarily associated with higher rates of response to histone deacetylase (HDAC) inhibitors and other epigenetic modifiers. Clinical trials of this approach are currently ongoing.**

[a] See References on TCLYM-A 4 of 4*.

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refractory PTCL.[114] An interim analysis of dose-expansion cohort (78 patients) reported an ORR of 50% (32% CR). This activity was similar to the previously reported ORR of 50% (n=8/16) in patients with PTCL from the phase I study.[115] Response rates were consistent across the most common subtypes including PTCL-NOS and AITL. Neutropenia (22%), infections (12%), elevated ALT (24%) or AST (22%), diarrhea (3%), rash (8%), decreased lymphocyte count (8%), and sepsis (6%) were the most frequent grade ≥3 adverse events. This trial is ongoing with a targeted enrollment of 125 patients. The panel consensus supported the inclusion of duvelisib (75 mg twice daily for 2 cycles followed by 25 mg twice daily until disease progression) as an option for patients with relapsed/refractory PTCL.

ALK Inhibitors

Crizotinib is FDA-approved for pediatric patients and young adults with relapsed or refractory ALCL, ALK-positive.[116,117] Crizotinib also has demonstrated activity in adult patients with relapsed/refractory ALCL, ALK-positive after at least one line of prior cytotoxic therapy.[118] In a phase II study of 12 patients (median age at enrollment was 31 years; range 18–83 years), crizotinib (250 mg twice daily) resulted in an ORR of 83% (58% CR). The estimated 2-year PFS and OS rates were 65% and 66%, respectively. Alectinib, a second-generation ALK inhibitor, also has shown activity in relapsed or refractory ALCL, ALK-positive.[119] In an open-label phase II trial of 10 patients (aged ≥6 years; median age 19.5 years), alectinib (300 mg twice daily; patients weighing less than 35 kg were given a reduced dose of 150 mg twice daily), resulted in an ORR of 80% with estimated 1-year PFS and OS rates of 58% and 70%, respectively (alectinib was approved in Japan for relapsed/refractory ALCL, ALK-positive based on this study). Crizotinib and alectinib are included as options for patients with relapsed or refractory ALCL, ALK-positive. Crizotinib does not have central nervous system penetration. Since alectinib is also active in patients with central nervous system involvement, it would be an alternative option for patients with central nervous system involvement of ALK-positive ALCL.[120,121]

Other Single Agents

Data to support the use of monotherapy with other single agents are mainly from small single-institution series (alemtuzumab,[122,123] bortezomib,[124] cyclosporine,[125,126] gemcitabine,[127] and lenalidomide[128,129]).

Alemtuzumab and gemcitabine have shown activity resulting in an ORR of 50%–55% (CR 30%–33%) in the

SUPPORTIVE CARE

Tumor Lysis Syndrome (TLS)

- **Laboratory hallmarks of TLS:**
  - **High potassium**
  - **High uric acid**
  - **High phosphorous**
  - **Low calcium**
  - **Elevated creatinine**
- **Symptoms of TLS:**
  - **Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.**
- **TLS features:**
  - **Consider TLS prophylaxis for patients with the following risk factors:**
    - ◊ **Spontaneous TLS**
    - ◊ **High tumor burden or bulky disease**
    - ◊ **Elevated WBC count**
    - ◊ **Bone marrow involvement**
    - ◊ **Pre-existing elevated uric acid**
    - ◊ **Renal disease or renal involvement by tumor**
- **Treatment of TLS:**
  - **TLS is best managed if anticipated and treatment is started prior to chemotherapy.**
  - **Centerpiece of treatment includes:**
    - ◊ **Rigorous hydration**
    - ◊ **Management of hyperuricemia**
    - ◊ **Frequent monitoring of electrolytes and aggressive correction (essential)**
  - **First-line and at retreatment for hyperuricemia**
    - ◊ **Glucose-6-phosphate dehydrogenase (G6PD) testing is required prior to use of rasburicase. Rasburicase is contraindicated in patients with a history consistent with G6PD. In these patients, rasburicase should be substituted with allopurinol.**
    - ◊ **Low Risk Disease: Allopurinol or febuxostat beginning 2–3 days prior to chemoimmunotherapy and continued for 10–14 days**
    - ◊ **Intermediate Risk Disease: Stage I/II and LDH <2X ULN: Allopurinol or febuxostat OR Rasburicase if renal dysfunction and uric acid, potassium, and/or phosphate >ULN**
    - ◊ **High Risk Disease: Stage III/IV and/or LDH ≥2X ULN: Rasburicase**
  - **Rasburicase (Doses of 3–6 mg are usually effective.[a] One dose of rasburicase is frequently adequate. Re-dosing should be individualized.) is indicated for patients with any of the following risk factors:**
    - **Urgent need to initiate therapy in a high-bulk patient**
    - **Situations where adequate hydration may be difficult or impossible**
    - **Acute renal failure**
  - **If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.**

[a] There are data to support that fixed-dose rasburicase is very effective in adult patients.

TCLYM-B
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subset of patients with PTCL-NOS.[123,127] Reduced-dose alemtuzumab was less toxic, equally effective, and also associated with lower incidences of cytomegalovirus reactivation compared with standard-dose alemtuzumab.[123] Cyclosporine has been effective in patients with relapsed AITL following treatment with steroid or multiagent chemotherapy or HDT/ASCR.[125,126] Lenalidomide monotherapy has also been effective in the treatment of relapsed or refractory PTCL, resulting in an ORR of 24%. It has been particularly active in patients with relapsed or refractory AITL resulting in an ORR of 31% (15% CR).[128,129]

Combination Chemotherapy

Very limited data are available for the specific use of combination chemotherapy regimens in patients with relapsed or refractory PTCL (as discussed in the next section).[130–133]

Aggressive second-line chemotherapy with ICE (ifosfamide, carboplatin, and etoposide) followed by HDT/ASCR was evaluated in patients with relapsed/refractory PTCL.[130] Among 40 patients treated with ICE, 27 (68%) underwent HDT/ASCR. Based on intent-to-treat analysis, median PFS was 6 months from the time of last ICE therapy; 70% of patients experienced relapse within 1 year. Patients with relapsed disease had a significantly higher 3-year PFS rate compared with those with primary refractory (20% vs 6%; P=.0005).

Gemcitabine, dexamethasone, and cisplatin (GDP) followed by HDT/ASCR has also been shown to be effective for the treatment of patients with relapsed or refractory PTCL, resulting in an ORR of 72%–80% (CR, 47%–48%).[131,132] Among patients who were treated subsequently with HDT/ASCR, the 2-year posttransplant OS was 53% with no difference in survival rates between patients with relapsed and refractory disease (P=.23). For all nontransplanted patients, the median PFS and OS after treatment with GDP were 4 months and 7 months, respectively.[131] The results of a recent retrospective analysis showed that the gemcitabine, vinorelbine, and doxorubicin (GND) regimen was effective and well tolerated by patients with refractory or relapsed T-cell lymphomas (n=49; 28 patients with PTCL-NOS), with an ORR of 65% and a median OS of 36 months. The 5-year estimated OS rate was 32%.[133]

The inclusion of other combination chemotherapy regimens (eg, DHAP and ESHAP) for the treatment of relapsed/refractory PTCL are derived from aggressive lymphoma clinical trials that have also included a limited number of patients with PTCL.

SUPPORTIVE CARE

For other immunosuppressive situations, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections†.

Monoclonal Antibody Therapy and Viral Reactivation

- **Brentuximab Vedotin (anti-CD30 antibody-drug conjugate)**
  - **Progressive multifocal leukoencephalopathy (PML):**
    - ◊ **Caused by reactivation of the JC virus (JCV) and is usually fatal.**
    - ◊ **Diagnosis made by PCR of CSF and in some cases brain biopsy.**
    - ◊ **No known effective treatment.**
    - ◊ **Clinical indications may include changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems.**
- **Anti-CD52 Antibody Therapy: Alemtuzumab**
  - **CMV reactivation:**
    - ◊ **The current appropriate management is controversial; some NCCN Member Institutions use ganciclovir (PO or IV) preemptively if viremia is present, others only if viral load is rising.**
    - ◊ **CMV viremia should be measured by quantitative PCR at least every 2–3 weeks.**
  - **Antiinfective prophylaxis**
    - ◊ **Herpes simplex virus (HSV) prophylaxis with acyclovir or equivalent.**
    - ◊ **PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent.**
    - ◊ **Consider antifungal prophylaxis.**
    - ◊ **Consultation with an infectious disease expert may be necessary. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections†.**

Management of Tumor Flare Recommended for Patients Receiving Lenalidomide

- **Tumor flare reactions: Painful lymph node enlargement or lymph node enlargement with evidence of local inflammation, occurring with treatment initiation; may also be associated with spleen enlargement, low-grade fever, and/or rash.**
- **Treatment: Steroids (eg, prednisone 25–50 mg PO for 5–10 days); antihistamines for rash and pruritus (eg, cetirizine 10 mg PO once daily or loratadine 10 mg PO daily).**
- **Prophylaxis: Consider in patients with bulky lymph nodes (>5 cm); administer steroids (eg, prednisone 20 mg PO for 5–7 days followed by rapid taper over 5–7 days).**

Prevention of Pralatrexate-Induced Mucositis[c,d,e]

- **Vitamin B12 (cyanocobalamin) at a dose of 1000 mcg intramuscular to be started no more than 10 weeks prior to starting therapy with pralatrexate and then every 8–10 weeks.**
- **Oral folic acid 1–1.25 mg daily to be started within 10 days of starting therapy and continuing for 30 days after the last dose of pralatrexate.**
- **Consider use of oral leucovorin 25 mg 3 times daily for 2 consecutive days (total of 6 doses), starting 24 hours after each dose of pralatrexate.**

[c] Mould DR, Sweeney K, Duffull SB, et al. A population pharmacokinetic and pharmacodynamic evaluation of pralatrexate in patients with relapsed or refractory non-Hodgkin's or Hodgkin's lymphoma. Clin Pharmacol Ther 2009;86:190-196.
[d] Shustov AR, Shinohara MM, Dakhil SR, et al. Management of mucositis with the use of leucovorin as adjunct to pralatrexate in treatment of peripheral t-cell lymphomas (PTCL) – Results from a prospective multicenter phase 2 clinical trial. Blood 2018;132:2910.
[e] Koch E, Story SK, Geskin L. Preemptive leucovorin administration minimizes pralatrexate toxicity without sacrificing efficacy. Leuk Lymphoma 2013;54:2448-2451.

†To view the most recent version of these guidelines, visit NCCN.

Selection of Second-line Systemic Therapy

Not enough data are available to support the use of a particular regimen for second-line therapy based on the subtype, with the exception of ALCL. Brentuximab vedotin should be the preferred choice for second-line therapy for relapsed/refractory ALCL.[105–107]

Belinostat induced responses across all types of PTCL (with the exception of ALK-positive ALCL), and response rates were significantly higher for AITL than other subtypes.[110] Bendamustine and lenalidomide have also induced higher response rates in patients with AITL compared with those with other subtypes.[111,129] HDAC inhibitors may have superior activity in PTCL with TFH phenotype compared with non-TFH PTCL.[53,54] ALK inhibitors (crizotinib or alectinib) could be considered for ALCL, ALK-positive.[118–120] Pralatrexate has very limited activity in AITL compared with other subtypes.[112] Cyclosporine may be appropriate for patients with relapsed AITL after treatment with steroids or multiagent chemotherapy or HDT/ASCR.[125,126] However, the aforementioned studies were not sufficiently powered to evaluate the response rates in specific subtypes.

The selection of second-line chemotherapy regimen (single agent vs combination regimen) should be based on the patient's age, performance status, donor availability, agent's side effect profile, and goals of therapy. For instance, if the intent is to transplant, ORR or CR rate may be more important than the ability to give a treatment in an ongoing or maintenance fashion without cumulative toxicity. For patients who are intended for transplant soon, combination chemotherapy prior to transplant is often preferred if HDT/ASCR is being considered. Combination chemotherapy may also be preferred for patients who are ready to proceed to allogeneic HCT when a suitable donor has already been identified. However, if there is no donor available, the use of intensive combination chemotherapy is not recommended due to the inability to maintain a response for longer periods with the continuous treatment.

Results from the COMPLETE registry showed that treatment with single agents were often as effective, with a trend toward increased CR rate as combination regimens (41% vs 19%; P=.02).[134] The median OS (39 vs 17 months; P=.02) and PFS (11 vs 7 months; P=.02) were also higher among patients treated with single agents, and more patients receiving single agents received HCT (26% vs 8%, P=.07). Thus, for many patients with an intent to proceed to allogeneic HCT, the use of single agents or combination regimens may be appropriately used as a bridge to transplant. Single agents or lower

PRINCIPLES OF RADIATION THERAPY

General Dose Guidelines: (RT in conventional fraction sizes)
- **PTCL**
  - **Consolidation after chemotherapy CR: 30–36 Gy**
  - **Complementary after PR: 40–50 Gy**
  - **RT as primary treatment for refractory or non-candidates for chemotherapy: 40–55 Gy**
  - **In combination with HCT: 20–36 Gy, depending on sites of disease and prior RT exposure**

Treatment Modalities:
- **Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.**

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toxicity regimens may also be more appropriate for older patients with a limited performance status or for those patients who are unable to tolerate more intensive combination chemotherapy.

However, the preferential use of single agents versus combination regimens in patients with an intention to proceed to transplant has not been evaluated in a prospective randomized trial.

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Individual Disclosures for the NCCN T-Cell Lymphomas Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Weiyun Ai, MD, PhD	Daiichi-Sankyo Co.; Nurix	Kite Pharma; Kymera	None	Medical Oncology, Hematology/ Hematologic Oncology
Stephen Ansell, MD, PhD	None	None	None	Hematology/Hematologic Oncology
Jeffrey Barnes, MD, PhD	None	None	None	Medical Oncology
Stefan Barta, MD, MRCP, MS	Affimed; Curis; Daiichi-Sankyo Co.	Acrotech; Daiichi-Sankyo Co.; Kyowa Hakko Kirin Co., Ltd.; Monsanto; Seattle Genetics, Inc.	None	Medical Oncology, Hematology/ Hematologic Oncology
Jonathan Brammer, MD	Allovir; Celgene Corporation; Daiichi-Sankyo Co.; Seattle Genetics, Inc.; Secura-Bio	Kymera Therapeutics	Seattle Genetics, Inc.	Hematology/Hematologic Oncology
Mark Clemens, MD	None	None	None	Plastic/Reconstructive Surgery
Ahmet Dogan, MD, PhD	Genentech, Inc.; Takeda Pharmaceuticals North America, Inc.	PeerView; Physicians' Education Resource	None	Pathology
Francine Foss, MD[a]	None	None	Aurobindo; Daiichi-Sankyo Co.; Helsinn Therapeutics; Kyowa Hakko Kirin Co., Ltd.; Seattle Genetics, Inc.	Medical Oncology, Hematology/ Hematologic Oncology, Transplantation
Paola Ghione, MD	AstraZeneca Pharmaceuticals LP; Kite Pharma; Kyowa Hakko Kirin Co., Ltd.	None	None	Hematology/Hematologic Oncology
Aaron Goodman, MD	None	EUSA; Seattle Genetics, Inc.	Curio science	Hematology/Hematologic Oncology, Transplantation
Joan Guitart, MD	Elorac, Galderma, Solygenix	Kyowa Hakko Kirin Co., Ltd.	Medscape	Dermatology, Pathology
Ahmad Halwani, MD	Bayer HealthCare; Genentech, Inc.; Immune Design; Pharmacyclics; Roche Laboratories, Inc.	None	None	Allergy/Immunology, Hematology/ Hematologic Oncology
Bradley Haverkos, MD, MPH, MS	Viracta Therapeutics	None	Viracta Therapeutics	Medical Oncology
Richard Hoppe, MD	None	None	None	Radiation Oncology
Steven Horwitz, MD	Affimed; BeiGene; C4 Therapeutics; Celgene Corporation; CRISPR Therapeutics; Daiichi-Sankyo Co.; Kyowa Hakko Kirin Co., Ltd.; Seattle Genetics, Inc.; Secura Bio; Takeda Pharmaceuticals North America, Inc.; Trillium	Acrotech; Cimeo Therapeutics; Curio Science; Daiichi-Sankyo Co.; Kura Oncology, Inc.; Kyowa Hakko Kirin Co., Ltd.; Myeloid Therapeutics; Ono; Seattle Genetics, Inc.; Secura; Shoreline Biosciences; Takeda Pharmaceuticals North America, Inc.; Triangle insights; Tubulis; Vividion	None	Internal Medicine, Medical Oncology
Eric Jacobsen, MD	AbbVie, Inc.; Daiichi-Sankyo Co.; Merck & Co., Inc.; Verastem	ADC Therapeutics; Bayer HealthCare; Janssen Pharmaceutica Products, LP; Novartis Pharmaceuticals Corporation; Pharmacyclics	None	Medical Oncology
Deepa Jagadeesh, MD, MPH	ADCT therapeutics; AstraZeneca Pharmaceuticals LP; ATARA pharmaceuticals; Debiopharm; LOXO; MEI Pharma Inc.; Regeneron Pharmaceuticals, Inc.; RHIZEN pharmaceuticals; Seattle Genetics, Inc.; Trillium	None	MEI Pharma Inc.	Medical Oncology, Hematology/ Hematologic Oncology
Allison Jones, MD	None	None	None	Dermatology
Avyakta Kallam, MD, MBBS	None	None	None	Internal Medicine
Youn Kim, MD[a]	Corvus; Crispr Therapeutics; Eisai Inc.; Elorac; Galderma; Innate; Kyowa Hakko Kirin Co., Ltd.; Portola Pharmaceuticals, Inc.; Soligenix; Trillium	Corvus; Innate	Galderma; Kyowa Hakko Kirin Co., Ltd.; Mundipharma; Regeneron Pharmaceuticals, Inc.; sanofi-aventis U.S.; Secura Bio	Dermatology, Medical Oncology
Kiran Kumar, MD, MBA	AstraZeneca Pharmaceuticals LP	None	Varian Medical Systems, Inc.	Radiation Oncology
Neha Mehta-Shah, MD, MSCI	AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; C4 Therapeutics; Celgene Corporation; Corvus; Daiichi-Sankyo Co.; Genentech, Inc.; Innate Pharmaceuticals; Secura Bio; Verastem Pharmaceuticals	C4 Therapeutics; Daiichi-Sankyo Co.; Kyowa Hakko Kirin Co., Ltd.; Ono Pharmaceuticals; Secura Bio	None	Medical Oncology, Hematology/ Hematologic Oncology
Elise Olsen, MD	Affimed; elorac; Galderma; Kyowa Hakko Kirin Co., Ltd.	Kyowa Hakko Kirin Co., Ltd.; Pfizer Inc.; Sologenix	None	Dermatology, Medical Oncology
Saurabh Rajguru, MD	None	None	None	Medical Oncology, Hematology/ Hematologic Oncology
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Jonathan Said, MD	None	None	None	Pathology
Aaron Shaver, MD, PhD	None	None	None	Hematopathologist
Lauren Shea, MD	None	None	None	Hematology/Hematologic Oncology
Michi Shinohara, MD	Astex Pharmaceuticals; Cabaletta Bio; Elorac	None	None	Dermatology, Pathology
Lubomir Sokol, MD, PhD	EUSA; Kyowa Hakko Kirin Co., Ltd.	Daiichi-Sankyo Co.; Dren Bio; Kyowa Hakko Kirin Co., Ltd.	None	Internal Medicine, Medical Oncology, Hematology/ Hematologic Oncology
Carlos Torres-Cabala, MD	None	None	None	Pathology
Ryan Wilcox, MD, PhD	Affimed; Astex Pharmaceuticals; Corvus; CTI BioPharma Corp.; Merck & Co., Inc.	Adagene; Astex Pharmaceuticals	None	Medical Oncology, Hematology/ Hematologic Oncology
Peggy Wu, MD, MPH	None	None	None	Dermatology
Jasmine Zain, MD	None	Kyowa Hakko Kirin Co., Ltd.; scura bio	Kyowa Hakko Kirin Co., Ltd.; Seattle Genetics, Inc.	Medical Oncology, Hematology/ Hematologic Oncology

Hema Sundar, PhD, has disclosed receiving an employment/governing board, patent, equity, or royalty from Progenra.
The remaining NCCN Guidelines Staff have no conflicts to disclose.
[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
Francine Foss, MD: Therakos, Inc.
Youn Kim, MD: UpToDate