Peripheral T-cell Lymphomas (PTCL)[1]

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[1] This algorithm contains the following subtypes: PTCL - not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK) positive and ALK negative, enteropathy associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), hepatosplenic gamma-delta T-cell lymphoma (HSGDTL), primary cutaneous gamma-delta T-cell lymphoma (PCGDTL), extranodal natural killer T-cell lymphoma (ENKTCL), and adult T-cell leukemia//lymphoma (ATLL).
The following subtypes are **not** included in this algorithm: T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia (T-LGL), primary cutaneous ALCL, breast implant-associated (BIA)-ALCL and all other cutaneous T-cell lymphoma (See Cutaneous T-cell Lymphoma (CTCL) algorithm).

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Peripheral T-cell Lymphomas (PTCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

PATHOLOGIC DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block or 15 unstained slides representative of the tumor. Re-biopsy if consult material is nondiagnostic.
- Adequate morphology and immunophenotyping to establish diagnosis
  - Flow cytometry immunophenotypic studies: CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD16, CD25, CD26, CD14, CD45, CD52, CD56, CD57, CD94, TCRbeta, TCRgamma, CD30, and TRCB1
  - Paraffin Panel: CD20, CD4, CD8, CD3, CD30 and/or other pan-T-cell markers (CD2, CD5, CD7, CD43), Ki-67, EBER-ISH

OF USE IN CERTAIN CIRCUMSTANCES TO DETERMINE SUBGROUP:

- TBX21/CXCR3/GATA3 and CCR4 to assess PTCL-TBX21 and PTCL-GATA3 plus ICOS and PD1 to exclude lymphomas with follicular helper phenotype (in cases of PTCL- NOS)
- BetaF1, CD25, CD30 [(mycosis fungoides (MF)/Sezary syndrome (SS) - large cell transformation (LCT)]
- TCR delta, CD94 (HSGDTL, PCGDTL, SPTCL, and MEITL)
- CD10, BCL-6, PD1, CXCL13, CD21, ICOS, and IDH2 R172K (AITL/TfH)
- CD15, ALK1, EMA (anaplastic cell lymphoma)
- CD103, CD56 (EATL)
- CD56 with or without CD3 (ENKTCL)
- CD1a, CD34, TdT (T lymphoblastic lymphoma)
- TCL-1, FOXP3, CD25 (T-cell prolymphocytic leukemia and adult T-cell leukemia/lymphoma)
- FISH studies to detect DUSP22 and TP63 (ALK negative ALCL)
- Molecular studies to detect clonality of the *TCR* genes
- NGS studies (end lymphoma panel) to assess the mutational landscape

STRONGLY RECOMMENDED:

- Fine needle aspiration (FNA) or core biopsy for tissue array/banking by protocol

INITIAL EVALUATION

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
  - Consider Dermatology consult for comprehensive skin assessment if cutaneous involvement is present or suspected
  - Performance status
  - B symptoms (Unexplained fever > 38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss > 10 percent of body weight ≤ 6 months of diagnosis)
  - Calculation of Prognostic Index for PTCL-Unspecified (PIT)[1] (See Appendix A)
- CBC with differential, BUN, creatinine, albumin, AST, bilirubin, serum calcium, alkaline phosphatase, uric acid, LDH
- Beta-2-microglobulin
- Screening for HIV 1 and 2, hepatitis B and C (HBcAb, HBaAg, HCVAb)
- HTLV 1/2 serology
- If HSGDTL, ENKTCL or PCGDTL **or** if fever > 38°C, pancytopenia, and transaminitis in the appropriate clinical setting, conduct an HLH work up including EBV by PCR, ferritin, fibrinogen, triglycerides, CRP, natural killer (NK) subset panel, T-NK flow cytometry and cytokine panel which includes IL-2sR (sCD25)
- Unilateral or bilateral bone marrow biopsy with aspirate
- PET/CT
- Lifestyle risk assessment[2]
- MUGA scan or echocardiogram

OF USE IN SELECTED CASES:

- CT head or MRI with contrast
- EBV with PCR (AITL/TfH, ENKTCL)
- Pregnancy test
- Lumbar puncture, if paranasal sinus, testicular, parameningeal, orbit, CNS, paravertebral, bone marrow or HIV lymphoma
- Serum immunoelectrophoresis (SPEP)
- If suspected EATL, work up for celiac disease
- Discuss fertility options and sperm banking for patients of child bearing potential (refer to Fertility Preservation Prior to Cancer Treatment algorithm)

See Page 3: Induction therapy

SPTCL = subcutaneous panniculitis-like T-cell lymphoma TfH = T follicular helper

[1] Not used to determine the choice of treatment

[2] See Physical Activity, Nutrition, Obesity Screening and Management, and Tobacco Cessation Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

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INDUCTION THERAPY

Stages I - IV →

- ALCL
  - BV-CHP with or without ISRT[1]
  - Other options: CHOEP or CHOP with or without ISRT[1]
  - Consider abbreviated chemotherapy with ISRT[1] for limited stage ALK positive or ALK negative DUSP22 positive
- PTCL-NOS, nodal PTCL, and AITL
  - BV-CHP (preferred for CD30-positive) **or**
  - CHOEP **or**
  - CHOP **or**
  - Dose-adjusted EPOCH
- HSGDTL, PCGDTL, EATL and MEITL
  - HCVAD **or**
  - Dose adjusted EPOCH
- ENKTCL
  - Stage I/II: DeVIC with ISRT[1]
  - Stage III/IV: SMILE **or** DDGP **or** P-GEMOX
- ATLL[2]
  - BV-CHP (preferred for CD30-positive) **or**
  - Dose adjusted EPOCH **or**
  - CHOEP **or**
  - HCVAD
- CTCL and large cell transformation: Refer to Cutaneous T-cell Lymphoma (CTCL) algorithm

INTERIM RESPONSE

After 2-4 cycles, repeat all positive studies[3]

- Complete or partial response[4,5] → Complete current treatment; See Page 4 for evaluation, response, treatment and follow-up
- No response or progressive disease[4,5] → See Page 5 for refractory or relapse therapy

FOLLOW-UP

ALK = anaplastic lymphoma kinase
BV-CHP = brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone,
CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone
CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone
DDGP = cisplatin, dexamethasone, gemcitabine, pegaspargase
DeVIC = dexamethasone, etoposide, ifosfamide, carboplatin
EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
HCVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
ISRT = involved site radiation therapy
P-GEMOX = pegaspargase, gemcitabine, oxaliplatin
SMILE = steroid, methotrexate, ifosfamide, L-asparaginase, etoposide

[1] For limited stage patients, radiation therapy can be considered as consolidation after a complete metabolic response to systemic therapy, particularly if abbreviated systemic therapy (3-4 cycles). For all patients, radiation therapy can be considered to sites of bulky disease or for an incomplete response after systemic therapy. ISRT and advanced RT techniques should be used. Doses vary based on clinical scenarios (*e.g.*, consolidation, salvage, palliation) and can range from 20-50Gy.

[2] For chronic ATLL or smoldering, consider anti-retroviral [zidovudine (ZDV), azidothymidine (AZT), bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®)] and interferon alfa (IFN alpha) **or** mogamulizumab, skin directed therapy (if applicable) or radiotherapy

[3] PET scans should be used to assess residual abnormalities on CT scan, especially if done pretreatment

[4] Partial response includes a biological measure of disease: fluorodeoxyglucose (FDG)-avid disease with reduced uptake compared to baseline PET/CT scan. A positive PET/CT at the end of treatment proved to be lymphoma on biopsy is considered to be residual/refractory disease.

[5] For response assessment, refer to: Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067. doi: 10.1200/JCO.2013.54.8800

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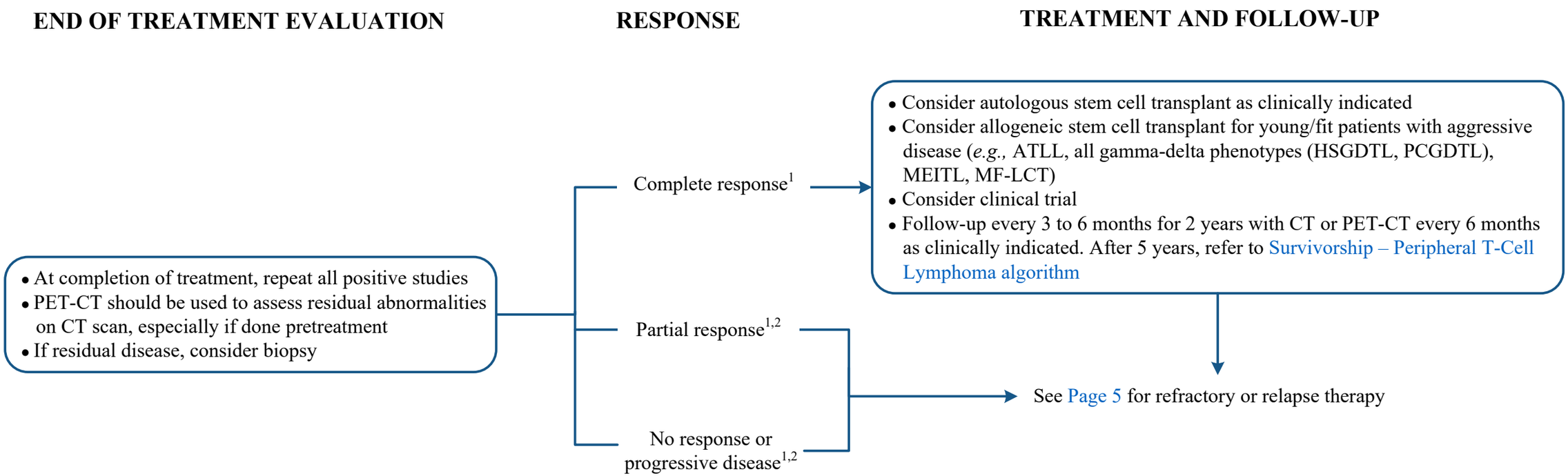
Peripheral T-cell Lymphomas (PTCL)

Note: Consider Clinical Trials as treatment options for eligible patients.



[1] For response assessment, refer to: Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067. doi: 10.1200/JCO.2013.54.8800

[2] Partial response includes a biological measure of disease: fluorodeoxyglucose (FDG)-avid disease with reduced uptake compared to baseline PET/CT scan. A positive PET/CT at the end of treatment proved to be lymphoma on biopsy is considered to be residual/refractory disease.

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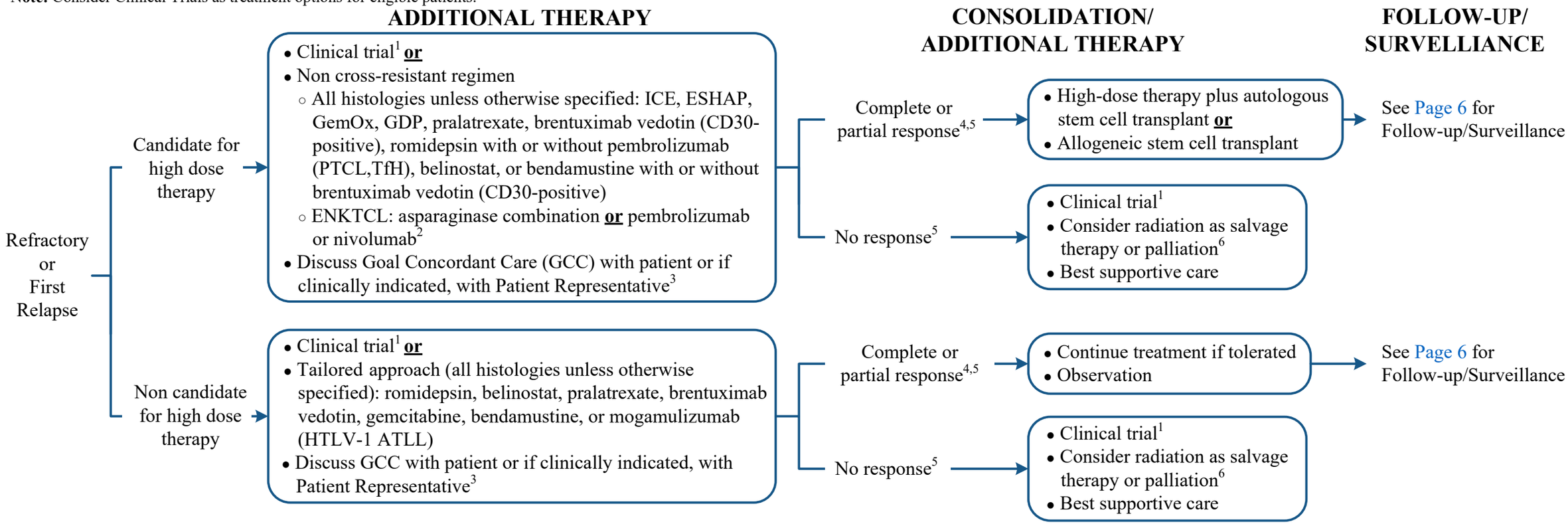

ICE = ifosfamide, carboplatin, etoposide
ESHAP = etoposide, methylprednisolone, high dose cytarabine, cisplatin
GemOx = gemcitabine and oxaliplatin
GDP = gemcitabine, dexamethasone, and cisplatin

[1] Clinical trials or individual regimens: patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval

[2] The use of checkpoint inhibitors prior to allogeneic stem cell transplant may result in increased transplantation-related mortality and severe hyperacute graft versus host disease (GVHD)

[3] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

[4] Partial response includes a biological measure of disease: fluorodeoxyglucose (FDG)-avid disease with reduced uptake compared to baseline PET/CT scan. A positive PET/CT at the end of treatment proved to be lymphoma on biopsy is considered to be residual/refractory disease.

[5] For response assessment, refer to: Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067. doi:10.1200/JCO.2013.54.8

[6] For limited stage patients, radiation therapy can be considered as consolidation after a complete metabolic response, particularly if abbreviated systemic therapy (3-4 cycles). For all patients, radiation therapy can be considered to sites of bulky disease or for an incomplete response after systemic therapy. ISRT and advanced RT techniques should be used. Doses vary based on clinical scenarios (*e.g.*, consolidation, salvage, palliation) and can range from 20-50Gy.

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FOLLOW-UP/SURVELLIANCE

- Follow-up every 3 to 6 months for 2 years with CT or PET-CT every 6 months as clinically indicated
- After 5 years, refer to Survivorship – Peripheral T-Cell Lymphoma algorithm

RELAPSE #2 OR GREATER

If disease progression
- Clinical trial[1] **or**
- Other individual approach (*e.g.*, romidepsin with or without pembrolizumab, belinostat, pralatrexate, brentuximab vedotin (CD30 positive PTCL), gemcitabine, bendamustine) **or**
- Consider lenalidomide or duvelisib or azacytidine or ruxolitinib (if *JAK/STAT* mutations and/or *pSTAT3* expression)

[1] Clinical trials or individual regimens: patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval

APPENDIX A: Prognostic Index for PTCL - Unspecified (PIT)[1]

Risk Factors	Prognostic Risk	Number of Risk Factors
• Age > 60 years • LDH > 1 times normal • Performance status 2 – 4 • Bone marrow involvement	• Group 1 • Group 2 • Group 3 • Group 4	0 1 2 3 or 4

[1] Other prognostic scoring systems have been proposed and validated, but none are currently used to impact PTCL treatment

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