Onkološki inštitut
Institute of Oncology
Ljubljana

SZD
Sekcija
za internistično onkologijo

5. LIMFOMSKA ŠOLA

LIMFOMI PREBAVIL

28. november 2025

Strokovni in organizacijski odbor strokovnega srečanja:
doc. dr. Lučka Boltežar
prof. dr. Barbara Jezeršek Novaković
doc. dr. Gorana Gašljević
prof. dr. Veronika Kloboves Prevodnik

5. LIMFOMSKA ŠOLA: LIMFOMI PREBAVIL
ZBORNIK

Urednici:
prof. dr. Barbara Jezeršek Novaković
doc. dr. Lučka Boltežar

Tehnična urednica in oblikovanje:
Zvezdana Vukmirović, mag. posl. ved.

Izdajatelj in založnik:
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo pri SZD

Ljubljana, november 2025

Publikacija je brezplačno dostopna na spletnih straneh Onkološkega inštituta Ljubljana https://www.onko-i.si/publikacije-strokovnih-dogodkov-oi

CIP - Kataložni zapis o publikaciji Narodna in univerzitetna knjižnica, Ljubljana

PROGRAM

1. SKLOP – B LIMFOMI PREBAVIL

8.30– 8.35	**Uvodni nagovor** doc. dr. Gorana Gašljević
8.35 – 9.05	**Multidisciplinary approach in lymphoma diagnostics, the Lund experience** assoc. prof. Mats Ehinger, Lund, Sweden
9.05 – 9.35	**Classification (WHO5/ICC2022) of indolent and aggressive B-cell lymphomas in GIT** prof. Andrew Wotherspoon, London, UK
9.35 – 9.55	**Pomen endoskopij pri B limfomih prebavil ter sledenje bolnikov** Gašper Boltežar, dr. med.
9.55 – 10.10	**Zdravljenje indolentnih B limfomov prebavil** Milica Miljković, dr. med.
10.10 – 10.30	**Zdravljenje agresivnih B limfomov prebavil** prof. dr. Barbara Jezeršek Novaković
10.30 – 10.45	**Vloga obsevalnega zdravljenja pri indolentnih in agresivnih B limfomih prebavil** doc. dr. Marija Skoblar Vidmar
10.45 – 11.00	**Diskusija**
11.00 – 11.15	**Odmor s kavo**

2. SKLOP – T LIMFOMI PREBAVIL

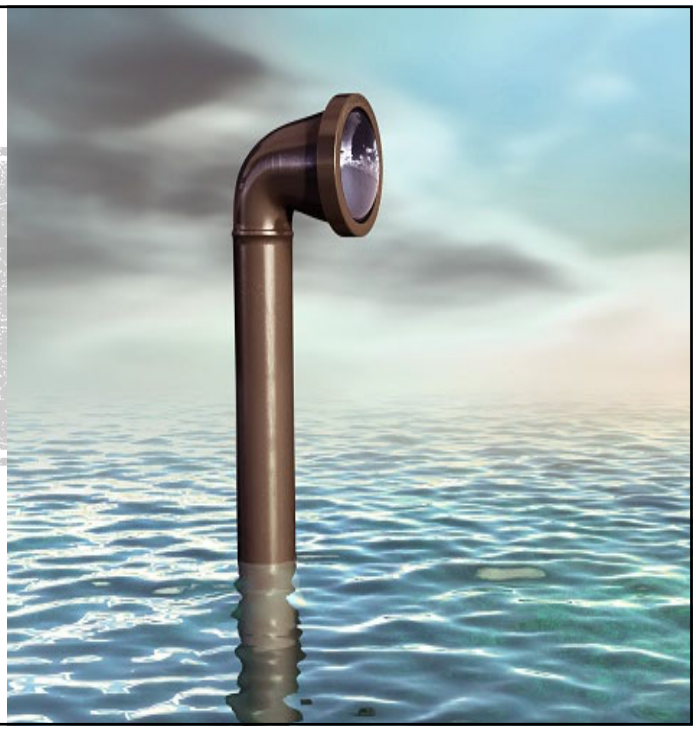
11.15 – 11.35	**Classification (WHO5/ICC2022) of T-cell lymphomas of the GIT** prof. Andrew Wotherspoon, London, UK
11.35 – 11.50	**Vloga citopatologa in patologa v diagnostiki T limfomov** prof. dr. Veronika Kloboves Prevodnik, doc. dr. Gorana Gašljević
11.50 – 12.10	**Zdravljenje celiakije, kdaj posumiti na T limfom?** doc. dr. Jurij Hanžel
12.10 – 12.30	**Zdravljenje T limfomov prebavil** doc. dr. Lučka Boltežar
12.30 – 12.45	**Pomen avtologne in alogenične transplantacije krvotvornih matičnih celic pri T limfomih** Klara Šlajpah, dr. med.
12.45 – 13.00	**Diskusija**
13.00 – 14.00	**Kosilo**
14.00 – 15.30	**Mikroskopiranje – delavnice samo za citologe/patologe** Gorana Gašljević, Barbara Gazić, Biljana Grčar Kuzmanov, Milan Car, Aleš Rode, Veronika Kloboves Prevodnik, Jera Jeruc

3. SKLOP – PRIMERI

14.00 – 14.10	**Primer bolnika z MALT limfomom želodca** Kristina Levpušček, dr. med. dr. Tanja Južnič Šetina
14.10 – 14.20	**Primer bolnika z agresivnim B-celičnim limfomom želodca** Anja Žižek, dr. med., Urška Rugelj, dr. med.
14.20 – 14.30	**Primer bolnika s T-celičnim limfomom prebavil I** Matej Panjan, dr. med. Aleš Christian Mihelač, dr. med.
14.30 – 14.40	**Primer bolnika s T-celičnim limfomom prebavil II** Rozala Arko, dr. med., dr. Monika Jagodic
14.40 – 15.00	**Diskusija**
15.00	**Zaključek srečanja** prof. dr. Barbara Jezeršek Novaković

KAZALO

ROLE OF ENDOSCOPY IN B-CELL LYMPHOMA



Gašper Boltežar
DC Bled
5. Limfomska šola, 28.11.2025

ENDOSCOPY

- Upper endoscopy – esophago-gastro-doudenoscopy (EGDS)
- Lower endoscopy – colonoscopy
- In the middle – enteroscopy
- Virtual – capsule endoscopy

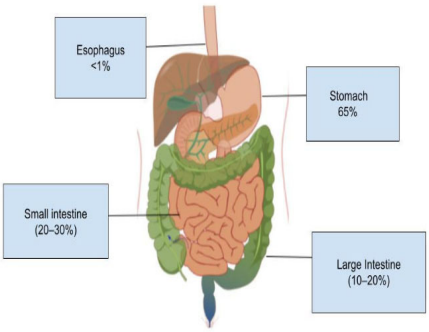
- Diagnostic – screening, sampling, follow-up
- Therapeutic – polyp removal, haemostasis, dillatation, stenting, foreign body removal

SYMPTOMS, LEADING TO ENDOSCOPY

- Abdominal pain
- Weight loss
- GI bleeding
- Nausea, vomiting or early satiety
- Diarrhea
- B symptoms

LYMPHOMA OF GI TRACT - LOCATION

- Esophageal – extremely rare
- Stomach – most common site of primary GI lymphoma
- Small intestine – second most common site
- Colon and rectum - predominantly cecal region



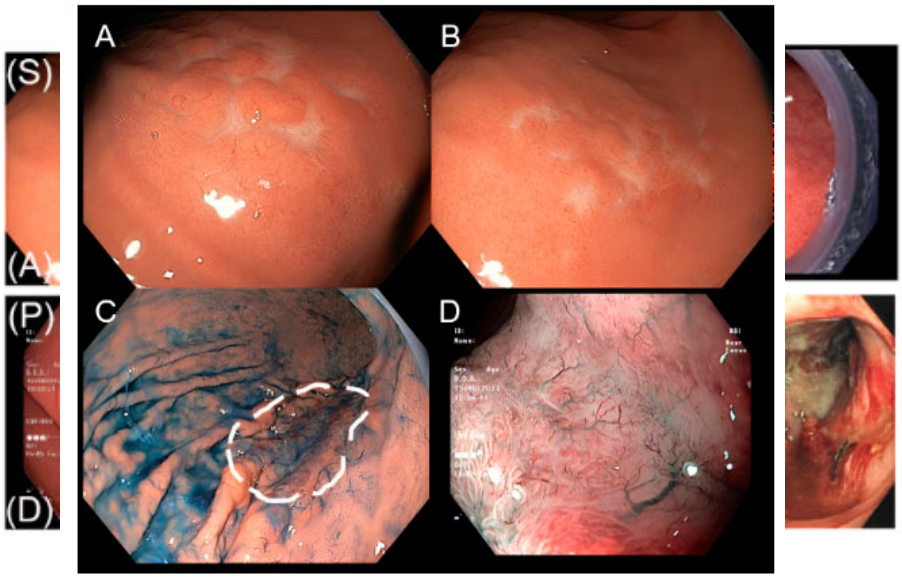
Nagesh, Lymphatics, 2025

CLINICAL PRESENTATION

Subtype	Presentation
MALT Lymphoma	Indolent; dyspepsia, epigastric pain, nausea; associated with *H. pylori*; responds to eradication therapy
Diffuse Large B-Cell Lymphoma (DLBCL)	Aggressive; mass effect, bleeding, perforation, B symptoms; rapid progression
Mantle Cell Lymphoma (MCL)	Multiple lymphomatous polyposis; diarrhea, abdominal discomfort, obstruction
EATL	Associated with celiac disease; severe pain, diarrhea, weight loss, perforation; aggressive course
Extranodal NK/T-Cell Lymphoma	Rare, EBV-associated; GI bleeding, perforation, abdominal pain; systemic symptoms often present

Nagesh, Lymphatics, 2025

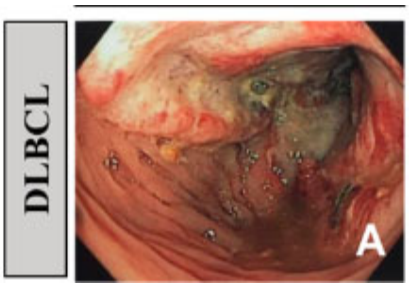
ENDOSCOPIC FEATURES OF GI LYMPHOMA



Tran, Diagnostics, 2023

DIFFUSE LARGE B-CELL LYMPHOMA

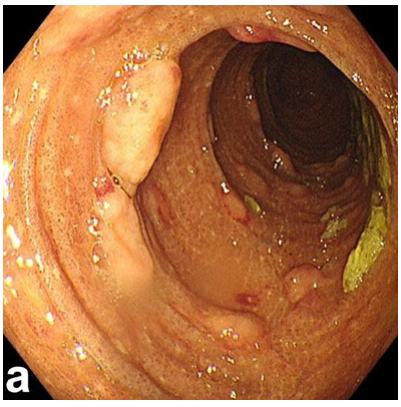
- High grade lymphomas can involve the stomach in 50-60% of cases
- Represent 20-30% of GI NHL
- *H. pylori* infection present in 35% of cases
- Succesful eradication is associated with durable remission in 50-60% (especially in DLBCL with MALT component)
- Endoscopic pattern is ulcerative (in most cases), confined to body or fundus



Vetro, World J of Gastroent, 2014
Nagesh, Lymphatics, 2025

DIFFUSE LARGE B-CELL LYMPHOMA

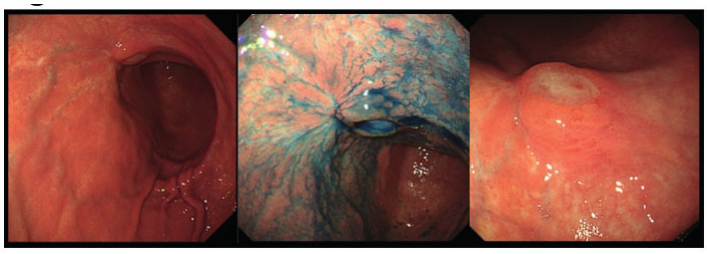
- 50-80% of cases in small and large intestine
- Polypoid in 25%, ulcerative in 54%, multiple polyp in 5%, diffuse infiltrating in 6% and mixed type in 5%
- Intestinal perforation more common compared to other lymphoma
- Bulky mass in cecal region can be often appreciated with physical examination or on US of the abdomen
- Surgical intevention can often precede colonoscopy due to urgent presentation



Stanojevic, World J Gastointest Oncol, 201
Terada, Am J Blood Res, 2011

DIFFUSE LARGE B-CELL LYMPHOMA

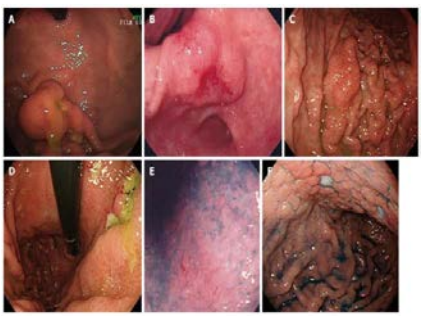
- Endoscopy may be a part of diagnostics
- Follow up endoscopies are generally not recommended
- Endoscopic remission rates may differ from clinical remission
- Often clinician order follow-up endoscopies for screenig for relapse disease

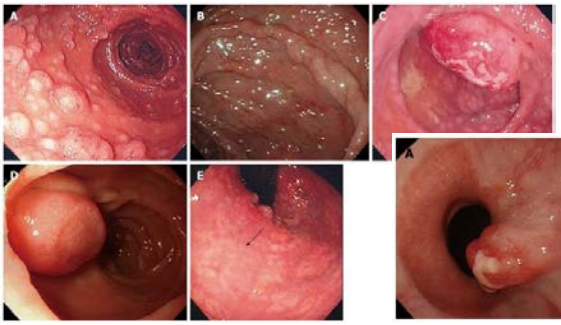


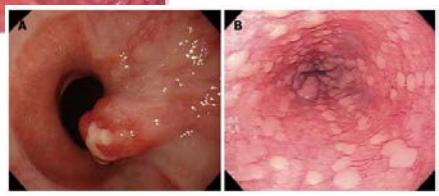
Lee, Ann of Oncol, 2014
Cameron, BJ Haem, 2024

MANTLE CELL LYMPHOMA

- GI involvement in up to 90%
- Often manifesting as multiple lymphomatous polyposis with diarrhea
- GI involvement can be also only microscopic



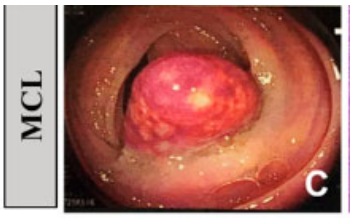




Morton, Blood, 2006
Campo, Blood 2015
Dey, J Clin Oncol, 2024

MANTLE CELL LYMPHOMA

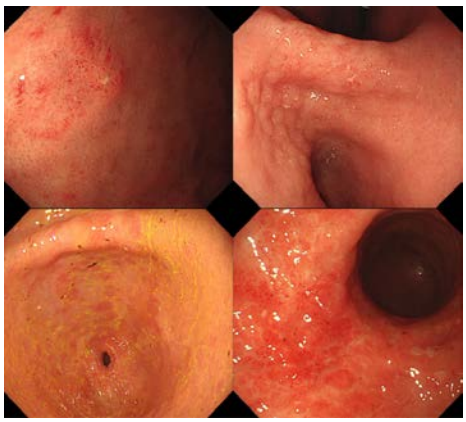
- Many advocate upper and lower endoscopy during work-up in all.
- In all patients with apparent early-stage MCL (ie, non-bulky stage I or stage II) to identify more extensive disease that might affect management
- Endoscopy not recommended for follow-up but…
- May diagnose recurrence when CT/PET do not



Jerkeman, HemaSphere, 2025
Han, PlosOne, 2020

MALT LYMPHOMA

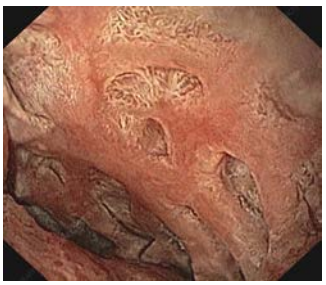
- Usually presents with most benign symptoms
- GI tract involved in 50% of cases, especially in stomach
- Delay in diagnosis
- Endoscopic features vary – from chronic gastritis (~12%) to mimicking adenocarcinoma - ulcerated mass (>50%)
- Most frequently located in lower parts of stomach
- Strongly associated with *H. pylori* infection (and other infections)
- The only lymphoma a gastroenteologist can cure ☺

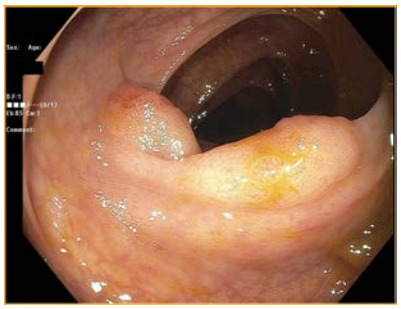


Zullo, J Clin Gastroenterol, 2010
Vetro, World J of Gastroent, 2014

MALT LYMPHOMA

- Duodenal variants have usually multiple erosions and nodular elevations in the duodenal bulb
- Jejunal and ileal lesions are usually ulcerative in apperance
- Colonic lesions can mimic normal mucosa or colorectal adenocarcinoma

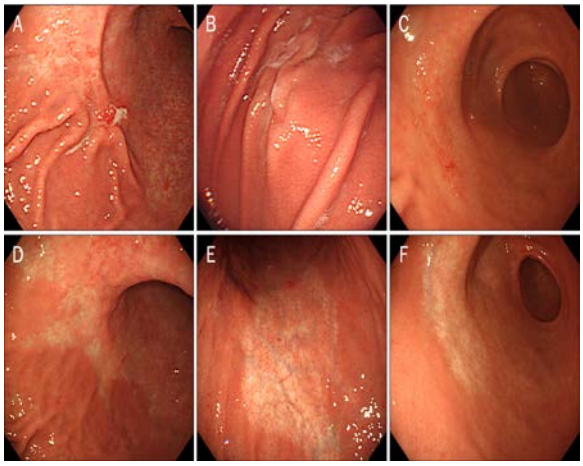




Vetro, World J of Gastroent, 2014

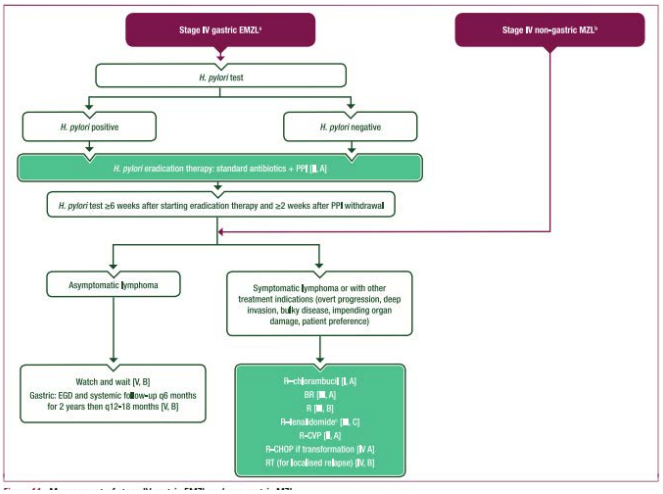
MALT LYMPHOMA

- Endoscopy needed on (almost) every step of the way
  - Diagnosis
  - Conformation of remission
  - Follow up
- Tumor can infiltrate the submucosa – simple biopsies are sometimes not enough (stomach, rectum) – need for guided biopsies or „well" biopsies



Freedman, UpToDate, 2024
Watanabe, Rare Tumors, 201

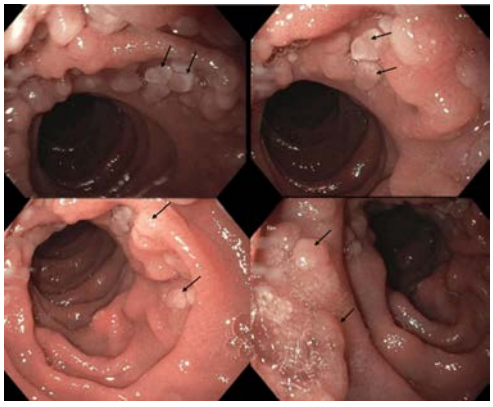
MALT LYMPHOMA



Eyre, Annals of Oncol, 2025

FOLLICULAR LYMPHOMA – DUODENAL TYPE

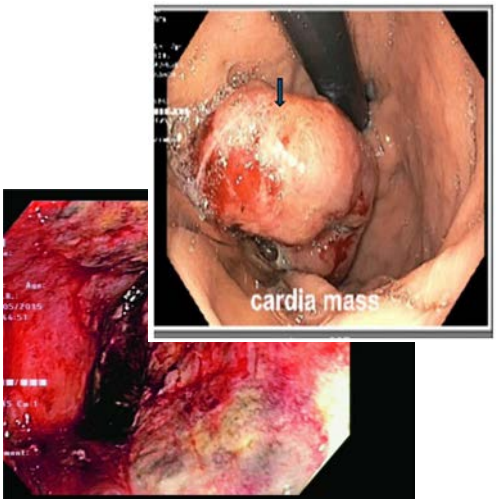
- Tumor, confined to intesitne
- Typically presents as multiple small polyps
- Very rare
- Duodenal-type FL is often discovered incidentally and appears to follow a very indolent course
- Must be differentiated from systemic FL involving the gastrointestinal tract.



Freedman, UpToDate, 2025

BURKITT LYMPHOMA

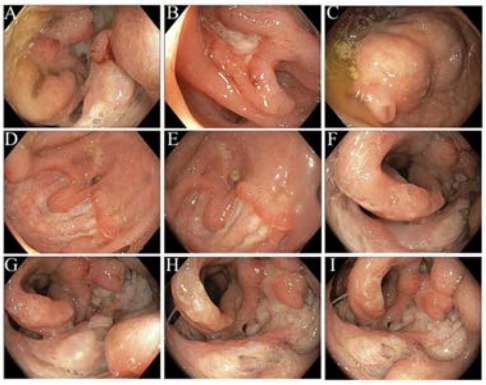
- Very rare
- Usually found in small and large intestine (ileocecal region),
- Origin in upper GI tract only in case reports
- Protruding ulcerated lession
- May present as an emergency and mimic apendicitis – urgent resection



Saad, Gastro y Hepatol, 2018
Čubranić, Acta Clin Croat, 2019

HODGKIN'S LYMPHOMA

- Very rare
- <1% of gastric lymphoma
- The imflamatory background of Hodgkin's can resemble chronic inflamatory disease in large intestine
- Described only in small series

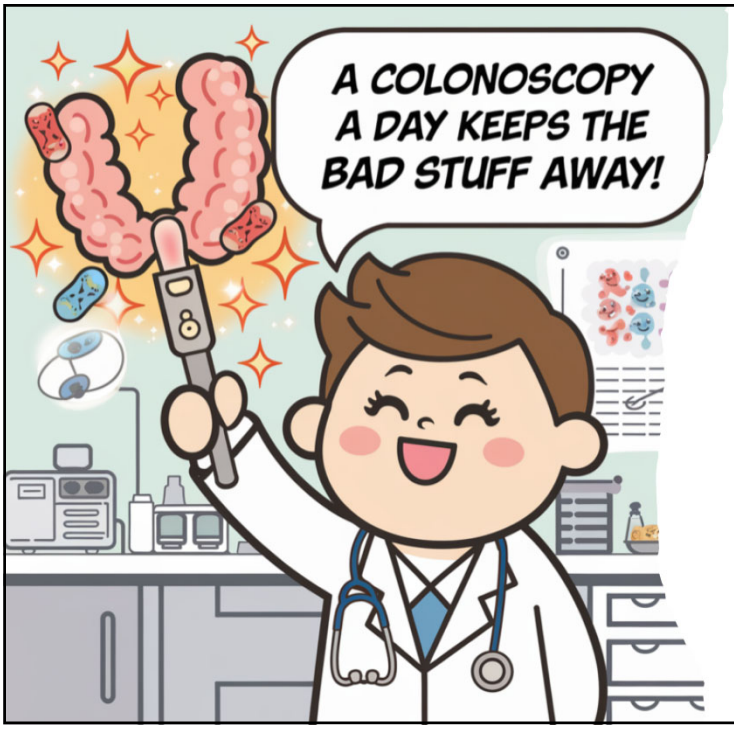


Thomas, BMJ Open Gastro, 2019

TO SUM UP…

- Endoscopy is often part of a diagnostic work-up
- Rarely is it needed in follow-up
- May be needed in case of complications during treatment (e.g. bleeding) or after treatment (e.g. stenosis of GI tract due to fibrosis)

- If not sure, give us a call, we'll scope (almost) anything… ☺



THANK YOU FOR YOUR ATTENTION!

Zdravljenje indolentnih B limfomov prebavil

5. Limfomska šola, Limfomi prebavil
Onkološki Inštitut v Ljubljani
28.11.2025

Milica Miljković spec.internistične onkologije

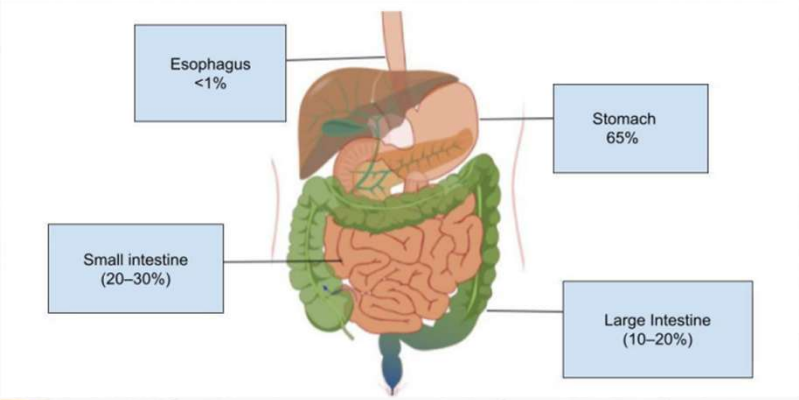
Content

- Pathogenesis and staging of indolent B cell lymphoma
- Treatment of :
  MALT (mucus associated lymphoid tissue) lymphoma
  FL (follicular lymphoma)
  MCL (mantle cell lymphoma)

Pathogenesis

- Helicobacter pylori, Campylobacter jejuni
- Human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell lymphotropic virus-1 (HTLV-1)
- Inflammatory bowel disease and immunosuppression
- Celiac disease
- Genetic aberrations

Sites of involvement of gastroinetstinal lymphoma



https://doi.org/10.3390/lymphatics3040031

Staging

- Endoscopy/Colonoscopy
- Capsule Endoscopy and Balloon-Assisted Enteroscopy
- Bone marrow
- CT/MRI
- PET/CT

STAGING OF EMZL OF THE STOMACH: COMPARISON OF DIFFERENT SYSTEMS

Lugano Staging System for Gastrointestinal Lymphomas		Lugano Modification of Ann Arbor Staging System	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension
Stage I	Confined to GI tract[a]			
	I_1 = mucosa, submucosa	I_E	T1 N0 M0	Mucosa, submucosa
	I_2 = muscularis propria, serosa	I_E	T2 N0 M0	Muscularis propria
		I_E	T3 N0 M0	Serosa
Stage II	Extending into abdomen			
	II_1 = local nodal involvement	II_E	T1-3 N1 M0	Perigastric lymph nodes
	II_2 = distant nodal involvement	II_E	T1-3 N2 M0	More distant regional lymph nodes
Stage IIE	Penetration of serosa to involve adjacent organs or tissues	II_E	T4 N0 M0	Invasion of adjacent structures
Stage IV[b]	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement		T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/ distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

Zucca E, Bertoni F, Yahalom J, Isaacson P. Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT lymphoma) in Armitage et al eds. Non-Hodgkin's Lymphomas. Philadelphia: Lippincott, 2010:242. (http://lww.com)

Treatment of stomach MALT

- **MALT lymphoma, HP +, stage I–II.E**:
  Eradication therapy for 14 days:

1. **Esomeprazole 40 mg twice daily** (for 4 weeks)
2. **Clarithromycin 500 mg twice daily**
3. **Amoxicillin 1000 mg twice daily (metronidazole 400 mg three times)**

- To confirm successful eradication, a urea breath test or stool H. pylori antigen test is recommended, performed **no earlier than 6 weeks** after starting eradication therapy and at least **2 weeks after** stopping the proton pump inhibitor.
- If you confirm HP, repeat **gastroscopy** and biopsy at 6 months.

Ann Oncol. 2025;36(11):1263-1284
DOI: 10.6016/ZdravVestn.2615

Treatment of stomach MALT

- If the **biopsy sample remains H. pylori–positive** on follow-up gastroscopies, eradication therapy should be repeated — but using an alternative antibiotic regimen:
- **Second-line eradication therapy (14 days):**

1. Esomeprazole 40 mg twice daily
2. Amoxicillin 1000 mg twice daily or **Pylera** 4x3 caps (10 dni)
3. Levofloxacin 500 mg once daily

- **Third-line regimen (10 days):**

1. Esomeprazole 40 mg twice daily
2. Amoxicillin 500 mg four times daily
3. Metronidazole 400 mg four times daily

Pylera (bismuth subcitrate potassium, metronidazole, tetracycline)

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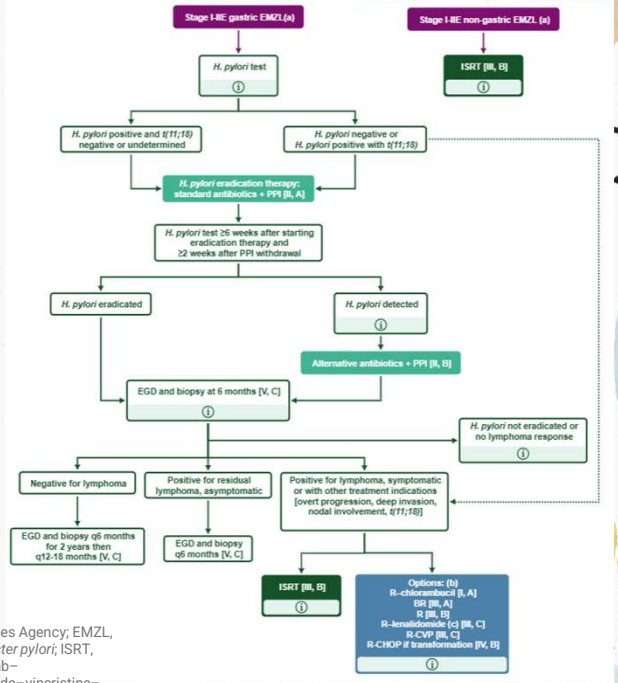
Treatment of MALT



BR, bendamustine–rituximab; EGD, oesophagogastroduodenoscopy; EMA, European Medicines Agency; EMZL, extranodal marginal zone lymphoma; FDA, Food and Drug Administration; *H. pylori*, *Helicobacter pylori*; ISRT, involved-site radiotherapy; PPI, proton pump inhibitor; q, every; R, rituximab; R-CHOP, rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone; R-CVP, rituximab–cyclophosphamide–vincristine–prednisone; RT, radiotherapy. ***Ann Oncol.* 2025;36(11):1263-1284**

MorningSun study design: 1L MZL cohort

Key inclusion criteria

- Symptomatic MZL (splenic, nodal, and extranodal, including gastric/MALT)
- Previously untreated, with an indication to start systemic therapy
- ECOG performance status 0–2

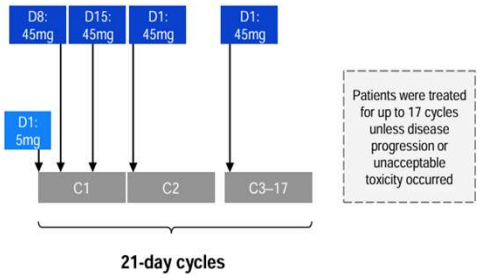
CRS mitigation

- Mosunetuzumab SC step-up dosing in C1
- Corticosteroid prophylaxis* was mandatory in C1–2 and optional thereafter
- Hospitalization was not mandatory

Endpoints

- Primary: INV-assessed ORR by Lugano criteria
- Key secondary: PFS, DOR, DOCR, time to response, safety

Mosunetuzumab SC administration

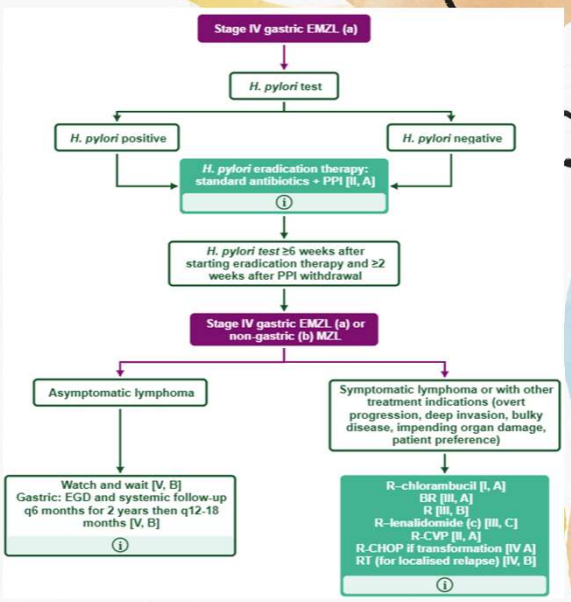


*Dexamethasone (20mg) or methylprednisolone (80mg); premedication with oral acetaminophen or paracetamol and/or diphenhydramine could also be administered prior to administration of mosunetuzumab.
C, cycle; CRS, cytokine release syndrome; D, day; DOCR, duration of complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; INV, investigator; MALT, mucosa-associated lymphoid tissue; ORR, objective response rate; PFS, progression-free survival.

ORR: 77.8%; CR: 63.9%

Burke EHA 2025

Treatment of MALT



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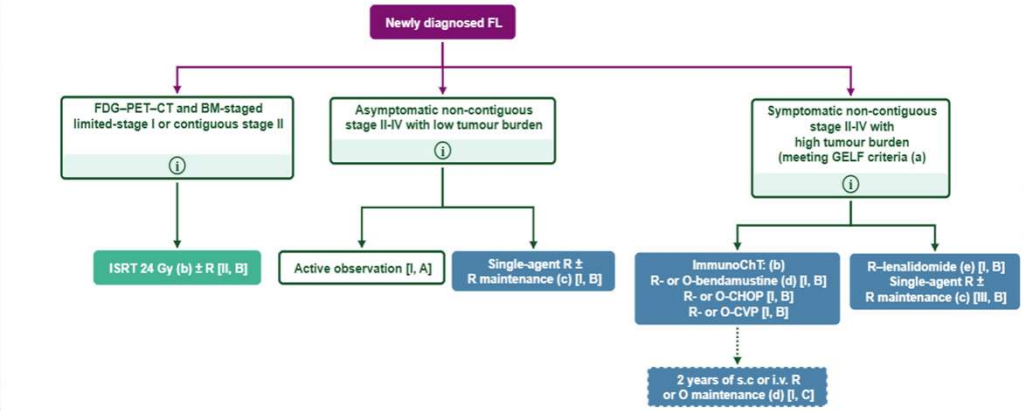
Characteristics and treatment of gastrointestinal (GI) FL

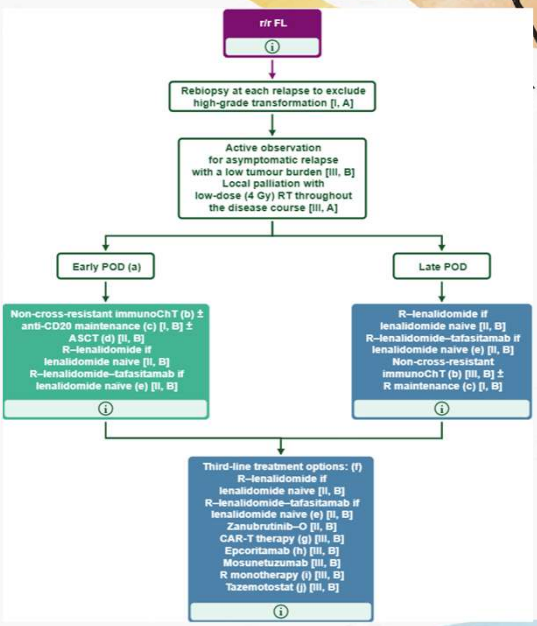
- FL is less common in the GI tract and can present with multiple nodules
- Duodenum is most common affected
- 1-3% of primary GI lymphoma
- Follow up or radiation or systemic treatment

Treatment of FL



BM, bone marrow; CHOP, cyclophosphamide–doxorubicin–vincristine–prednisone; CT, computed tomography; CVP, cyclophosphamide–vincristine–prednisone; EMA, European Medicines Agency; FDA, Food and Drug Administration; FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; ImmunoChT, immunochemotherapy; ISRT, involved site radiotherapy; i.v., intravenous; O, obinutuzumab; PCP, Pneumocystis pneumonia; PET, positron emission tomography; R, rituximab; s.c., subcutaneous.
***Ann Oncol*. 2025;36(11):1263-1284**

Treatment of R/FL

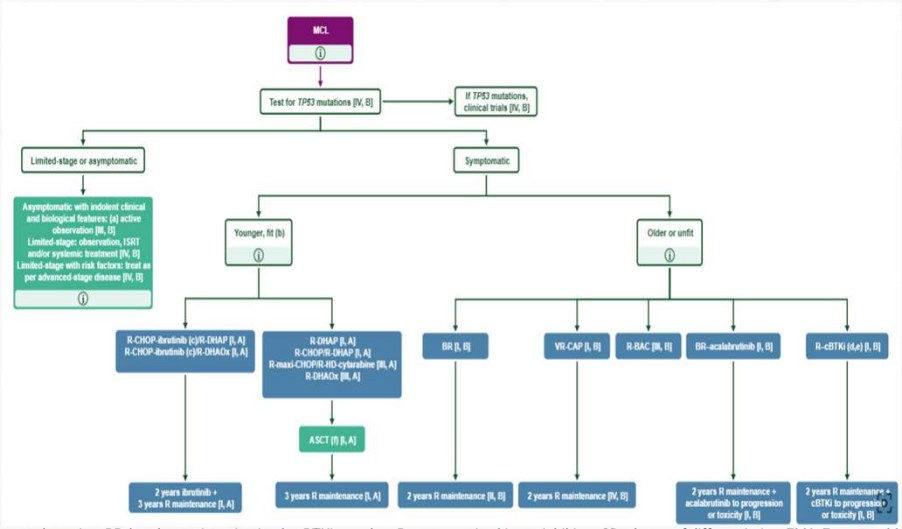


AlloSCT, allogeneic stem-cell transplantation; ASCT, autologous stem-cell transplantation; CAR-T, chimeric antigen receptor T-cell; EMA, European Medicines Agency; EZH, enhancer of zeste homologue; FDA, Food and Drug Administration; immunoChT, immunochemotherapy; FL, follicular lymphoma; O, obinutuzumab; POD, progression of disease; R, rituximab; r/r, relapsed or refractory; RT, radiotherapy. ***Ann Oncol*. 2025;36(11):1263-1284**

Characteristics and treatment of gastrointestinal (GI) MCL

- MCL typically presents as polyposis, involving multiple polyps or nodules throughout the GI tract.
- Classic MCL is the most common pathological variant
- Primary GI MCL 4-9% of all NHL
- Secondary GI MCL 15-30% of all NHL
- In advanced stage of MCL 90% have GI involvement

Treatment of MCL



ASCT, autologous stem-cell transplantation; BR, bendamustine–rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; CD, cluster of differentiation; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD, high dose; ISRT, involved-site radiotherapy; LN, lymph node; MCL, mantle cell lymphoma; MRD, minimal residual disease; R, rituximab; R-BAC, rituximab–bendamustine–cytarabine; R-CHOP, rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone; R-DHAOx, rituximab–dexamethasone–high-dose cytarabine–oxaliplatin; R-DHAP, rituximab–dexamethasone–high-dose cytarabine–cisplatin; R-maxi-CHOP, rituximab plus maximum strength cyclophosphamide–doxorubicin–vincristine–prednisone; VR-CAP, bortezomib–rituximab–cyclophosphamide–doxorubicin–prednisone. ***Ann Oncol.*** **2025;36(11):1263-1284**

Phase II Multicenter Study of BOVen

Dosing:

Zanubrutinib 160 mg oral twice daily | Obinutuzumab 1000 mg IVPB Cycle 1: day 1, 8, 15 Cycle 2-8: day 1 | Venetoclax 400mg oral daily 5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily

After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:

- CR and uMRD → Stop treatment
- <CR and/or dMRD → Continue ZANU and VEN

Key Eligibility Criteria:

- Previously untreated MCL (except localized RT prior)
- ***TP53* mutation (of any variant allele frequency)**
- ECOG ≤2, adequate organ and hematologic function (ANC >1, PLT >75, HGB ≥9 (unless due to MCL))

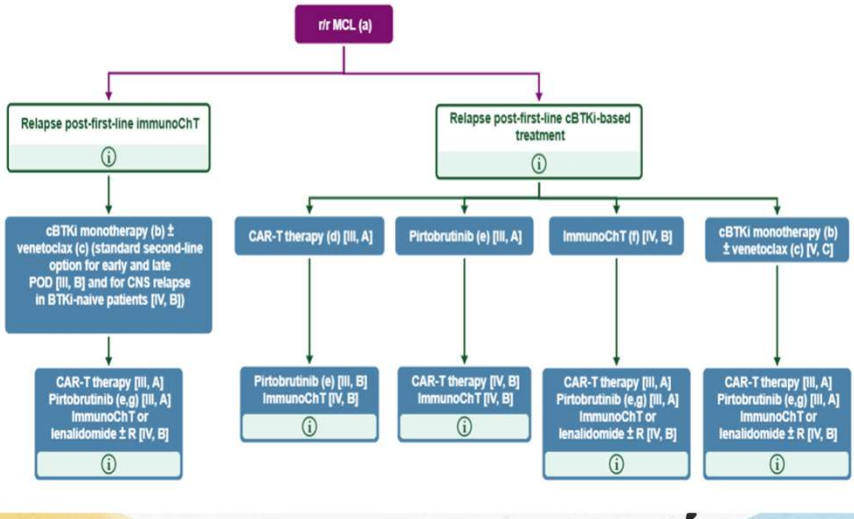
Primary Endpoint:

- 2-year progression-free survival.
- A promising 2-yr PFS rate ≥55% and an unacceptable rate ≤30%
- If ≥11 patients were progression-free at 2 years, the treatment regimen would be declared effective

2 letni PFS: 72%
ORR: 96%; CR: 88%

ICML 2025

Treatment of R/R MCL



AlloSCT, allogeneic stem-cell transplantion; CAR-T, chimeric antigen receptor T-cell; cBTKi, covalent Bruton tyrosine kinase inhibitor; CNS, central nervous system; EMA, European Medicines Agency; FDA, Food and Drug Administration; immunoChT, immunochemotherapy; MCL, mantle cell lymphoma; POD, progression of disease; R, rituximab; r/r, relapsed or refractory.

Ann Oncol. 2025;36(11):1263-1284

Treatment of Aggressive B-cell Lymphomas of the Gastrointestinal Tract

Barbara Jezeršek Novaković
Institute of Oncology Ljubljana
5th Lymphoma School
November 28th, 2025

Ann Hematol (2006) 85:849–856
DOI 10.1007/s00277-006-0172-7

ORIGINAL ARTICLE

A single-center study of treatment outcomes and survival in patients with primary gastric lymphomas between 1990 and 2003

Barbara Jezeršek Novaković · Marjeta Vovk · Tanja Južnič Šetina

Received: 19 May 2006 / Accepted: 3 July 2006 / Published online: 30 August 2006

Abstract Primary gastric lymphomas are the most common extranodal non-Hodgkin's lymphomas and are divided into indolent (low grade) and aggressive (high grade) types. They are mainly the disease of middle age, with a male predominance reported by most of the studies. For several years, surgery played a central role in diagnosis, staging, and treatment of this entity, yet recently there has been a move away from a surgical approach to conservative treatment. To determine the role of surgery as the initial treatment modality, we performed this retrospective single-center research on 245 patients with primary gastric lymphoma who were treated according to our protocol between 1990 and 2003. The patients' characteristics, distribution of histological types, treatment results, and disease-specific survival were followed. According to the histology, 59.2% had diffuse large B-cell lymphoma (DLCL), 26.1% MALT lymphoma, 9.8% mixed lymphoma (indolent and aggressive at the same time), while other types were infrequent. In total, 161 patients (65.7%) were treated with surgical resection as the initial treatment, which was then followed or not by additional therapy (chemotherapy, chemotherapy and radiotherapy, radiotherapy) depending on the histological type of lymphoma and the extent of residual disease after surgery. In 84 patients (34.3%), the treatment approach was conservative. The selection of treatment (chemotherapy, chemotherapy and radiotherapy, radiotherapy or *Helicobacter pylori* eradication only) was based on the histological type of lymphoma, considering also the patients' physical condition. The disease-specific survival in the group of patients who underwent surgery was statistically significantly better than in patients who were treated conservatively ($p=0.049$). At 5 years, it was 96.9% for the group treated with surgery and 89.8% in patients treated conservatively. However, the results were biased, as the patients who were treated conservatively were either in a worse performance status or presented with a more extensive disease. Similarly, in the DLCL type the disease-specific survival was better in the surgically treated group (97.2%) than in the conservatively treated patients (89.2%). The difference was barely significant ($p=0.046$) and again the results have to be considered with caution due to the selection of patients in a worse performance status or with a more extensive disease for conservative treatment. In the MALT lymphoma and mixed lymphoma types, there were no differences in the disease-specific survival between both treatment groups. Regarding the statement that for conservative treatment patients were selected who were unsuitable for the resection on account of concomitant diseases or due to the fact that the process was inoperable, we believe that the conservative approach gives comparable outcomes to the approach including initial surgery. The existing evidence thus no longer justifies surgery as the standard initial treatment and preference should be given to conservative treatment approaches.

Keywords Conservative treatment · Primary gastric lymphomas · Surgical treatment · Single center study

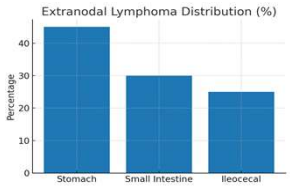
B. Jezeršek Novaković (✉) · M. Vovk · T. Južnič Šetina
Department of Medical Oncology,
Institute of Oncology Ljubljana,
Zaloška 2,
1000 Ljubljana, Slovenia
e-mail: bjezersek@onko-i.si

Introduction

Gastrointestinal tract lymphomas are predominately of NonHodgkin's (NHL) type. They are rather rare and

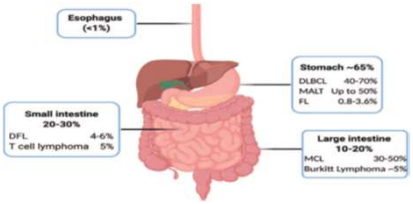
Epidemiology

- Extranodal lymphomas: ~30–40% of NHL
- GI tract = most common extranodal site (up to 40% of all extranodal NHL)
- Common sites: stomach (65%), small intestine (20%–30%), colon (10%–20%); uncommon: esophagus (<1%), hepatobiliary system and pancreas (<1%)



Epidemiology

- Majority of GI lymphomas are NHL of B-cell lineage with DLBCL and MALT lymphoma comprising the greater part of cases
- T-cell lymphomas are uncommon - account for 4% to 6% of GI tract lymphomas



Pathological Entities

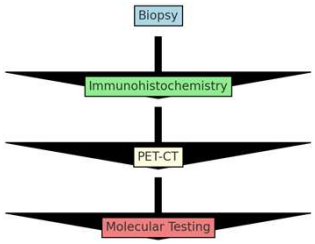
- Diffuse Large B-cell Lymphoma (DLBCL) – most common
- High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
- Burkitt Lymphoma – ileocecal region

Clinical Presentation

- Abdominal pain, obstruction, perforation
- GI bleeding
- B-symptoms (fever, weight loss, night sweats)
- Often mimics GI adenocarcinoma or IBD

Diagnostic Workup

- Endoscopic biopsy
- Histopathology with IHC
- PET-CT for staging
- Bone marrow biopsy, molecular profiling



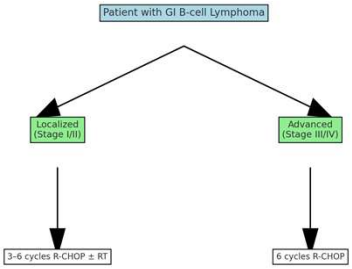
Treatment Principles

- Lugano staging system
- Systemic therapy is mainstay
- Surgery/radiation reserved for complications
- Localized vs advanced stages guide therapy

Stage	Extent of lymphoma
I	Confined to GI tract (single primary, or multiple non-contiguous lesions)
II	Extending into abdomen from primary GI site II_1 = local nodal involvement II_2 = distant nodal involvement
II E	Penetration of serosa to involve adjacent organ or tissues Specify site of involvement, e.g. IIE (pancreas) If both nodal involvement and involvement of adjacent organs, denote stage using both a subscript (1 or 2) and E, e.g. II_1E (pancreas)
IV	Disseminated extra-nodal involvement or concomitant supra-diaphragmatic nodal involvement

First-line Therapy (DLBCL)

- R-CHOP is standard backbone
- Localized: 3–6 cycles ± RT
- Advanced: 6 cycles R-CHOP; R-polatuzumab CHP
- Comparable outcomes to nodal DLBCL



High-grade B-cell Lymphoma

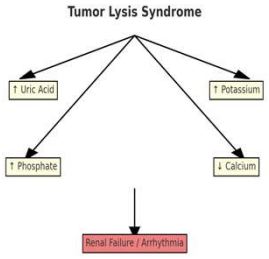
- High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements = poor prognosis with R-CHOP
- Intensified regimens: **DA-EPOCH-R**, R-CODOX-M/IVAC
- CNS prophylaxis required

Burkitt Lymphoma

- Requires intensive short-course therapy
- Regimens: **BFM protocol**, R-CODOX-M/IVAC, R-HyperCVAD
- High-dose methotrexate essential
- CNS prophylaxis mandatory

Supportive Care

- Prevent tumor lysis syndrome (esp. Burkitt)
- Monitor for GI perforation during therapy
- Nutritional and supportive management

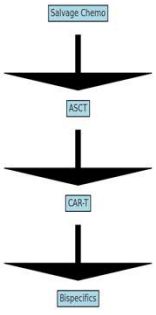


Role of Surgery & Radiation

- Surgery only for emergencies: perforation, bleeding, obstruction
- Radiation: rarely, selected localized gastric DLBCL following R-CHOP

Relapsed/Refractory Disease

- Salvage chemoimmunotherapy (R-DHAP, R-ICE*)*
- Autologous stem cell transplant (ASCT) if eligible
- Novel therapies: CAR-T, Polatuzumab-R-bendamustine, Tafasitamab + lenalidomide
- Clinical trial participation encouraged



Prognosis

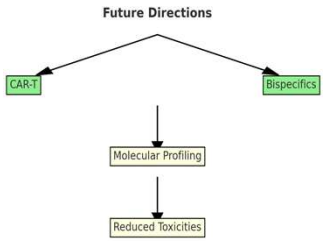
- Depends on histology, IPI, stage, *MYC/BCL2* status
- Adverse events: GI perforation, bleeding
- PET-CT (Deauville) for response assessment
- The 5 years OS in gastric DLBCL is between 84% and 100%, and complete remission is achieved in 92% to 100% of patients with R-CHOP±RT

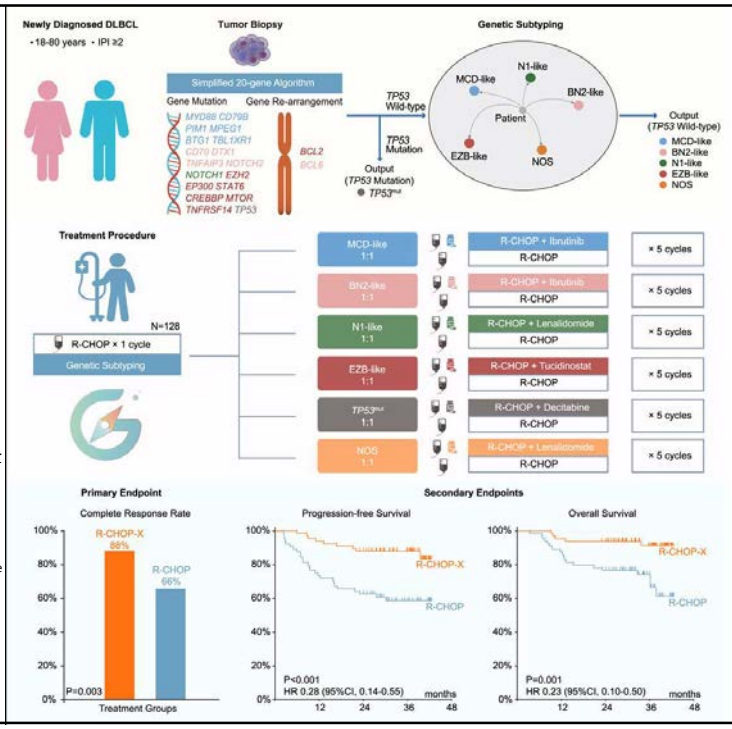
Follow-up

- Regular clinical assessment
- Imaging as indicated
- Long-term surveillance

Future Directions

- Molecular profiling for precision therapy
- Bispecific antibodies (glofitamab, epcoritamab)
- CAR-T earlier in treatment algorithm
- Reducing late toxicities

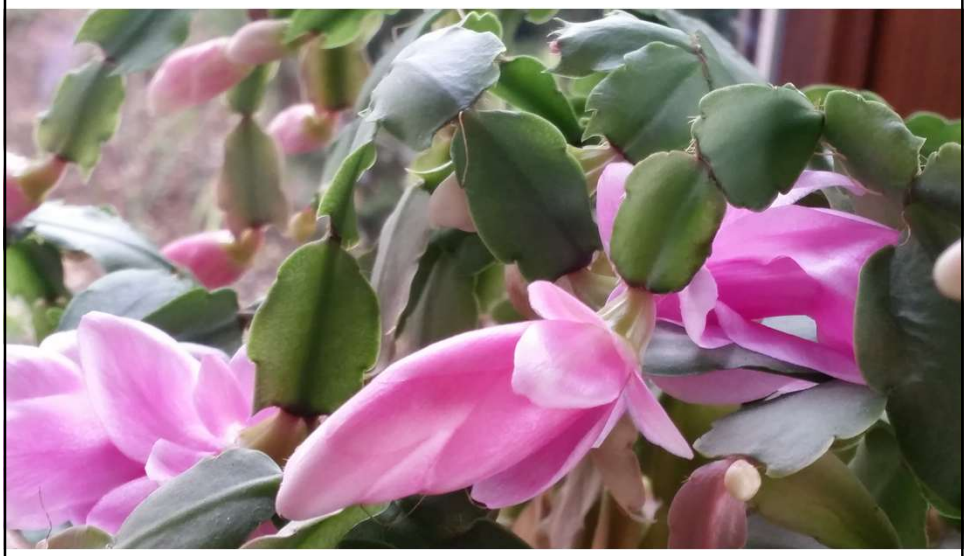




Genetic subtype-guided immunochemotherapy in diffuse large B cell lymphoma: The randomized GUIDANCE-01 trial
Zhang, Mu-Chen et al.
Cancer Cell, Volume 41, Issue 10, 1705 - 1716.e5

Conclusion

- Prompt systemic therapy required
- R-CHOP standard, intensified therapy for high-grade biology
- Novel immunotherapies transforming relapse treatment
- Multidisciplinary care is key



ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

The role of radiotherapy in the treatment of indolent and aggressive gastrointestinal B-cell lymphomas

Marija Skoblar Vidmar

Ljubljana, 28. 11. 2025

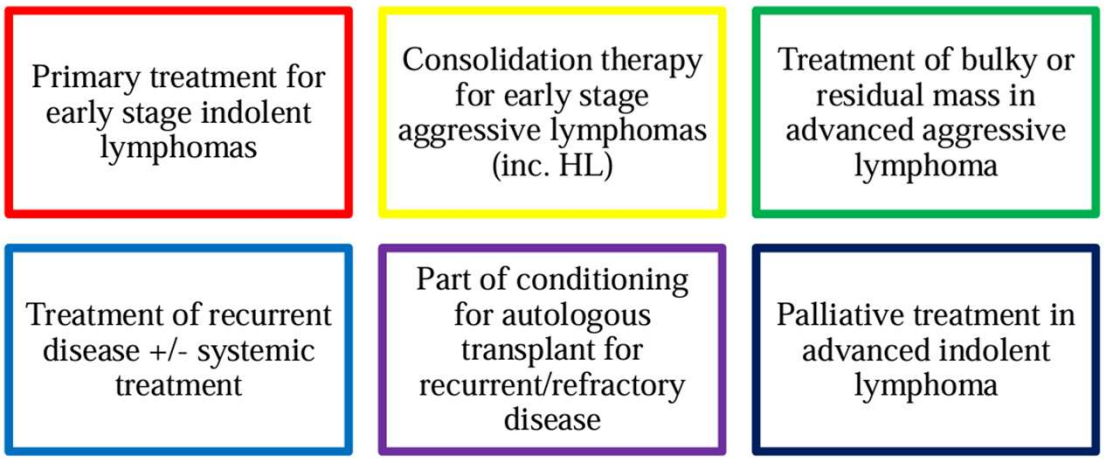
Introductory remarks

Primum non nocere (Hippocrates) is a fundamental concept in medicine.
In radiotherapy, the concept of precision medicine is achieved through the precise application of radiation dose to a precisely defined area (target volume).

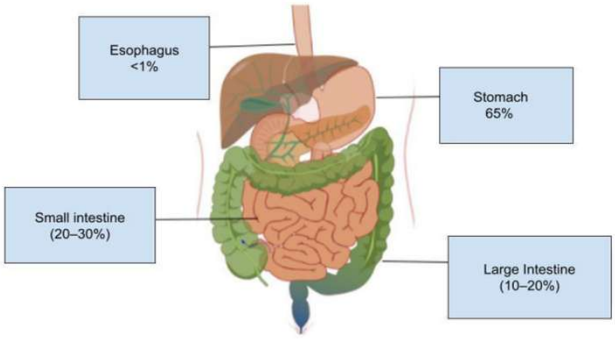
GOAL: To kill the tumor and to spare the normal tissue.

Lymphoma – radiosensitive disease

- Radiotherapy has historically played – and continues to play – a meaningful role in their management.
- Most active single modality in the treatment of some types of lymphoma.
- Part of the combined modality treatment.
- Often as a consolidatory treatment after primary chemotherapy.



Sites of involvement of GI lymphoma



Nagesh, V.K.; et al. Gastrointestinal Lymphomas: A Comprehensive Review of Epidemiology, Clinical Features, Diagnosis, Histopathology, and Management. Lymphatics 2025

Radiotherapy for Indolent Lymphoma

Gastric MALT lymphoma
Duodenal type follicular lymphoma

- ✓ Highly effective
- ✓ Organ – preserving
- ✓ Often curative modality for localized disease

- Modern techniques and dose-de-escalation strategies continue to refine the balance between excellent tumor control and minimal toxicity.

Lugano Staging System for Gastrointestinal Lymphomas		Lugano Modification of Ann Arbor Staging System	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension
Stage I	Confined to GI tract[a]			
	I_1 = mucosa, submucosa	I_E	T1 N0 M0	Mucosa, submucosa
	I_2 = muscularis propria, serosa	I_E	T2 N0 M0	Muscularis propria
		I_E	T3 N0 M0	Serosa
Stage II	Extending into abdomen			
	II_1 = local nodal involvement	II_E	T1-3 N1 M0	Perigastric lymph nodes
	II_2 = distant nodal involvement	II_E	T1-3 N2 M0	More distant regional lymph nodes
Stage IIE	Penetration of serosa to involve adjacent organs or tissues	II_E	T4 N0 M0	Invasion of adjacent structures
Stage IV[b]	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement		T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/ distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

Clinical Indications

- **Stage I–II.1** gastric MALT lymphoma *HP*+
- Persistent 12 months after eradication therapy, and the patient has translocation 11/18.
- If the patient does not have a confirmed 11/18 translocation, or if this information is unavailable, RT is administered only if, 18 months after diagnosis, the biopsy remains positive for lymphoma and negative for *HP*.
- If the patient is symptomatic, we repeat the gastroscopy earlier. In the case of progression, or if the patient is symptomatic, we initiate radiotherapy immediately.

Clinical Indications

- **Stage II. 2–II.E** gastric MALT lymphoma *HP*+ or *HP*-
- In stage II.2 and II.E, radiotherapy may be considered based on an individual decision, similar to localized disease, taking into account the size of the radiation field.

Dose strategy

- 24 Gy – 30 Gy remains the traditional curative dose

CANCER RESEARCH AND TREATMENT

Original Article
Hematologic malignancy 2024

Long-term Clinical Efficacy of Radiotherapy for Patients with Stage I-II Gastric Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue: A Retrospective Multi-institutional Study

INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY · BIOLOGY · PHYSICS ASTRO

2019, RETROSPECTIVE DATA

Outcomes After Reduced-Dose Intensity Modulated Radiation Therapy for Gastric Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

Dose de-escalation

Current prospective evidence strongly supports the use of definitive radiation therapy **(24-25.5 Gy)** for the treatment of *H pylori*-independent stage IE gastric MALT lymphoma.

March 2025

CLINICAL INVESTIGATION

Reduced-dose Radiation Therapy for Stage IE Gastric Mucosa-Associated Lymphoid Tissue Lymphoma: A Multi-Institutional Prospective Study (KROG 16-18)

Dose de-escalation

Trial – in progress

This trial studies the effectiveness of low-dose radiation therapy with **20 Gy** in 10 fractions for the treatment of patients with stage I-II stomach or duodenal Lymphoma (Marginal Zone or Follicular)

Marginal Zone Lymphoma/Follicular Lymphoma

Trial to assess the Efficacy of Low Radiation Dose of 20 Gy for the Treatment of Marginal Zone Lymphoma or Follicular Lymphoma Stage I-II localized in the Stomach or the Duodenum

Ultra low dose RT

THE LANCET Haematology 2025

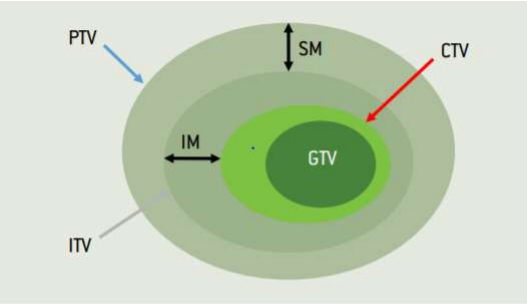
Response-adapted ultra-low-dose 4 Gy radiation as definitive therapy of gastric MALT lymphoma: a single-centre, pilot trial

- ✓ Single-centre, single-arm, prospective trial at MD Anderson Cancer Center (Houston, TX, USA)
- ✓ Most patients had a complete response after 4 Gy radiotherapy; all who required an additional 20 Gy had a complete response within 12 months.

Treatment Planning and Delivery

- Involved site radiotherapy – ISRT
- Reduced inter- and intrafractional target motion (DIBH, 4D – CT)
- Restriction of oral intake before treatment - daily treatments are scheduled for the early morning
- Nongaseous diet throughout the course of therapy
- Supine position
- Daily CBCT

ISRT – irradiation volumes



GTV – Gross Tumor Volume
CTV – Clinical Tumor Volume
It encompasses the GTV as well as the volume of tissue involved by malignant cells, including regions of subclinical disease.
ITV – Internal Target Volume
Represents the internal margin added to the CTV to account for expected physiological movements of the target, such as respiration, peristalsis, or organ filling.
PTV –planning target volume
A geometric concept that incorporates the ITV plus a setup margin (SM), ensuring adequate dose delivery despite internal motion and patient setup uncertainties.

GTV	Visible tumor	Tumor definition
CTV	GTV + microscopic spread	Biological target
ITV	CTV + motion	Accounts for internal movement
PTV	ITV + setup uncertainties	Ensures dose coverage despite positioning errors

Organs at risk and dose constraints

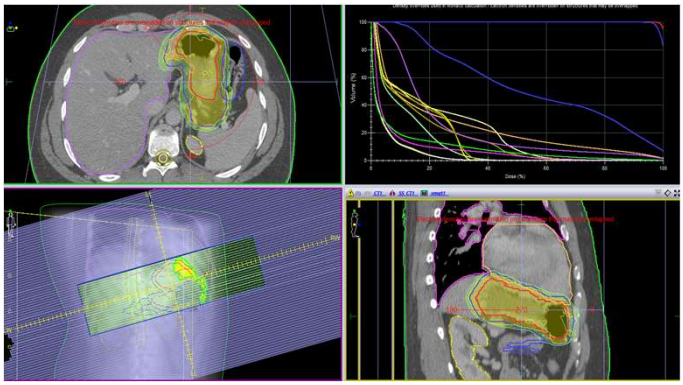
- The unique radiosensitivity of lymphoid malignancies means that dose constraints for normal tissues used for solid tumors are not applicable.
- Modern conformal techniques should be used for lymphomas, not primarily as in solid tumors, to allow a high target dose to be delivered, but to minimize the risk of long-term complications.
- A major problem is not acute toxicity; it is late effects.

ILROG Dose Constraints for Lymphoma

Organ	Constraint
Heart	Mean <5–10 Gy; V25 <10%; LAD mean <10 Gy
Lungs	Mean <13–15 Gy; V20 <30%
Breasts (young women)	Mean <4 Gy ideal; V4 as low as possible
Thyroid	Mean <26 Gy; V25 <50%
Parotids	Mean <20 Gy
Spinal cord	Max <36–40 Gy
Liver	Mean <15–18 Gy; V30 <30%
Kidneys	Mean <18 Gy; V20 <30%
Stomach/Bowel	Max <30–32 Gy; V15 as low as possible

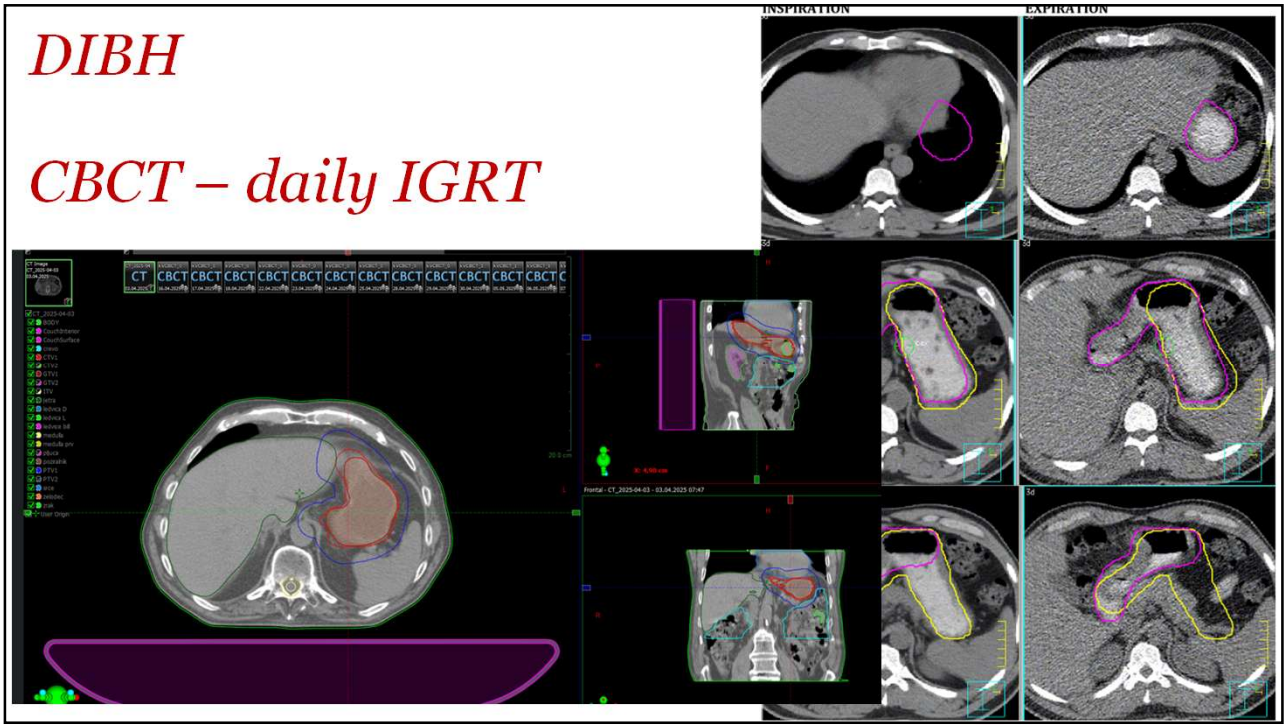
VMAT / IMRT

- Precise dose shaping for the tumor while sparing normal tissues, reducing acute and long-term toxicity.
- OAR Protection: Limits dose to liver, kidneys, bowel, and pancreas.



DIBH

CBCT – daily IGRT



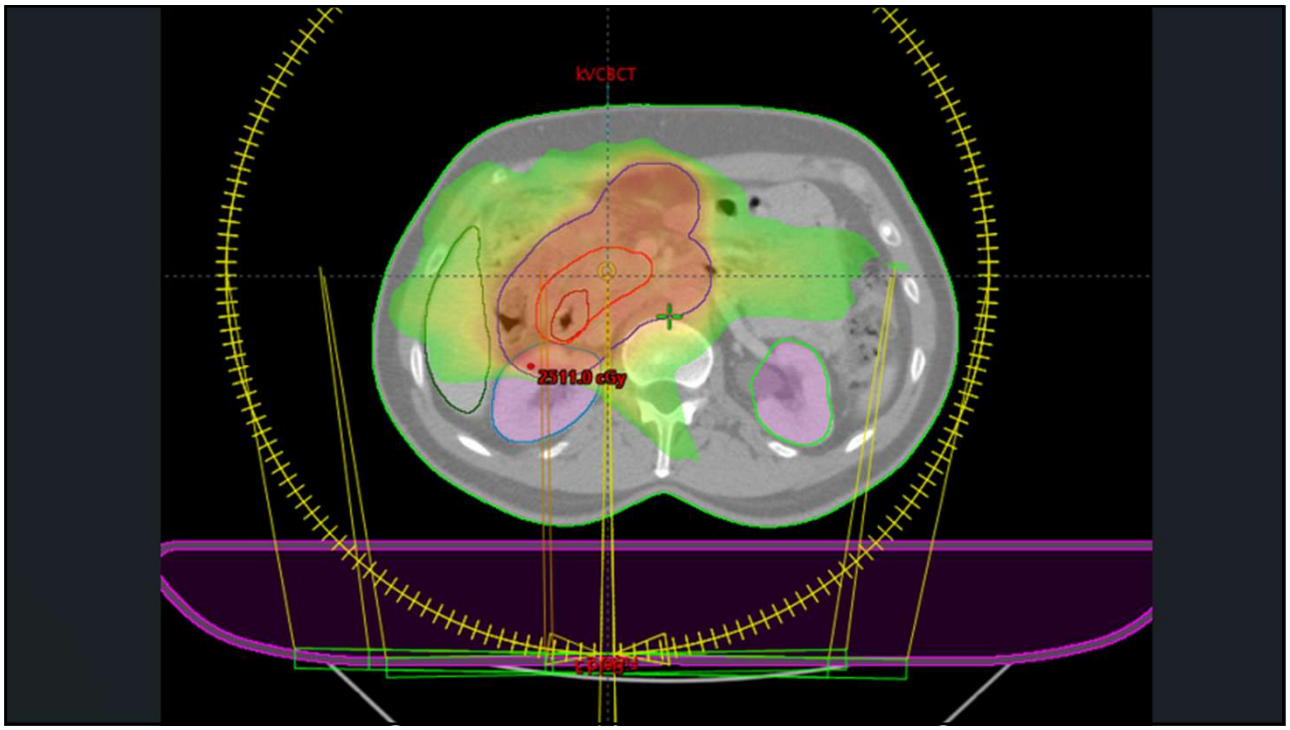
Duodenal type FL

- Duodenal-type FL (DFL), which was recognized in the 2017 World Health Organization classification, is a rare and specific variant of FL that is predominantly involved in the second portion of the duodenum.

CANCER RESEARCH AND TREATMENT
http://e-crt.org/

Radiation Therapy Outcome and Clinical Features of Duodenal-Type Follicular Lymphoma

✓ In 2018, on 20 patients, a retrospective analysis



Aggressive lymphoma

Front Oncol. 2024 Sep

Outcomes and toxicities in patients with diffuse-large B cell lymphoma involving the gastrointestinal tract and digestive organs

Retrospective GI-DLBCL (n=204; 65 received RT): 5-yr OS 88%, PFS 84%, 82% CR

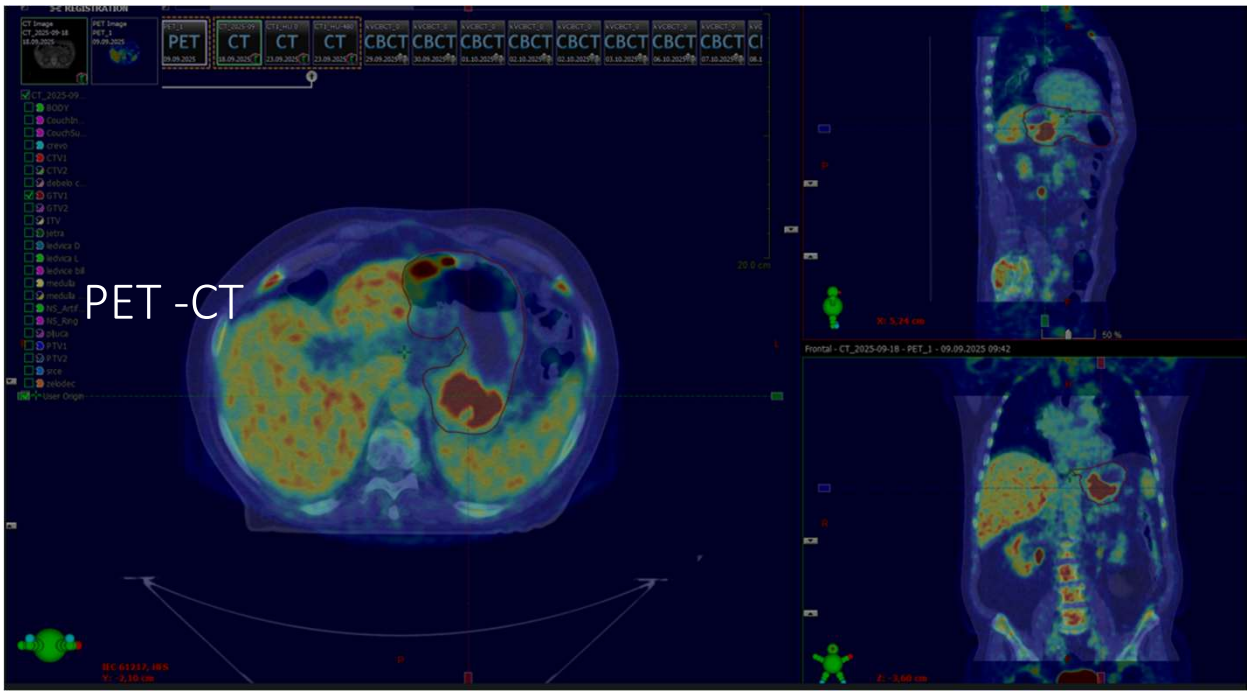
- Stomach-directed RT vs. RT to other sites correlated with improved PFS and OS (p<0.04).
- Mitigate the relapse risk associated with incomplete disease response or bulky disease.
- In the RT group, excellent local control, minimal late toxicity.

Purpose of combined-modality therapy

✓Combined-modality treatment is important because a subset of aggressive lymphomas arises from or coexists with an indolent component.

This indolent clone may persist after systemic therapy and remains highly radiosensitive, making RT an effective modality for achieving local control.

Zimmermann et al.Radiotherapy for Non-Hodgkin's lymphoma: still standard practice and not an outdated treatment option; . Radiation Oncology (2016)



Relapsed/Refractory DLBCL

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Role of Radiation Therapy in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group

- As a part of the salvage program
- Improved local control and clinical outcomes
- Can provide effective palliation
- In selected cases, it can be administered with curative intent if the relapsed/refractory disease is localized.
- Doses are higher – 45 – 50 Gy

Conclusions

- RT provides excellent local control and is often *curative* in localized indolent GI lymphomas.
- Modern RT techniques (IMRT/VMAT, IGRT, ISRT) allow precise tumor targeting while *sparing organs at risk*, reducing acute and long-term toxicity.
- RT improves outcomes in aggressive GI lymphomas, especially as *post-systemic consolidation*.
- In palliative care, RT can rapidly *relieve symptoms* (pain, bleeding, obstruction), improving quality of life.

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The role of cytopathologists and pathologists in the diagnostics of T-cell lymphomas of the GIT

Vloga citopatologov in patologov v diagnostiki T limfomov iz GIT

Assoc. prof. Veronika Kloboves Prevodnik, MD, PhD
Assist. prof. Gorana Gašljević, MD, PhD
Institute of Oncology Ljubljana, Slovenia

Institute of Oncology Ljubljana, 28th November 2025

The role of pathologists in the diagnostics of T-cell lymphomas of the GIT

- Diagnostics of primary tumors according to the WHO5/ICC2022 Classification
- Bone marrow staging
- Diagnostics of progression/recurrent disease when cytology has failed

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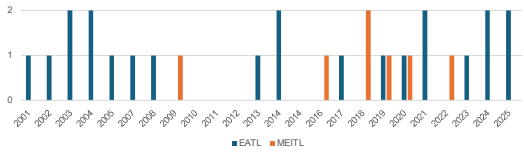
T-cell lymphomas of the GIT at the Institute of Oncology Ljubljana *(Data provided by Assist. Prof. Lučka Boltežar)*

- 29 cases of T-Cell lymphomas of the GIT diagnosed and treated at Institute of Oncology Ljubljana from 2001 to 2025
  - 22 enteropathy-associated T-cell lymphomas (EATL)
  - 7 monomorphic epitheliotropic intestinal T-cell lymphomas (METL)



- Cytopathological examination
  - 11 cases

The role of cytopathologists in the diagnostics of T-cell lymphomas of the GIT

- Bone marrow staging
  - Bone marrow aspiration performed simultaneously with trephine biopsy
- Diagnostics of treatment response, progressive and recurrent disease
- Flow cytometric diagnostics of refractory celiac disease (RCD)

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Accurate cytopathological diagnosis of T-cell lymphomas of the GIT based on

- Clinical data
- Morphological features
- Immunophenotypic studies
  - Flow cytometry
  - Immunocytochemistry
- Molecular studies
  - Clonality analysis (BIOMED II)

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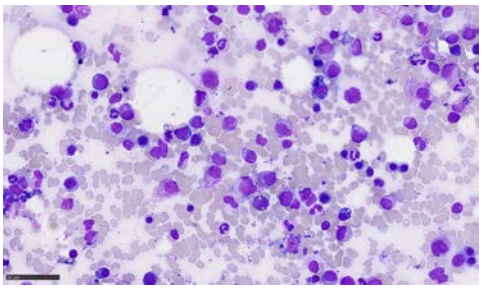
Bone marrow examination



Flow cytometry: 0.3% of the cells are with aberrant immunophenotype (CD3+, CD5-, CD7+, CD2+, CD4- CD8+, CD56-, CD30-) Differential diagnosis: T-CUS

Clonality analysis (Biomed II): Monoclonal T-cells

Histology: 1% lymphoma cells (a few large, atypical, CD3+, CD5- cells)

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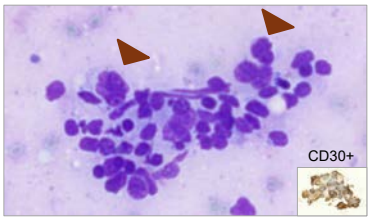
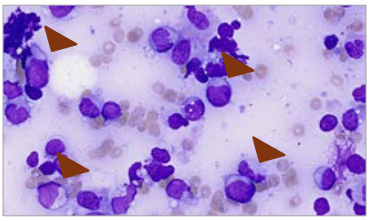
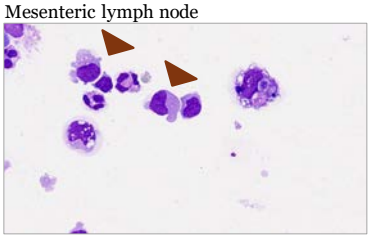
Progressive/recurrent disease



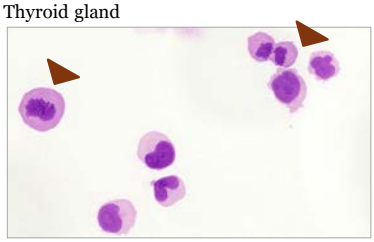
Mesenteric lymph node



Thyroid gland



Pleural effusion



Cerebrospinal fluid

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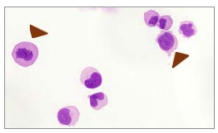
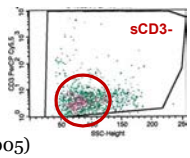
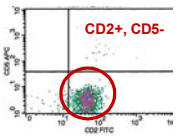
Flow cytometric immunophenotyping in progressive/recurrent disease is challenging

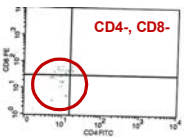
- Lymphoma cells are difficult to find and display
  - Mixed with numerous reactive T-cells, as well as B-cells
- Dedicated at least 10 color antibody panels
  - Backbone markers: sCD3, cCD3, CD4, CD8, CD103
  - Additional markers: CD5, CD7, CD2, CD56, TCR $_{\text{alpha/beta}}$, TCR $_{\text{gamma/delta}}$, CD30
- T-cell gene rearrangement studies (Biomed II) are mandatory



Cerebrospinal fluid (from 2005)







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Celiac disease

- Gluten-sensitive enteropathy which is an immune mediated inflammatory disease of the small intestine seen in genetically predisposed individuals and is caused by sensitivity to gluten.
  - Clinical presentation: broad spectrum, ranging from fully asymptomatic to severe morbid conditions from malabsorption to micronutrition deficiency with failure to retrieve
  - Serology: IgA or IgG celiac disease specific antibodies (*anti-deamidated gliadin peptide, anti-tissue transglutaminase, auto-Ab; anti-endomysial Ab)*
  - Histology: > 25 IELs /100 epithelial cells, villous atrophy and crypt hyperplasia.
- The characteristic histological features associated with CD are not pathognomonic and are shared by other conditions
- Treatment: strict adhesion to long life gluten-free diet, GFD)
  - RESPONDERS ➔ complete remission of the disease
  - NON-RESPONDERS
    - Poor patient compliance and/or inadherent food contamination with gluten
    - Due to the intrinsic factors which result in RCD

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Clinicopathological presentation of celiac disease

- **Active celiac disease**
  - Positive serology, villous atrophy, with or without symptoms
- **Silent celiac disease**
  - Positive serology, villous atrophy without symptoms
- **Latent celiac disease**
  - Positive serology, no villous atrophy
- **Refractory celiac disease (type 1 and type 2)**
  - Persistent villous atrophy with no clinical improvement or even recurrent malabsorptive symptoms despite the adherence to a strict gluten-free diet for > 12 months
- **EATL**
  - Aggressive, primary T-cell lymphoma of intraepithelial lymphocytes (IELs) which exhibits variable cell pleomorphism and usually occurs in patients with celiac disease

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Refractory celiac disease

- Defined as any CD with clinical and histological unresponsiveness to 12 months of strict GFD
- Prevalence of 0.3-0.4% among CD patients
- Diagnosed between 40 and 60 years of age
- The incidence progressively decreased
  - Timely diagnoses
  - Availability of gluten-free products
- Two subtypes:
  - RCD type 1: Normal IELs (sCD3+, cCD3+, CD8+,usually TCR alpha/beta+)
  - RCD type 2: Immunophenotypically aberrant IELs (sCD3-, CD3+, CD8-)

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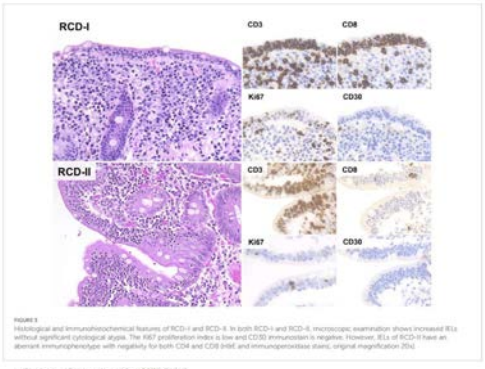
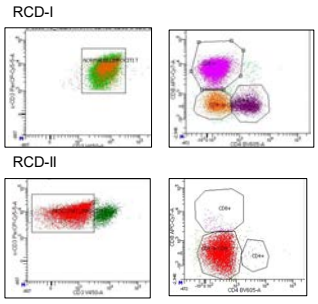
Histological, IHC and flow cytometric features of RCD-I and RCD-II



Front. Oncol. 13:1273305.
doi: 10.3389/fonc.2023.1273305

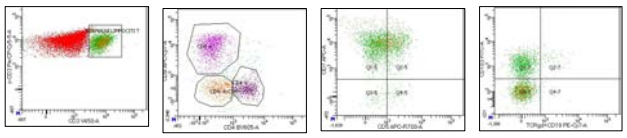


Polyclonal, phenotypically normal IELs

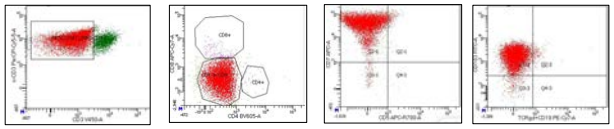
- **Clonal immunophenotypically aberrant IELs**
- **>50% on immunohistochemistry**
- **> 20% on flow cytometry**

Flow cytometric analysis of IELs in RCD-II

- IELs with normal immunophenotype:
  - sCD3+, cCD3+, CD4 or CD8+, small subset of CD4 and CD8-, TCR alpha/beta+, CD103+, CD5-, CD30-



- > 20% IELs with aberrant immunophenotype :
  - sCD3-, cCD3, CD4-, CD8-, TCR alpha/beta-, CD103+, CD5-, CD30-



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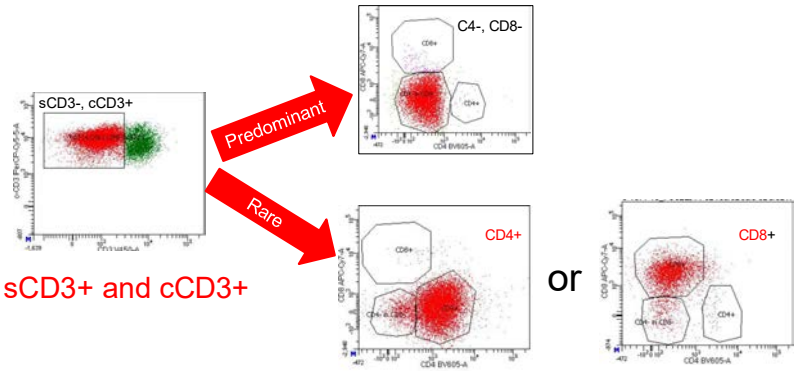
Unexpected IELs immunophenotype in RCD-II



sCD3+ and cCD3+

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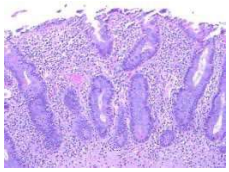
Immunophenotypic features of CD, RCD and EATL

Histology: /
FC: high TCRγ8CD8+ and low sCD3-, cCD3+
Biomed II: Polyclonal T-cells

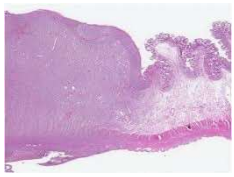
Active celiac disease



https://www.pathologyoutlines.com/topic/smallbowelceliacsprue.html

Histology: > 25 CD3+, CD8+/100 epithelial cells
FC: < 5% of sCD3-, cCD3+, and increase of TCRγ8CD8+
Biomed II: Polyclonal T-cells/rarely and transitionally monoclonal T-cells

Refractory celiac disease type1



https://www.nature.com/articles/modpathol201585

Refractory celiac disease type 2

Histology: > 50% cells CD3+, CD8-
FC: > 20% IELs with abberant immunophenotype: sCD3-, c-CD3+, CD4-, CD8-, CD103+, CD30-
Biomed II: Monoclonal T-cells

EATL

Histology: CD3+, CD5-, CD7+, CD4-, CD8-, CD56-, CD103-+, CD2+/-, **CD30+, high proliferative activity**
FC: Lymphoma cells: sCD3-, c-CD3+, CD4-, CD8-, CD103+, **CD30+**
Biomed II: Monoclonal T-cells

Distinguishing features of CD, RCD-I, RCDII and EATL

	CD	RCD-I*	RCD-II	EATL
B symptoms	–	–	-/+	+
Small bowel occlusions	–	–	–	+
Abdominal masses	–	–	–	+
Mesenteric lymphadenopathies	–	–	–	+
Aberrant IEL morphology	–	–	-/+	+
Aberrant IEL phenotype	–	–	+	+
Proliferation index	Low	Low	Low	High
CD30 expression	–	–	–	+
Infiltration of the LP	–	–	+ (minimal)	+ (massive)
Treatment	Gluten-free diet	Corticosteroids +/- Immunosuppression	Corticosteroids +/- Chemotherapy +/- ASCT	Chemotherapy + ASCT
5-year overall survival	≈100%	80-95%	44-58%	11-20%

*RCD-I is distinguished from CD on clinical grounds only (i.e. persistence of malabsorption and villous atrophy after ≥12 months of strict gluten-free diet)
CD, Celiac disease; RCD-I, Refractory celiac disease type I; RCD-II, Refractory celiac disease type II; EATL, Enteropathy-associated T-cell lymphoma; IELs, Intraepithelial lymphocytes; LP, Lamina Propria; ASCT, Autologous stem cell transplantation.

Scarmozzino et al. Front. Oncol. 13:1273305. doi: 10.3389/fonc.2023.1273305

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Role of flow cytometry in diagnostics of celiac disease

- Diagnosis and monitoring of RCD-II
- Distinction of multiple T-cell populations with altered proportions in active disease and even after gluten withdrawal
  - **Intraepithelial lymphogram**
    - Suport the diagnosis of CD with non-specific clinico-pathological presentation
  - **Blood lymphogram**
    - Non-invasive diagnostics of CD
- Multicolor flow cytometers and multiplex antibody panels must be used
  - CD45, CD19, s-CD3, cCD3, CD8, CD4, CD103, CD5, CD7, CD56, TRCψ0, CD30

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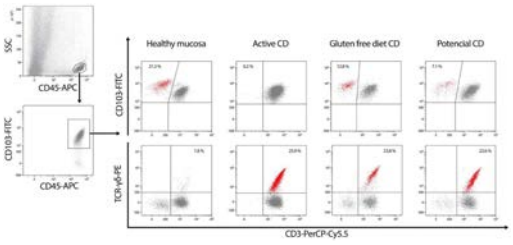
Intraepithelial lymphogram

- Ratio between TCRψ8^{+} CD8^{+} and sCD3^{-}IELs
  - ⬆ TCRψ0CD8+ and ⬇ sCD3^{-}, CD8^{-}, CD4^{-}
- It is recognized that it does not provide a 'gold standard' for the diagnosis of CD, but the use of flow cytometry phenotyping of IELs can reinforce the diagnosis of CD when it is not clear-cut.



Roy G. et al. Front. Immunol. 13:1081955. doi: 10.3389/fimmu.2022.1081955

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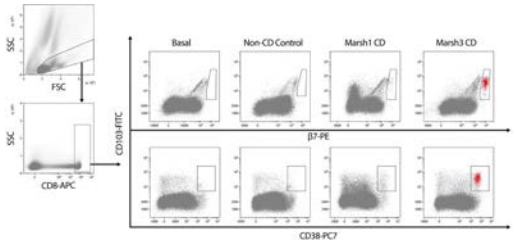
Blood lymphogram

- Gut-homing T-cells in blood
- 3-day gluten challenge accompanied by two blood extractions: one before gluten intake and the second 6 days later
- FC detection of CD103, integrin β7, CD38 and CD8
- Noninvasive diagnostics of CD



Roy G. et al. Front. Immunol. 13:1081955.
doi: 10.3389/fimmu.2022.1081955

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Conclusions

- Multicolor flow cytometry is a well-established method for diagnosing and monitoring RCD-II, and it can define different IELs populations more precisely than immunohistochemistry.
- The clinical utility of intestinal and blood lymphograms should be further explored.

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Managing coeliac disease and when to suspect T-cell lymphoma?

Jurij Hanžel

28th November 2025

MF UNIVERSITY OF LJUBLJANA Faculty of Medicine

Introduction

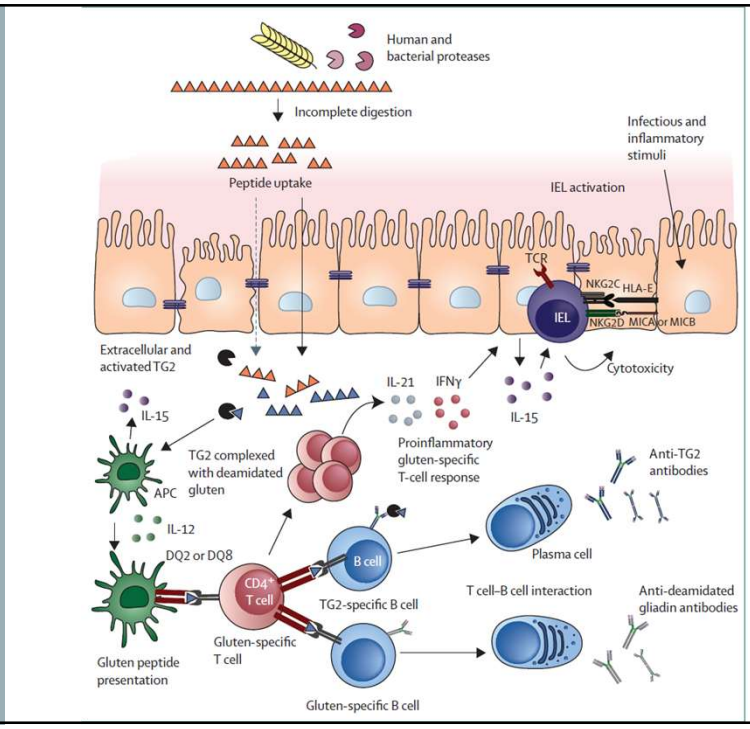
- Autoimmune disorder primarily affecting the small intestine in genetically susceptible individuals ingesting gluten
- Variable clinical presentation, diverse extraintestinal manifestations, potentially deadly
- Highly effective, but bothersome treatment – gluten-free diet

Epidemiology

- Average prevalence of ~1% (typical range 0.5–2%)
- Higher in Scandinavia (3% in Sweden), lowest in East Asia (dependent on HLA haplotypes)
- Commoner in females than males

Catassi C et al. Lancet 2022;399:2413-26.

Pathogenesis



Catassi C et al. Lancet 2022;399:2413-26.

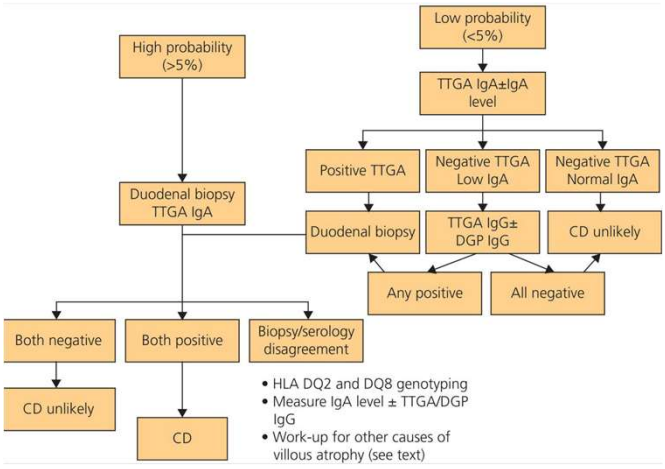
Clinical presentation

- Classical: child with diarrhea, poor appetite, weight loss, malnutrition
- Non-classical (commonest phenotype!): vague abdominal complaints, iron deficiency anaemia, elevated liver enzymes, fatigue
- Subclinical: identified through case-finding in high-risk groups

Diagnosis

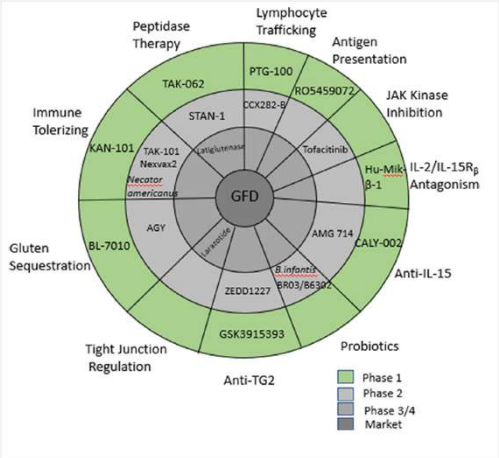
Essentially a combination of serology and histology (with some quirks)

Rubio-Tapia A et al. Am J Gastroenterol 2013; 108:656



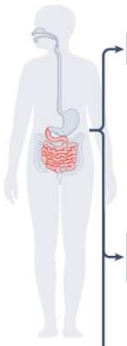
Treatment

- Gluten-free diet
- Disappointing results for interventions beyond diet



Klonarakis M et al. Aliment Pharmacol Ther 2022;55:1277-96.

a Test and parameters



CeD diagnosis

GFD	Monitoring	
	Dietician interview	Reference standard to evaluate GFD adherence and quality
	Urine and faecal GIP	Direct testing for evaluation of potential gluten exposure
	Questionnaires	Simple and practical tool to evaluate GFD adherence in case of dietician unavailability
CeD activity	TG2Ab	Useful for evaluation of chronic gluten exposure; not reliable for prediction of mucosal atrophy
	Blood tests	Assessment of blood counts, vitamins and micronutrients to assess nutritional status and intestinal function
	Symptom response	Symptoms improvement could indicate GFD responsiveness and remission of CeD activity
	Duodenal histology	Reference standard for evaluation of CeD activity; however, repeat biopsy should be based on patient characteristics rather than routinely performed. When performed should generally be >12 month after diagnosis
	Enteroscopy	To be used in cases of suspected CeD-related complications or RCeD
	TCR, flow cyt	Used to subtype refractory CeD in type I or II
	DXA	Can be considered for assessment of low BMD given prevalence of osteopenia and/or osteoporosis in CeD

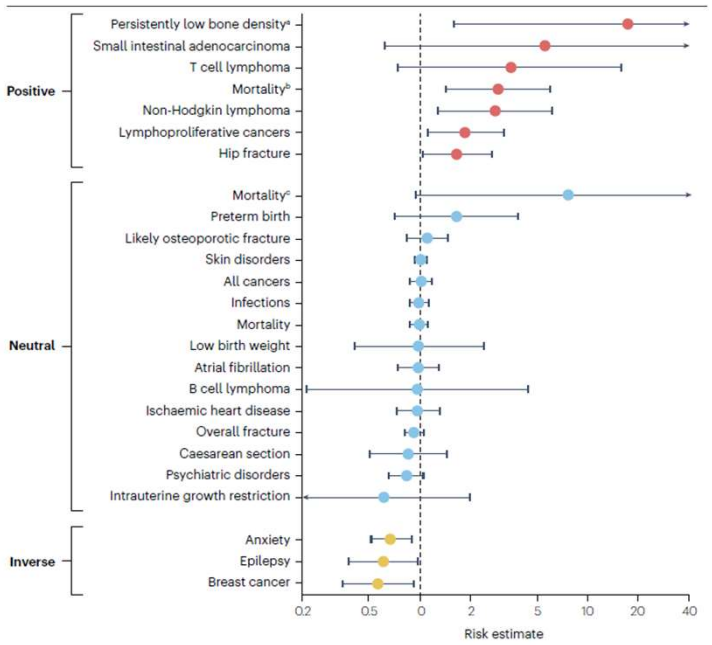
To be monitored on an yearly basis with the involvment of a dietician or nutritionist expert in GFD
To monitor and evaluate only in case of non-responsiveness to GFD, suspicion of a refractory state
To evaluate newly diagnosed patients with CeD with an additional risk factor for low BMD, e.g. menopause

Elli L et al. Nat Rev Gastroenterol Hepatol 2024;21:198-215.

Persistent villous atrophy is the driver of bad outcomes in coeliac disease.

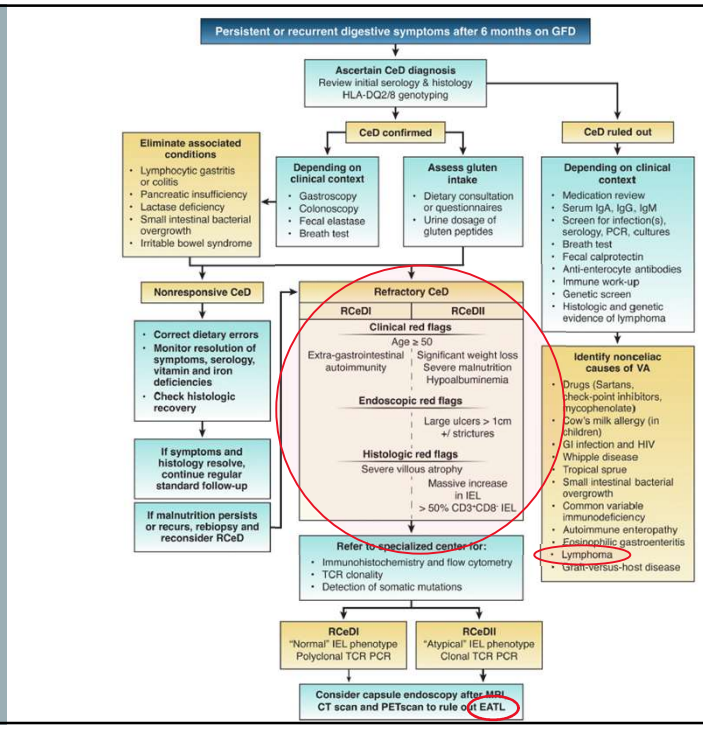
Even with persistent villous atrophy, serology can be normal.

What if villous atrophy persists?



Ludvigsson J et al. Nat Rev Gastroenterol Hepatol 2025;22:252-64.

Troubleshooting



Malamut G et al. Gastroenterology 2024;167:132-47.

Refractory coeliac disease

	RCD Type 1	RCD Type 2
Definition	Persistent or recurrent symptoms and villous atrophy despite strict gluten-free diet with *normal* intraepithelial lymphocytes (IELs).	Persistent or recurrent symptoms and villous atrophy despite strict gluten-free diet with *abnormal/clonal IELs*
Intraepithelial Lymphocytes (IELs)	Normal phenotype; polyclonal.	Abnormal phenotype: clonal, aberrant IELs lacking surface markers (e.g., CD3−/CD8− but cytoplasmic CD3+).
Immunophenotype	IELs show typical CD3+ and CD8+ expression. Polyclonal	Loss of CD8 and sometimes CD3 surface expression; monoclonal T-cell receptor rearrangements.
Risk of Progression to Lymphoma	Low	High
Prognosis	Generally favourable	Poorer prognosis due to malignant potential

Treatment and follow-up in RCD 1

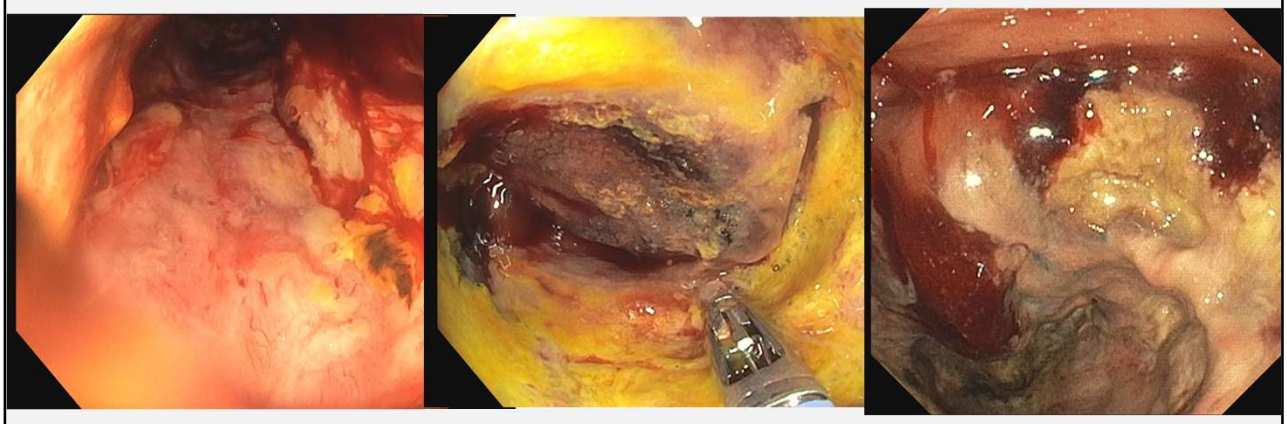
- Gluten-free diet
- Open-capsule budesonide – improves symptoms and histology in 90%
- Sparse data to support second-line treatment: thiopurines, TNF inhibitors

- The risk of progression to lymphoma is not 0 – regular small-bowel imaging

Treatment and follow-up in RCD 2

- Gluten-free diet
- Open-capsule budesonide: villous regeneration in ~60%
- Budesonide offers no protection against EATL
- Nutritional support
- Small-bowel imaging
- Disappointing anti-IL-15 and JAK inhibitor trials

When to suspect lymphoma?



When the pathologist takes a rather long time with their report ☺

~50% have undiagnosed coeliac disease when the lymphoma is diagnosed

Conclusions

- Smooth seas for the doctor treating patients with coeliac disease more than >95% of the time
- Once the diagnosis of refractory coeliac disease is established, the doctor should be on their toes
- Red flags: malnutrition, hypoalbuminaemia, anaemia
- Small-bowel imaging during follow-up of refractory coeliac disease

Treatment of T-cell lymphomas of gastrointestinal tract

Doc. dr. Lučka Boltežar, dr. med.
Institute of Oncology
November 2025

Published in 2025

Peripheral T- and natural killer-cell lymphomas: ESMO—EHA Clinical Practice Guideline for diagnosis, treatment and follow-up☆

F. d'Amore[1,2†], M. Federico[3†], L. de Leval[4], F. Ellin[5,6], O. Hermine[7,8], W. S. Kim[9], F. Lemonnier[10,11], J. S. P. Vermaat[12], G. Wulf[13], C. Buske[14], M. Dreyling[15] & M. Jerkeman[16], on behalf of the ESMO* and EHA Guidelines Committees*

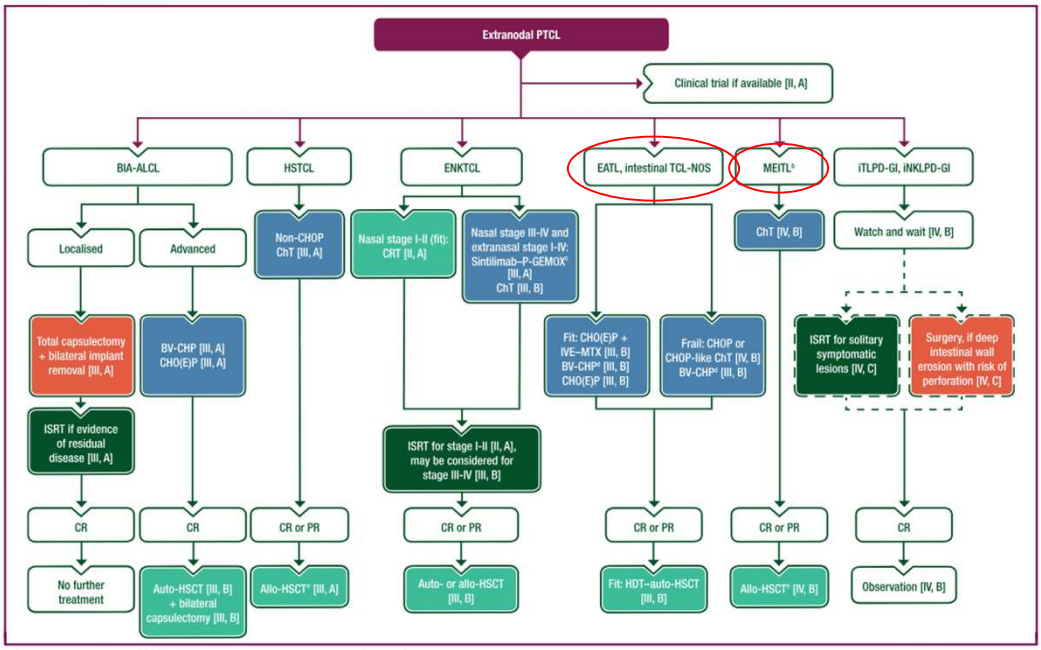


Figure 2. Overview of first-line treatment in extranodal PTCL.[a]

D'Amore, Annals of Oncology, June 2025.

EPI – EATL prognostic index

- IPI – international prognostic score and PIT - prognostic index for peripheral T-cell lymphoma have limited value for EATL
- EPI was developed by Netherland+Scottish group
- 3 risk groups:
  - **high-risk group**, characterized by the presence of B-symptoms - median overall survival (OS) of 2 months;
  - **intermediate-risk group**, comprising patients without B-symptoms and an IPI score ≥ 2 (med. OS 7 months);
  - **low-risk group**, representing patients without B-symptoms and an IPI score of 0 to 1 (med. OS 34 months).

De Baaij et al, Clin Cancer Res, 2015.

EATL & MEATL

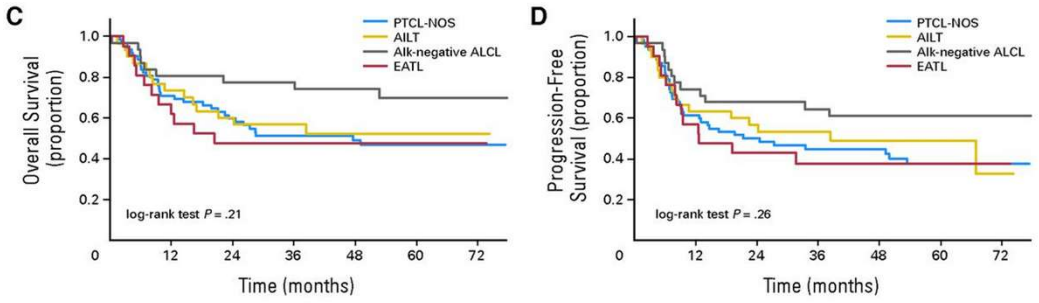
- Aggressive behaviour
- Suggested **intensified protocols** for fit patients: **CHOEP** (cyclophosphamide, doxorubicin, vincristine, prednisolone, etoposide) /+ **IVE-MTX** (ifosfamide, etoposide, epirubicin, methotrexate), or **Brentuximab vedotin-CHP** with autologous transplantation as consolidation front line
- For frail patients: modified COP protocol, monotherapy with bendamustin or gemcitabine

➢The high mortality rate in patients with EATL is due not only to tumoural aggressiveness and treatment refractoriness, but also to a deterioration in patient condition following prolonged malnutrition → thus weakening treatment tolerance.

D'Amore, Annals of Oncology, June 2025
Priporočila za obravnavo bolnikov z malignimi limfomi 2025

Nordic NLG-T-01 trial

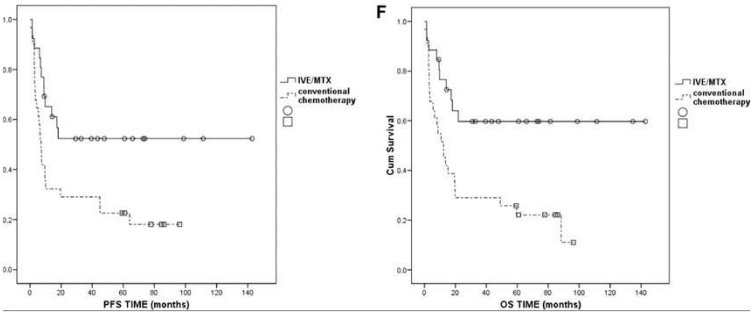
- Included 21 patients with EATL, 6 cycles of bi-weekly CHOP/CHOEP (<60 yrs) followed by autologous haematopoietic stem-cell transplantation in responding patients
- At a median follow-up of 60,5 months, 5-year progression-free survival (PFS) and OS rates in these patients were 38% and 48%, respectively. Due to patient- or disease-related frailty, however, these aggressive treatment schedules are only feasible in 40%-50% of EATL cases



D'Amore et al. J Clin Oncol, 2012. D'Amore, Annals of Oncology, 2025.

Scottish group

- Regimen IVE/MTX (ifosfamide, etoposide, epirubicin/methotrexate 1,5g/m2)-ASCT
- 26 patients were included, med. age 56 yrs, 14 finished ASCT
- Five-years PFS and OS were 52% and 60%, respectively, and were significantly improved compared with the historical group treated with anthracycline based chemotherapy



Sieniawski M, et al. Blood, 2010.

EATL 001 study

- Phase II study, which is evaluating brentuximab vedotin (BV)-CHP followed by consolidative high-dose chemotherapy (HDT)–ASCT in eligible responding patients with **CD30-positive** (≥10% positive tumour cells)
- Between 2018 and 2021, 14 patients were included
- The objective response rate at completion of induction was 79% (11/14) with a complete remission (CR) rate of 64% (9/14)
- The 11 responding patients underwent HDT–ASCT (of which two died of infectious complications)
- At a median follow-up of 2,1 years, the nine remaining patients were alive and relapse-free, translating into 2-year PFS and OS rates of 63% and 68%, respectively
- BV-CHP was well tolerated, allowing most patients to undergo HDT–ASCT

Sibon D, et al. Blood, 2021.

Romidepsin-CHOP

- Randomized phase III study of Ro-CHOP versus CHOP in adult patients with previously untreated peripheral T-cell lymphoma (PTCL); primary end point = PFS
- Romidepsin = potent, selective, class I histone deacetylase inhibitor has demonstrated activity in relapsed or refractory PTCL as a single agent
- Included 16 patients with EATL – 5 treated with romi-CHOP, 11 with only CHOP
- No significant difference in PFS between Ro-CHOP and CHOP for "other" PTCL histologies , not specified for EATL subcategory

Bachy E, et al. J Clin Oncol, 2022.

Our report in 2006

- Retrospective report treated in 1996-2004
- 15 patients - 10 (67%) patients had EATL and 5 (33%) had PTCL. Surgery was performed on 11 patients with 8 cases on an emergency basis
- All 15 patients received chemotherapy (predominantly CHOP). Six patients were treated with field radiotherapy as a part of the first treatment
- CR was achieved in 6 patients (40%) with a median duration of 5.3 months (range 2 to 12 months), stable disease in 3 patients (20%), and progressive disease in 6 patients (40%)
- 1-year OS was 33%

To be updated ☺

Jezersek B, et al. Oncology Reports, 2006.

Autologous transplant

- EBMT registry, transplantation from 2000-2007, 85 patients → 73 autologous SCT and12 allogeneic SCT
- ✓ Follow up data only for 22 patients → The median time from the diagnosis to ASCT was 6 months
- ✓ The median follow-up time for living patients was 45 months from ASCT
- ✓ During the follow-up relapse has been observed in 13 patients (59 %), the median time was only four months from ASCT
- ✓ The median disease-free survival (DFS) and OS were 9 months and 15 months, respectively
- ✓ 2-year OS was 45%

Jantunen E, et al. Blood, 2011.

Indolent T- and NK-cell lymphoproliferative disorders of the GI tract

- Aggressive approaches based on conventional combination ChT should only be used in case of verified dissemination and/or histological transformation
- An observational approach can be recommended, focusing primarily on ruling out disease progression and dissemination. Individual lesions may be endoscopically verified for risk of intestinal wall perforation (e.g. presence of deep erosions)
- ISRT may be considered in case of solitary symptomatic lesions
- Limited surgical resection may be considered in case of deep intestinal wall erosion (e.g. superficial mucosal erosion deepened by subsequent local infection or inflammation) with a high perforation risk

D'Amore, Annals of Oncology, June 2025.

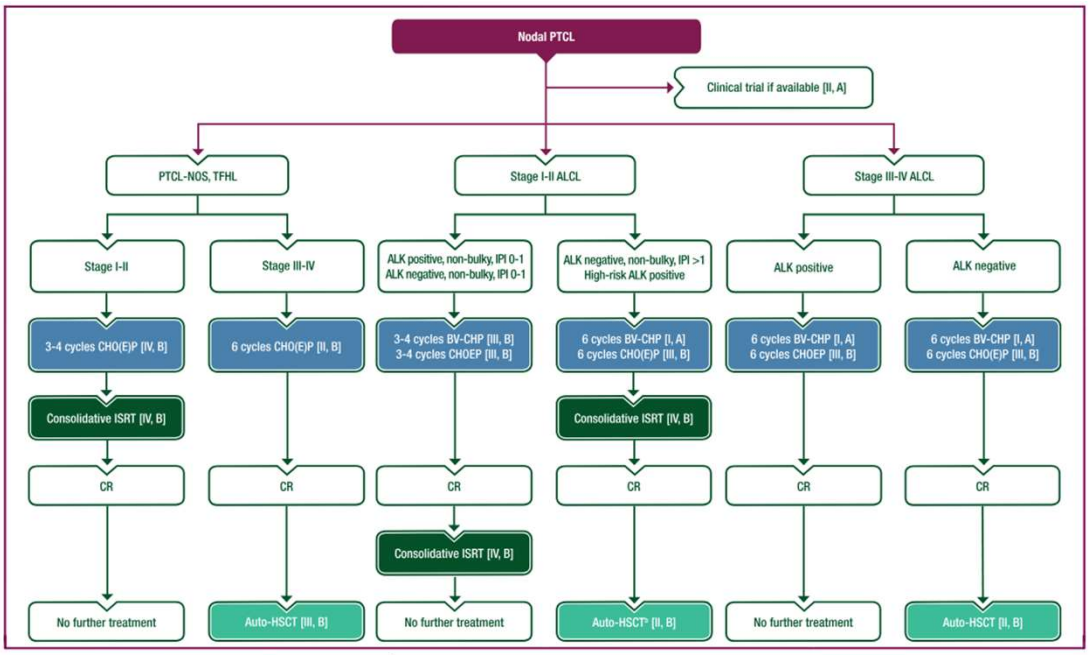


Figure 1. Overview of first-line treatment in nodal PTCL.[a]

D'Amore, Annals of Oncology, June 2025.

Relapse setting

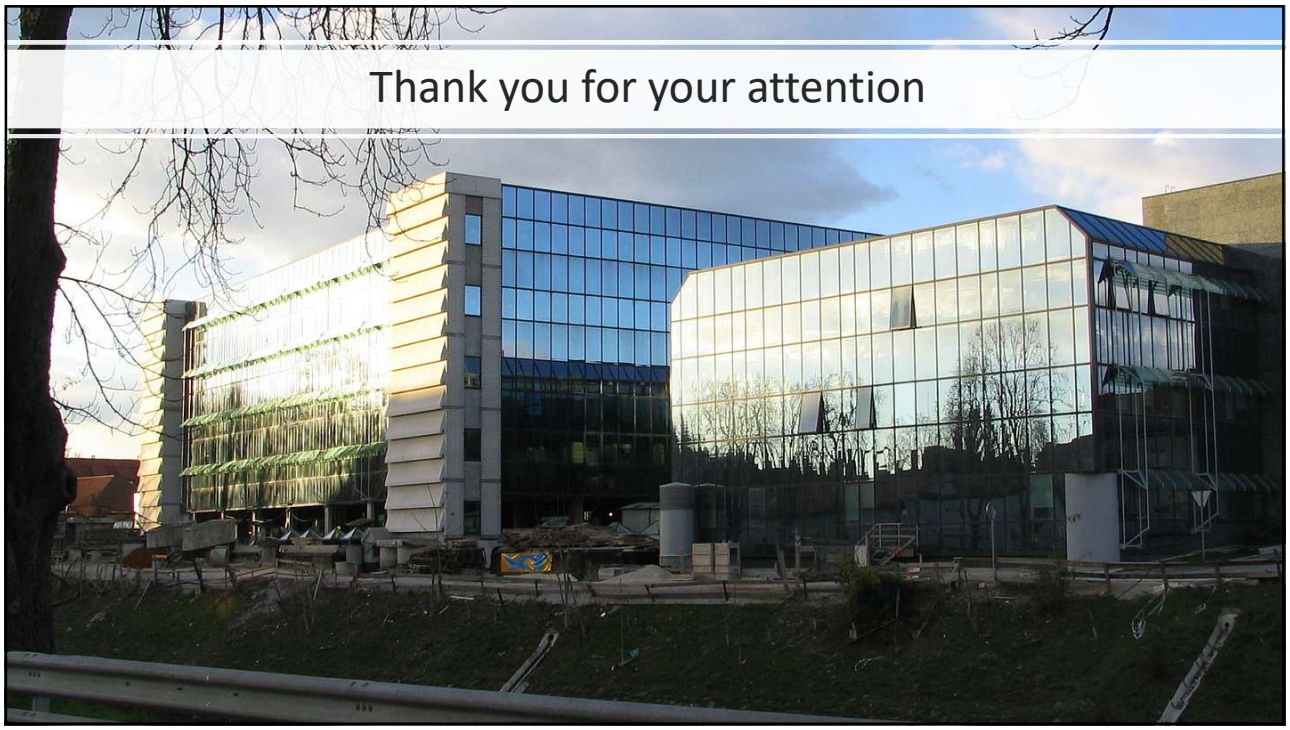
- Bendamustin
- Lenalidomide
- Bendamustin+lenalidomide
- Gemcitabine
- CD30+: brentuximab vedotinom + bendamustin
- Bortezomib
- Modified COP – when remission lasts at least 2 years
- Cyclophosphamide + etoposide
- Ruxolitinib (*JAK/STAT* mutation or >30% ekspression oSTAT3)

Priporočila za obravnavo bolnikov z malignimi limfomi 2025

Case report of CD30 CAR-T therapy

- 69-year-old male, EATL CS III.A.E.
- Refractory to CHOEP and ICE, but achieved a partial remission with 3 cycles of brentuximab-bendamustin and had consolidation therapy with a nonmyeloablative allo-SCT from a matched related donor. He received maintenance brentuximab vedotin after allo-SCT, but treatment was discontinued after 5 cycles because of neuropathy
- 10 months later – cutaneous noduls → RT, relapse → romidepsin+DLI, relapse → brentuximab vedotin+2nd DLI, relapse (CD30+) → CD30 CAR-T therapy → CR for 30 months at least

Voorhees TJ, et al. Blood Adv. 2020



The role of stem cell transplant (auto and allo) in T-cell lymphomas

Klara Šlajpah
University Medical Centre Ljubljana, Slovenia

5. Limfomska šola, Ljubljana, 28th November 2025

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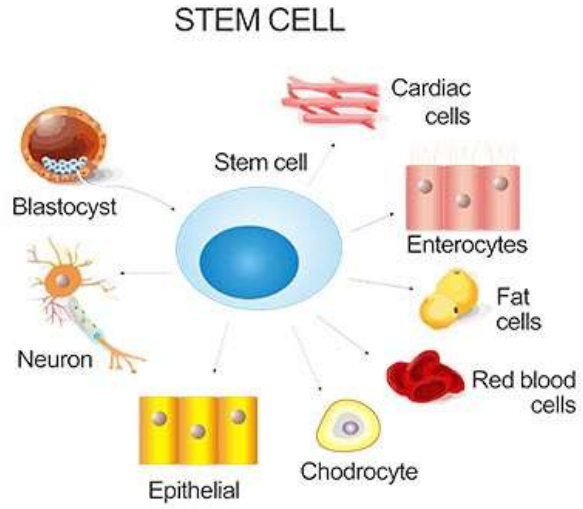
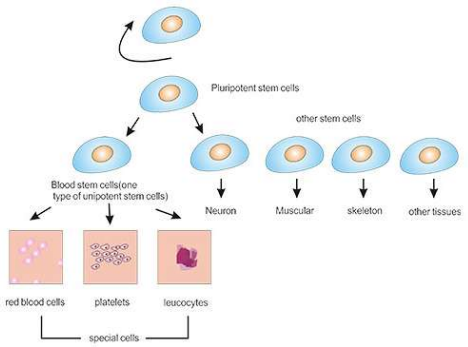


- Stem cells are cells with the potential to develop into many different types of cells in the body. They serve as a repair system for the body.
- There are two main types of stem cells: embryonic stem cells and adult stem cells

- They can divide and renew themselves over a long time
- They are unspecialized, so they cannot do specific functions in the body
- They have the potential to become specialized cells, such as muscle cells, blood cells, and brain cells



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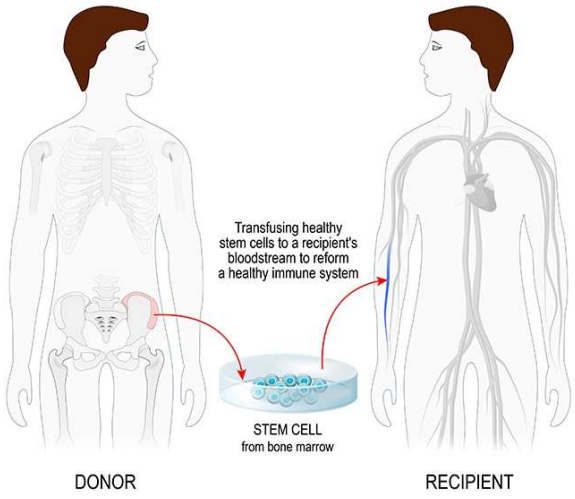
BONE MARROW TRANSPLANT



Any procedure in which hematopoietic stem cells from any donor and any source are infused into a recipient with the aim of fully or partially repopulating or replacing the recipient's hematopoietic system.

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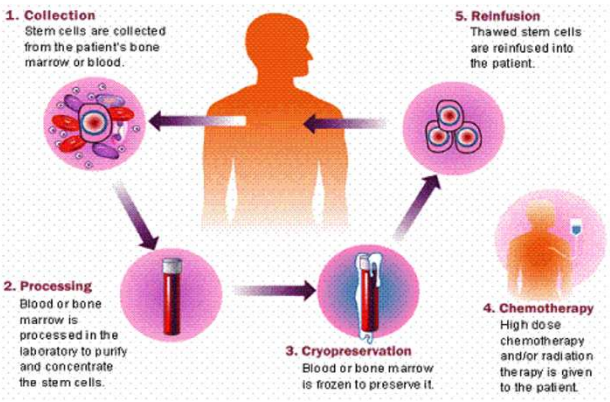
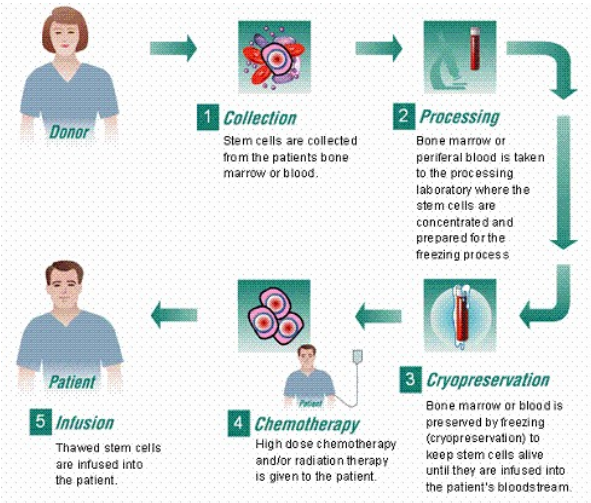
Autologous vs allogeneic transplant





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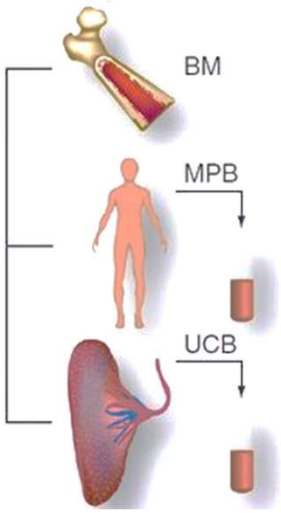
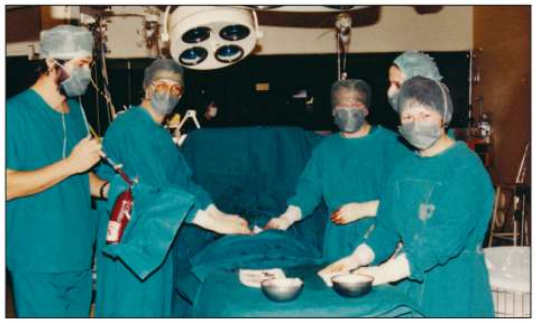
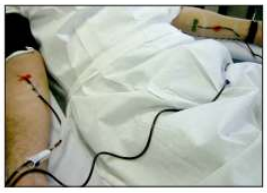
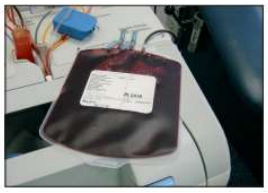
Source of hematopoietic stem cells





First bone marrow harvest at the University Medical Centre Ljubljana, December 1988.





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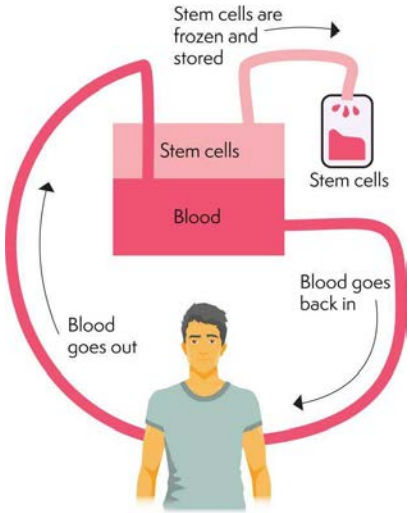
Mobilisation and collection of stem cells



- Mobilization with **chemotherapy plus G-CSF** is the preferred method for patients who will need decrease of tumour burden.
- G-CSF mobilization
- CD34+ cell count in the PB is the most important parameter of graft quality.
- Auto HSCT at least **2** × 10^6 CD34+ cells/kg BW.
- Allo HSCT at least **4** × 10^6 CD34+ cells/kg BW.
- Use of plerixafor

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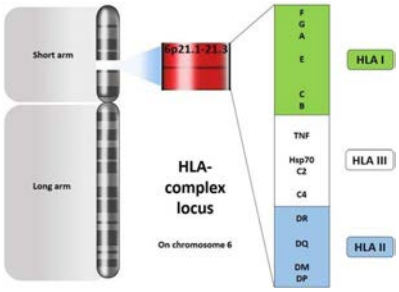
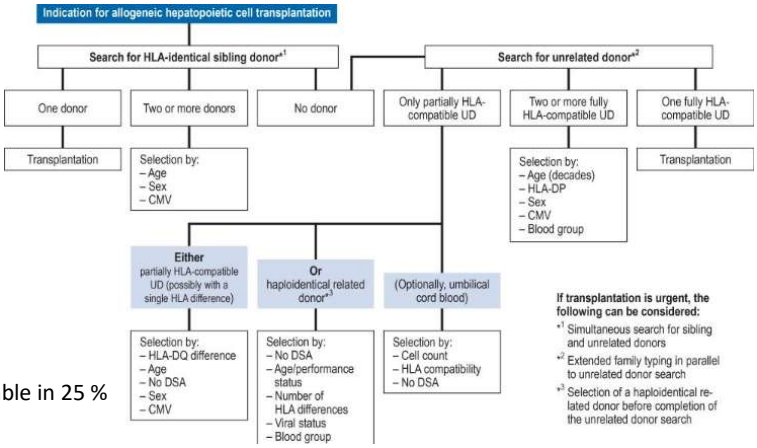
Donor selection



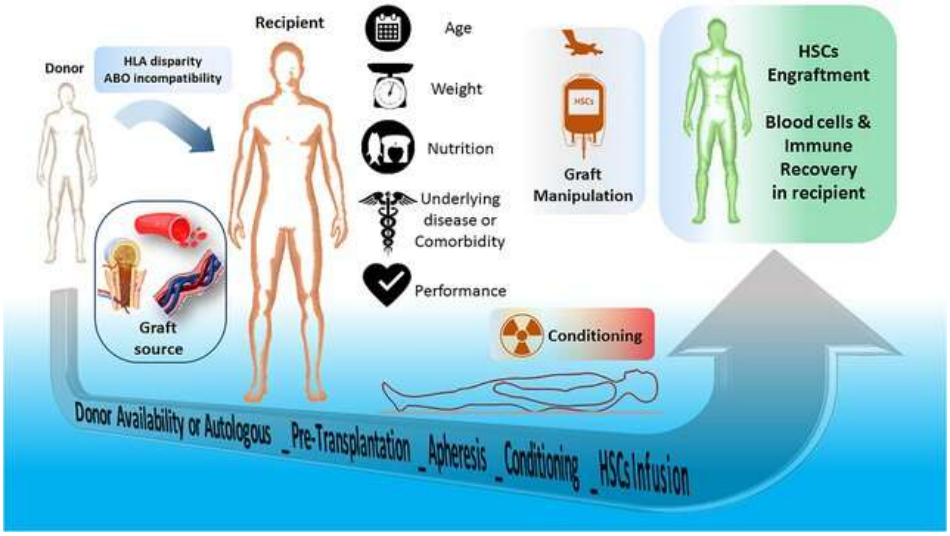


Best donors:

- 1st: HLA-matched sibling donor (MSD) – available in 25 % of patients.
- 2nd: HLA-matched unrelated donor (MUD).
- Alternatives: mismatched unrelated donor (MMUD), haploidentical related donor, UCB.

Fleischhauer K, et al. Dtsch Arztebl Int. 2023

Factors influencing the outcome of HSCT



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Indications for HSCT

Autologous HSCT

Malignant diseases

- Non-Hodgkin lymphoma
- Hodgkin lymphoma
- Multiple myeloma
- Neuroblastoma
- Ovarian carcinoma
- Germ-cell tumours

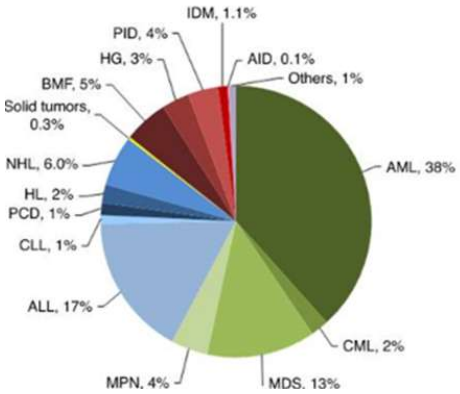
Non-malignant diseases

- Autoimmune disorders
- Systemic lupus erythematosus (SLE)
- Systemic sclerosis
- Amyloidosis

Allogeneic HSCT

Malignant disorders

- Acute myeloid leukemia (AML)
- Acute lymphoblastic leukemia (ALL)
- Chronic myeloid leukemia (CML)
- Chronic lymphocytic leukemia (CLL)
- Myeloproliferative neoplasms (MPN)
- Myelodysplastic syndromes (MDS)



Passweg JR, et al. Bone Marrow Transplant. 2023

Non-malignant disorders

- Aplastic anemia
- Severe combined immunodeficiency (SCID)
- Fanconi anemia
- Blackfan–Diamond anemia
- Wiskott–Aldrich syndrome
- Inborn errors of metabolism

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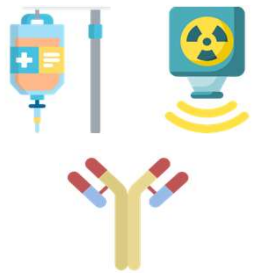
Transplant process – 5 steps



1. Conditioning
2. Stem cell infusion
3. Aplasia
4. Engraftment phase
5. Post-engraftment period

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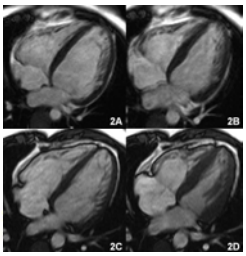
Complications

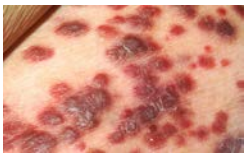
Autologous HSCT
Early
- Infections
- Bleeding
- Treatment-related toxicity

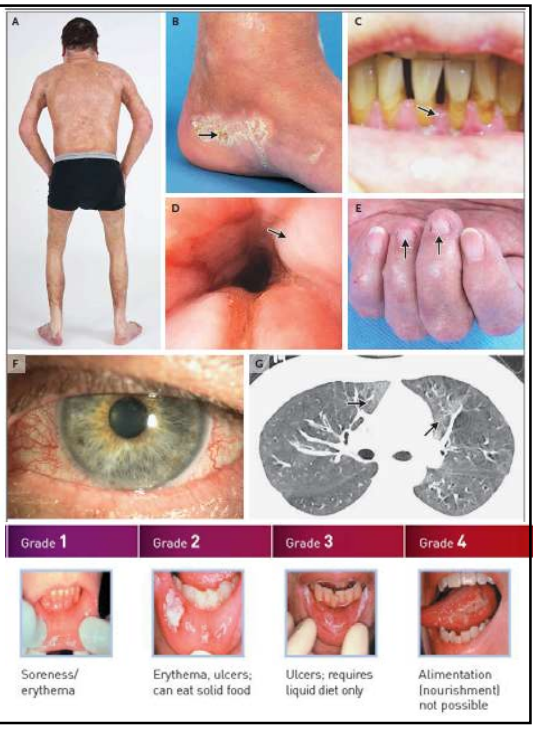
Late
- Disease relapse
- Infections
- Gonadal dysfunction/infertility
- Secondary malignancies
- Long-term treatment toxicity



Allogeneic HSCT
Early
- Infections
- Acute GVHD
- Bleeding
- Treatment-related toxicity
- Graft failure

Late
- Chronic GVHD
- Infections
- Disease relapse
- Gonadal dysfunction/infertility
- Secondary malignancies
- Long-term treatment toxicity

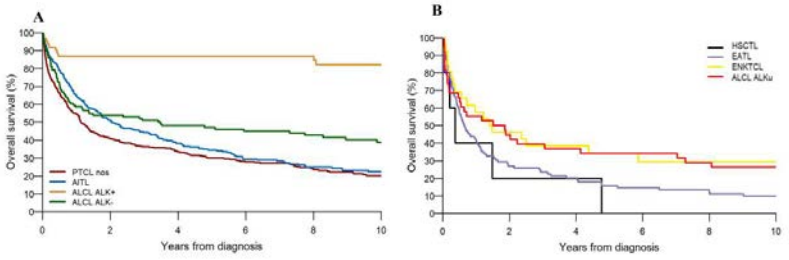




Prognosis of T cell lymphomas

- **In general POOR** (5yr OS 30-40%)
- Exceptions:
  - ALK positive ALCL
  - Cutaneous forms

- Also correlated to high IPI score at diagnosis (> 70% IPI ≥ 2)
- Poor compared to aggressive B cell lymphoma, especially in the rituximab Era



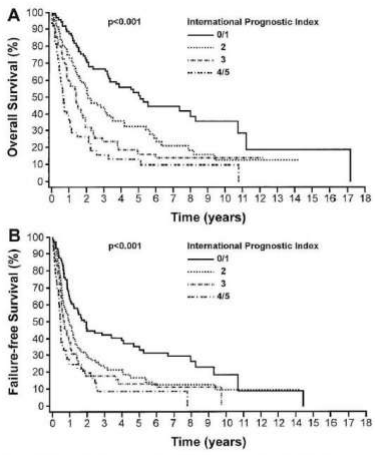


Figure 3. Survival. OS (A) and FFS (B) of patients with PTCL-NOS (n = 315) according to the IPI.

Weisenburger, Blood 2011
Reunamo et al, Sci Rep 2025

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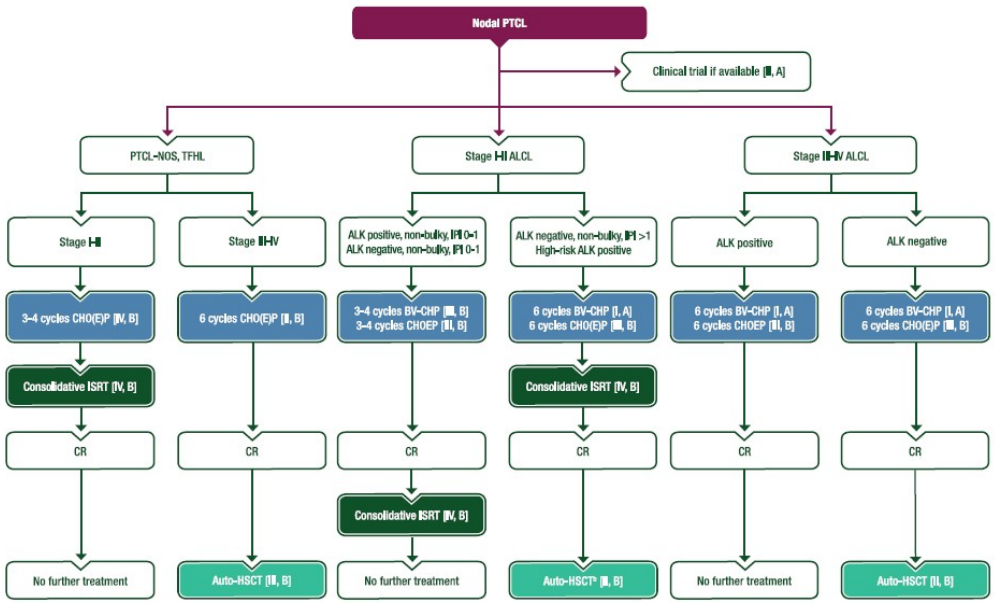
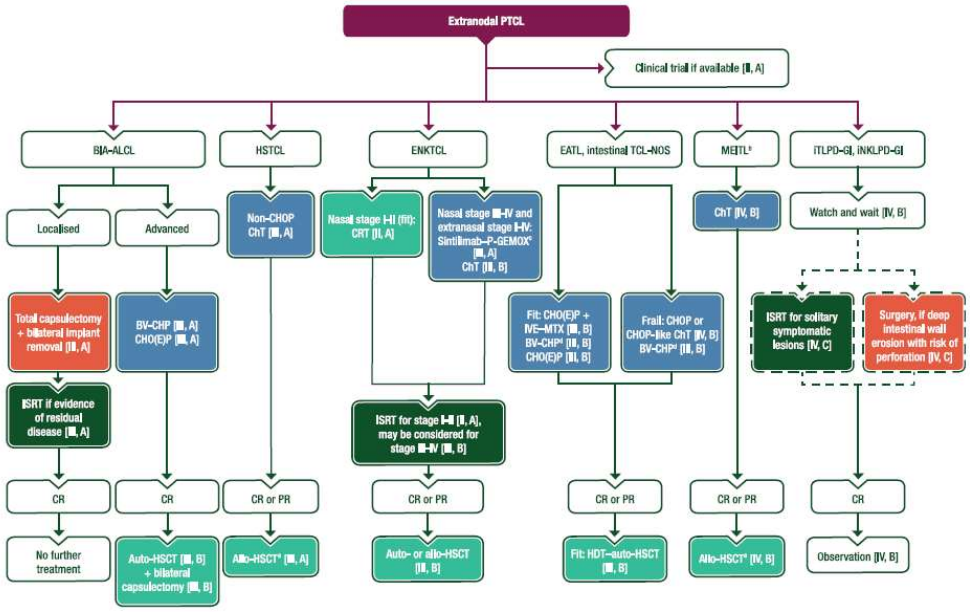
Strategies to improve first line treatment

1. Intensification of induction chemotherapy
2. **Consolidation by stem cell transplantation**
3. Combination of chemotherapy with new molecules



d'Amore et al. Ann Oncol. 2025



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Large prospective trials on auto HCT consolidation as part of PTCL frontline therapy

	GLA/LYSA AATT[10,11] (autoHCT arm only)	Nordic[8]	German[9]
Study type	RCT (auto vs allo)	Phase 2, prospective	Phase 2, prospective
Eligibility	NOS, AITL, ALCL ALK–, EATL, HSTL, SPPTCL	NOS, AITL, ALCL ALK–, EATL, HSTL, ENKTCL	NOS, AITL, ALCL ALK–, EATL, HSTL, ENKTCL
	18–60 y	18–67 y	18–65 y
N (% AITL+ALCL+NOS)	54 (78%)	160 (77%)	111 (85%)
AITL	31%	19%	33%
ALCL ALK–	17%	19%	14%
PTCL-NOS	30%	39%	38%
Period	2011–2014	2001–2007	2001–2010
Age (years; median [range])	50 (28–60)	57 (22–67)	49 (23–66)
PS > 1 (ECOG)	20%	29%	NA
aaIPI high/high-intermediate	56%	NA	58%
LDH>N	61%	62%	58%
Proceeded to HCT	63%	72%	68%
High-dose regimen	BEAM	BEAM	TBI/CY
Progression-free survival			
3 y	39%	48%	49%[b]
Long-term	35% (7 y)	44% (5 y)	30% (7 y)[b]
Overall survival			
3 y	70%	56%	56%[b]
Long-term	61% (7 y)	51% (5 y)	39% (7 y)[b]
Adverse factors	PFS: LDH > N[a]	OS, PFS: non-ALCL, age, PS >1	OS: aaIPI high/high-intermediate
Follow-up (mo)	84 (0–109)	61 (26–96)	59 (1–107)

a Pooled autoHCT and alloHCT.
b Estimated from published survival plots.

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Dreger and Schmitz. ASH Education Program 2024

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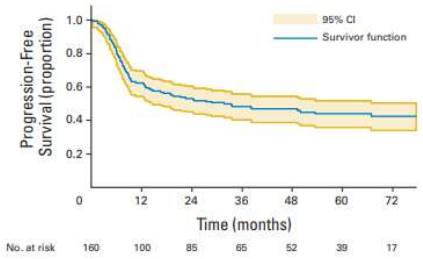
Consolidative auto HSCT in first response

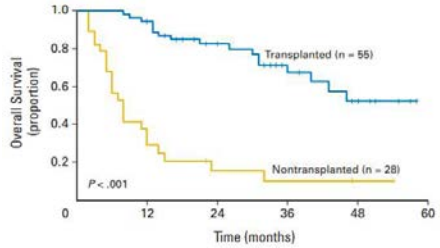
NLG-T-01 study



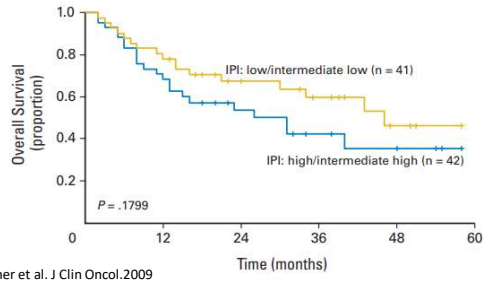
d'Amore et al. J Clin Oncol 2012

Patients in CR/PR proceeded to high-dose chemotherapy with BEAM/BEAC followed by up-front ASCT

- 5-year OS: 51%
- 5-year PFS: 44%
- Best outcomes in ALK-negative ALCL



estimated 3-year OS 48%, 3-year PFS 36%



Reimer et al. J Clin Oncol.2009

Consolidative auto HSCT in first response

Prospective German study

Wilhelm et al. Blood Cancer Journal 2016

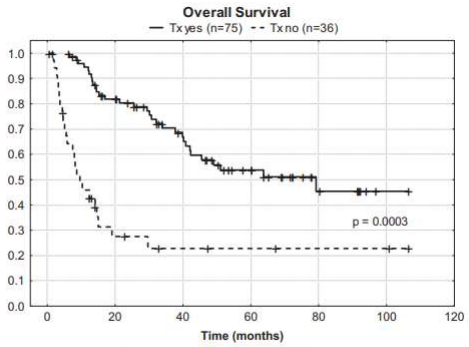
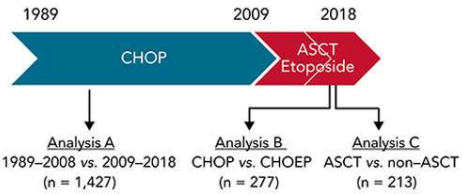


Figure 3. Kaplan–Meier curves for overall survival in patients who did and did not receive transplantation.

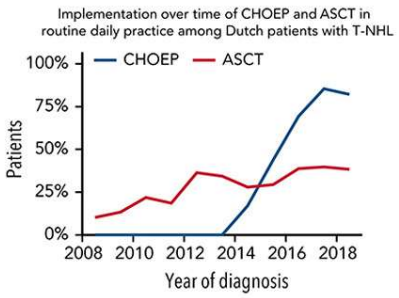
- 5-year OS, DFS and PFS were 44%, 54% and 39%
- CR rate was 59%
- 68% (75/111) actually received autoSCT; main reason for not transplanting was progression

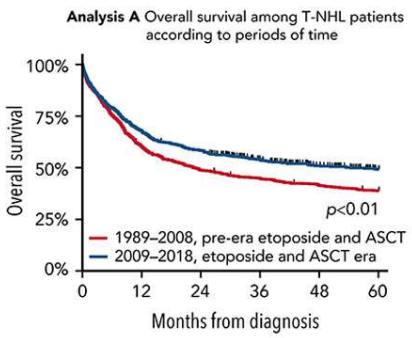
Patients aged 18–64 years with stage II–IV peripheral T-cell lymphoma (T-NHL; ALCL, AITL or PTCL NOS)

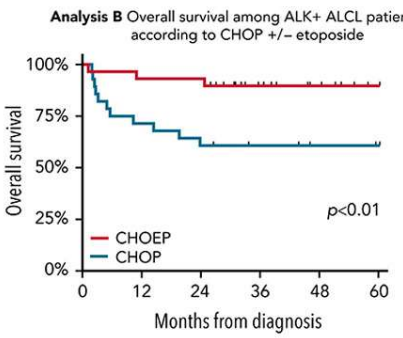
Brink et al. Blood 2022

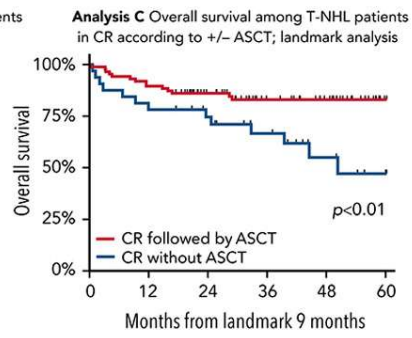


5-year OS of 82% compared with 47 %



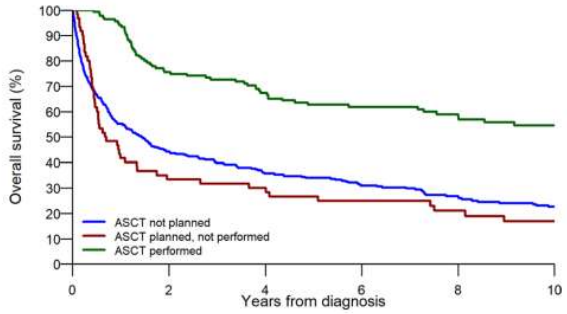






Consolidative auto HSCT in first response

A Finnish nationwide population based study

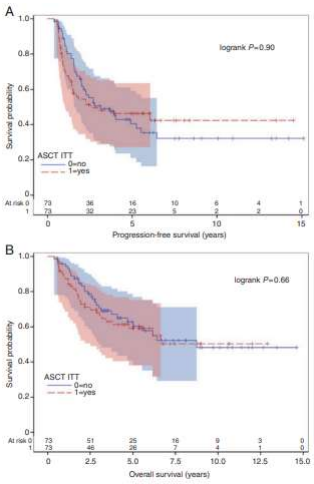


Reunamo et al, Sci Rep 2025

OS was better in patients (excluding ALK+ALCL) receiving high-dose chemotherapy compared to those for whom HDCT was not planned (HR 0.61; 95% CI 0.47–0.80).

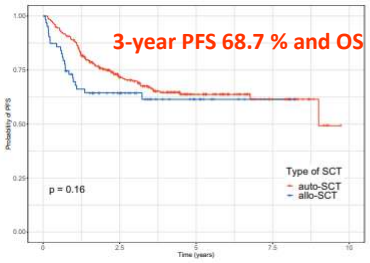
Consolidation with HDCT for eligible patients resulted in favourable survival.

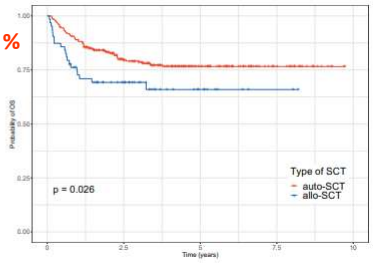
Consolidative HSCT in first response



Fossard et al. Annals of Oncology 2018

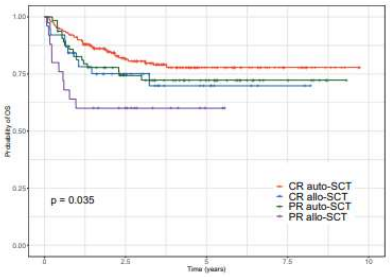
Neither the Cox multivariate model nor the propensity score analysis found a survival advantage in favour of ASCT as a consolidation procedure for patients in response after induction.





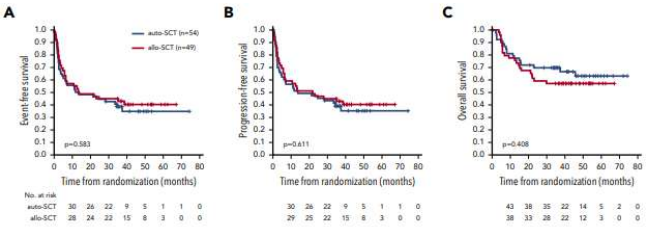
Baek et al. Blood Cancer Journal 2023

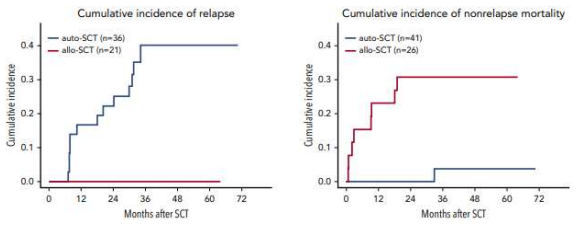
No significant difference in PFS between the auto- and allo-SCT groups. Better OS in auto-SCT; Patients with CR and underwent auto-SCT had superior long-term survival.



Auto vs allo HSCT in first response

Randomized phase 3 trial





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3-year EFS after allo-SCT 43%, 38% after auto-SCT
OS at 3 years was 57% vs 70% after allo- or auto-SCT.

The strong graft-versus-lymphoma effect after allo-SCT was counterbalanced by transplant-related mortality.

Patients with relapsing or refractory peripheral T-cell lymphoma should be offered allo-SCT.

Schmitz et al. Blood 2021

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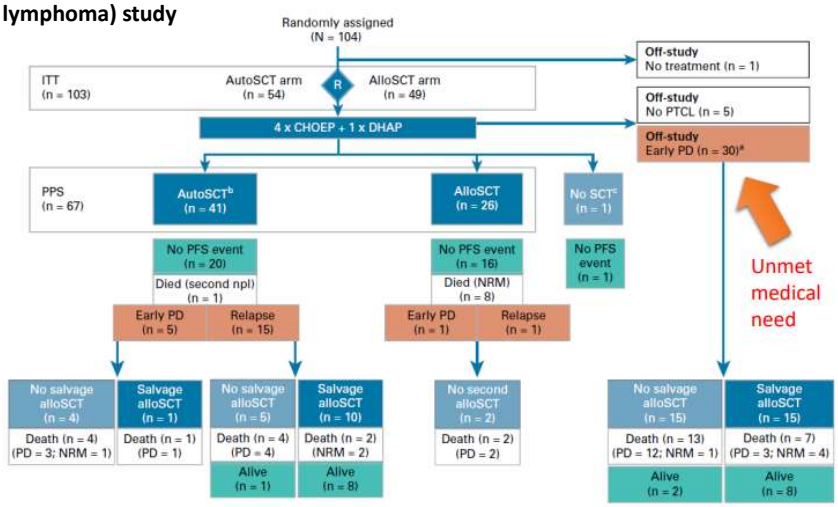
Consolidating with allo HSCT

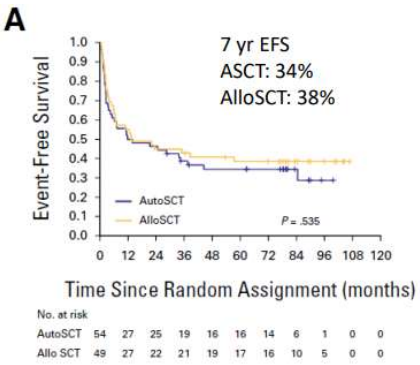
AATT (auto or allo transplant in T-cell lymphoma) study

Younger patients with PTCL (excluding stage I with IPI 0, randomised between BEAM/ASCT or allo-SCT after FBC (fludarabine 125 mg/m2 , busulfan 12 mg/kg, cyclophosphamide 120 mg/kg).

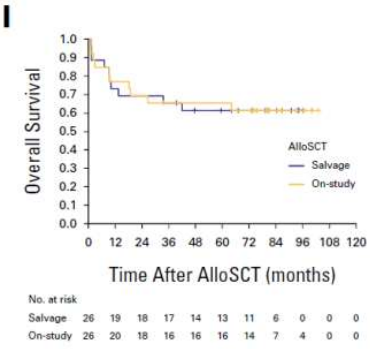
Prematurely stopped based on an interim analysis which estimated that it was highly unlikely that the primary objective, namely a 25% improvement of PFS at 3 y for allo-SCT, would be reached.



Tournilhac et al. JCO, 2024



Auto: 58% relapse, 3% NRM
Allo: 8% relapse, 31% NRM

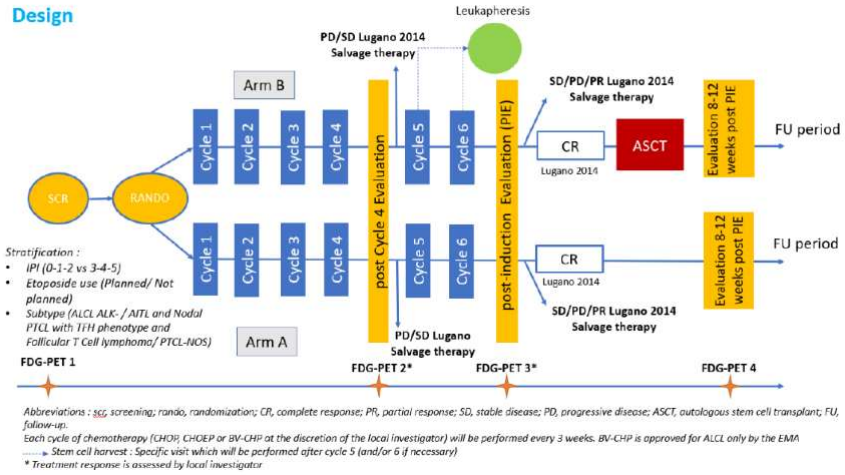


Unmet medical need:

- refractory pts not reaching transplant
- AlloSCT is currently not recommended as part of first-line consolidation. NRM 31%.
- AlloSCT is the treatment of choice for younger, transplant-eligible patients with relapsed/refractory PTCL. AlloSCT at relapse after autoSCT is good option.

Tournilhac et al. JCO, 2024

TRANSCRIPT: first RCT investigating the role of ASCT in CR1 in PTCL ongoing



Primary Endpoint: mPFS of patients in CR after 6 cycles of CHOP/CHOEP or BV-CHP with or without ASCT for patients with TFH lymphoma, PTCL, NOS or ALCL, ALK negative.

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Multicenter randomized phase III study of high-dose therapy with autologous stem cell transplantation versus observation for patients with newly diagnosed peripheral T-cell lymphoma who achieved complete metabolic response after induction therapy (JCOG2210,TRANSFERstudy)

Aims to **confirm the superiority** of the **high-dose therapy** over observation alone in terms of progression-free survival for patients with newly diagnosed peripheral T-cell lymphoma, who achieved **complete metabolic response** after induction terapy.

A total of 140 patients from 52 hospitals will be enrolled in **Japan** over 5.5years.

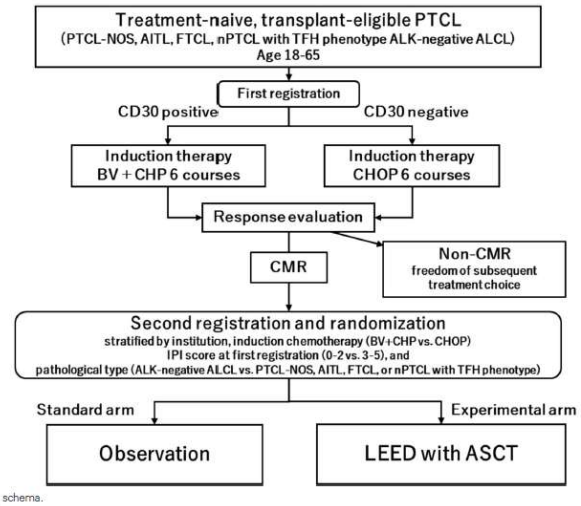

Figure 1. Study schema.

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Kita et al. Japanese Journal of Clinical Oncology 2025.

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Indications for HSCT in 2025

The only curative option for transplant-eligible patients with primary refractory PTCL or those who are in relapse.

In Hepatosplenic TCL (HSTL), Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma (MEITL), Extranodal NK/TCL (ENKTL), and Adult T-Cell Leukaemia/ Lymphoma (ATLL), allo-HCT is strongly recommended in first-line therapy.

Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto	CAR-T
PTCL	CR1				CO/II	GNR/III
	Chemosensitive relapse, ≥CR2/PR2	S/II	S/II	CO/III*	CO/II	GNR/III
	Refractory	CO/II	CO/II	CO/III	GNR/II	GNR/III
Primary CTCL	EORTC/ISCL Stages I–IIA (early)	GNR/III	GNR/III	GNR/III	GNR/III	GNR/III
	EORTC/ISCL Stages IIB–IV (advanced)	CO/III	CO/III	D/III**	GNR/III	GNR/III

*Haploidentical allo-HCT for PTCL and primary CTCL: S/II for chemosensitive relapse, ≥CR2/PR2.
**Haploidentical allo-HCT for primary CTCL: CO for Refractory and EORTC/ISCL Stages IIB–IV (advanced).

Greco et al. Bone Marrow Transplantation 2025

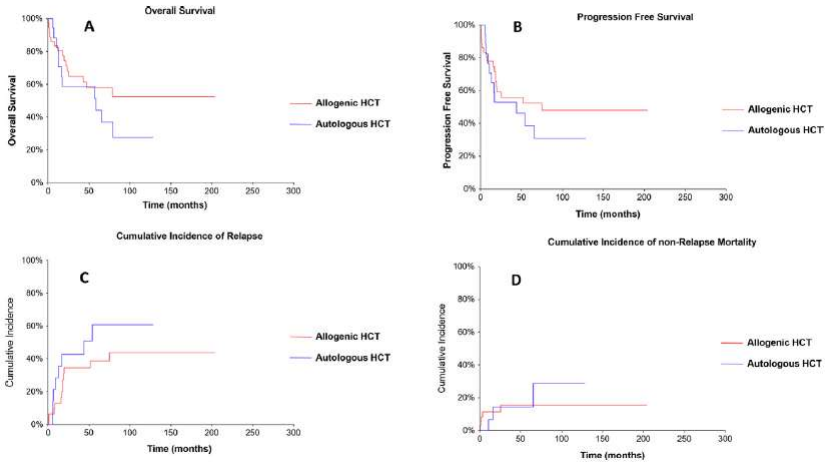
Indications for HSCT in rare PTCL

	Up-front consolidation		Salvage consolidation		Refractory
	autoHCT	alloHCT	autoHCT	alloHCT	alloHCT
Extranodal NK/T-cell lymphoma[45,46]					
Localized	-	-	+	+	+
Disseminated	+	-	+	+	+
Adult T-cell leukemia/lymphoma[33]					
Chronic/smoldering	-	-	-	E	E
Acute/lymphoma	-	+	-	+	+
Enteropathy-associated T-cell lymphoma[47,48]	+	-	E	E	E
Hepatosplenic T-cell lymphoma[32]	E	+	-	+	+

+ Recommendation based on evidence from registry studies and expert opinion.
E Recommendation based on expert opinion only.
- Not recommended.

Dreger and Schmitz. ASH Education Program 2024

Hepatosplenic T-cell lymphoma



Retrospective cohort of 53 patients: 36 had allo-HCT, 17 auto-HCT

- median OS 78.5 months, median PFS 54 months
- No significant difference between allo- and auto-HCT 3-year relapse / non-relapse mortality (NRM):
  - Allo-HCT: relapse 35%, NRM 16%
  - Auto-HCT: relapse 43%, NRM 14%

Moustafa et al. Transplantation and Cellular Therapy 2024

Both auto- and allo-HCT are effective consolidation strategies in HSTCL; eligible patients should be referred early for transplant evaluation.

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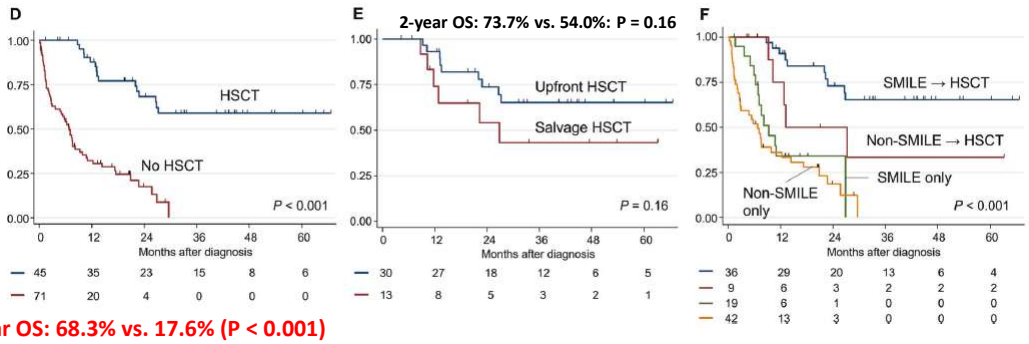
Advanced-stage extranodal NK/T-cell lymphoma

NKEA-Next study



2-year OS: 68.3% vs. 17.6% (P < 0.001)

42% (n = 45) underwent HSCT, including autologous HSCT (n = 19) and allogeneic HSCT (n = 26)
The prognosis was significantly better in patients who received HSCT than in those who did not.
Multivariate analysis showed SMILE and HSCT were significant factors for OS.

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Fujimoto et al. Leukemia 2025

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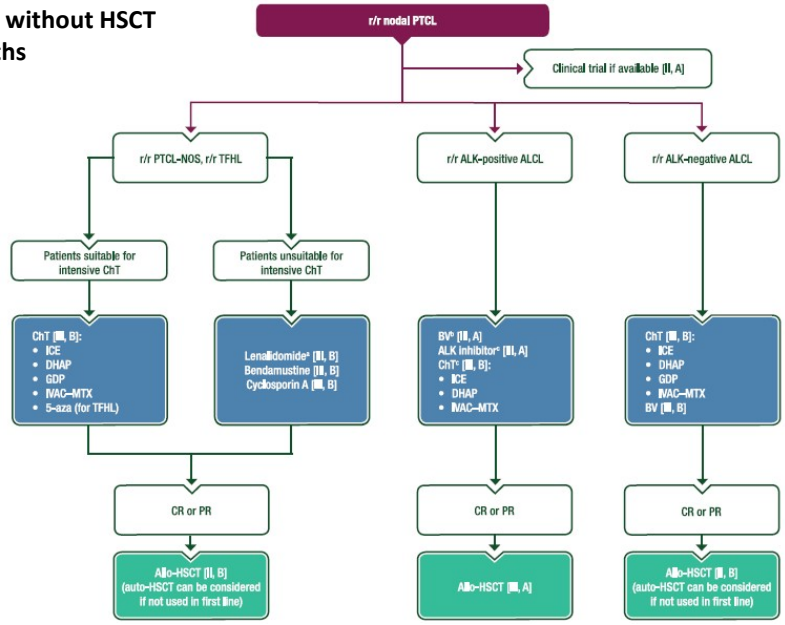
Poor outcomes without HSCT
OS 3 – 12 months



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d'Amore et al. Ann Oncol. 2025

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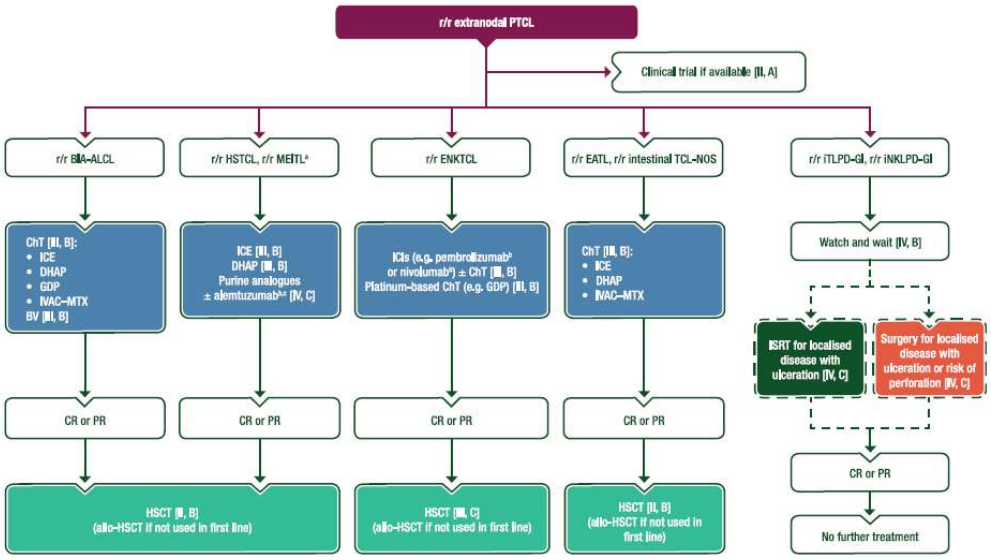

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d'Amore et al. Ann Oncol. 2025

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Prognosis and the effect of HCT in patients with R/R PTCL using the time point of relapse as baseline

Best long-term survival is achieved with allo-HCT

5-year OS ~50–65%

Allo-HCT can still provide durable survival in about **one-third** of patients even when disease is **resistant** at the time of transplant.

Dreger and Schmitz. ASH Education Program 2024

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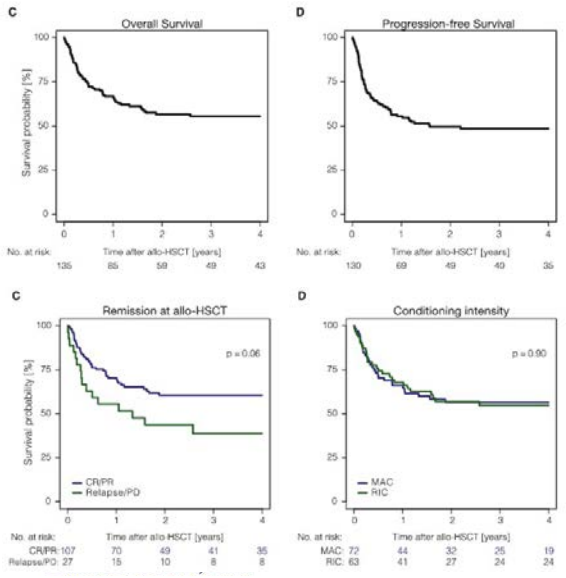
	GLA/LYSA AATT[10,11]	Heidelberg[12]	MDACC[13]	Milan INT[23]	Int. T-cell project[4]
Study type	RCT, post-hoc retrospective	Single-center retrospective	Registry retrospective	Single-center retrospective	Registry retrospective
Eligibility	NOS, AITL, ALCL ALK, EATL, HSTL, R/R on trial	Any R/R PTCL, consecutive	R/R AITL/NOS, consecutive	Any R/R PTCL, **alloHCT eligible**, consecutive	Any R/R PTCL
N	50	91	240	73	633
Relapsed	20 (40%)	44 (48%)	162 (67%)	38 (52%)	197 (31%)
Primary refractory	30 (60%)	47 (52%)	78 (33%)	35 (48%)	436 (69%)
Period	2011–2021	2001–2014	1999–2014	2001–2017	2006–2016
HCT for R/R disease	**26 (52%)**	**38 (42%)**	**67 (28%)**	**45 (62%)**	99 (16%)
AlloHCT	25 (50%)	31 (34%)	31 (13%)	45 (62%)	23 (4%)
AutoHCT	1 (2%)	7 (8%)	36 (15%)	-	76 (12%)
Strategy	Physician's discretion	ITT alloHCT	Physician's discretion	ITT alloHCT	Physician's discretion
Age (years; median [range])	50 (24–58)[a]	51/63 (21–72)[b]	60 (23–83)	55 (18–68)	59 (18–89)
PS >1 (ECOG) or <70% (Karnofsky)	20%[a]	NA	19%	NA	23%
Prior autoHCT (at study entry)	40%	48%/–[b]	18%	23%	8%
Overall survival from R/R (ITT)	**33% (crude)**	**20% (5 y)**	**20–24% (5 y)**	**34% (4 y)**	**23% (3 y)**
OS from R/R with alloHCT					
3 y	68%[c]	60%	52%[c]	57%[c]	
5 y	**65%**	**52%**	**52%**	**51% (4 y)**	
OS from R/R with autoHCT					
3 y		14%	55%[c]		48%[d]
5 y		**0%**	**32%**		**42%**[c,d]
OS from R/R without HCT					
3 y	11%[c]	3%	19%[c]	NA	18%
5 y	11%[c]	**3%**	**10%**	**19% (4 y)**	NA
Untransplanted patients among those surviving ≥3 y*	**2/18 (11%)**	**2/18 (11%)**	NA	**2/22 (9%)**	-
Follow-up from R/R (mo)	NA	70 (17–148)	NA	40 (9–192)	38 (1–96)

Allo HSCT for R/R NK/T-cell lymphoma



- 4.8 years follow-up
- 3-year PFS 49 % and OS were 56 %
- 1-year NRM 15 % and relapse 30 %

- Shorter time from diagnosis to allo-HSCT and lack of CR/PR at transplant were associated with worse PFS.

- **Durable survival for about half of heavily pretreated ENKTL patients.**

Bering et al. Leukemia 2023

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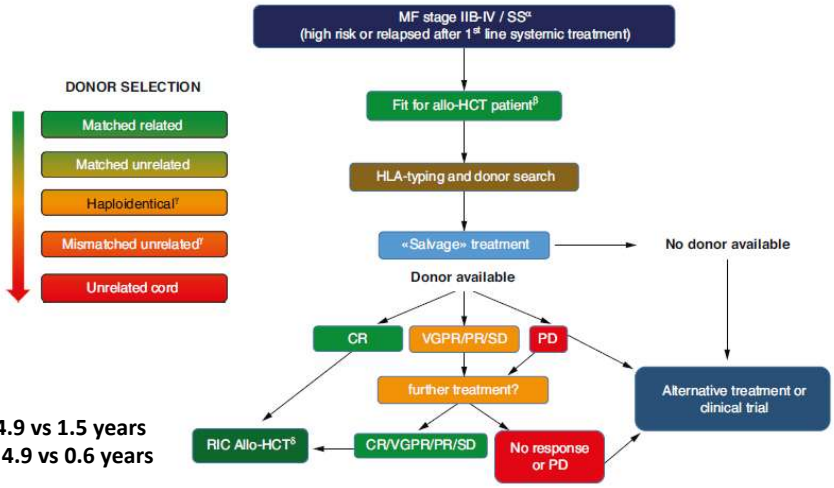
Cutaneous T-cell lymphomas



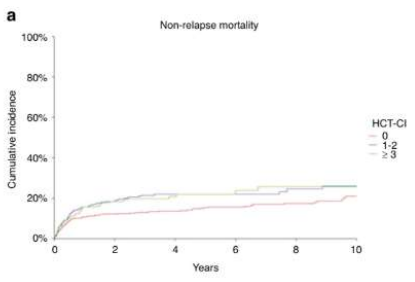
OS 4.9 vs 1.5 years
PFS 4.9 vs 0.6 years

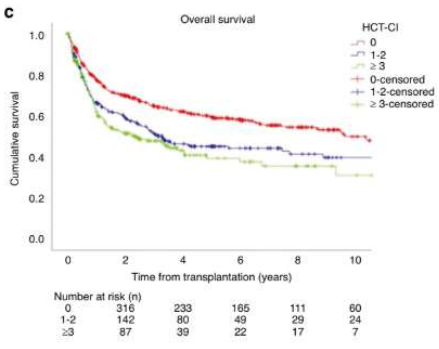
Damaj et al. Bone Marrow Transplantation 2025

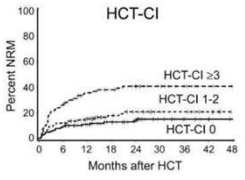
Transplant-related mortality and morbidity

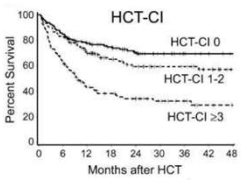
Comorbidity	Definitions	HCT-CI Weighted Score
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmia	1
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Diabetes	Requiring treatment with insulin or oral hypoglycemic but not diet alone	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5× ULN, or AST/ALT > ULN to 2.5× ULN	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Obesity	Patients with a body mass index > 35 kg/m^2	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Renal, moderate/severe	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatic	2

Sorror. Blood 2005
Janscak M, et al. Bone Marrow Transplant. 2024



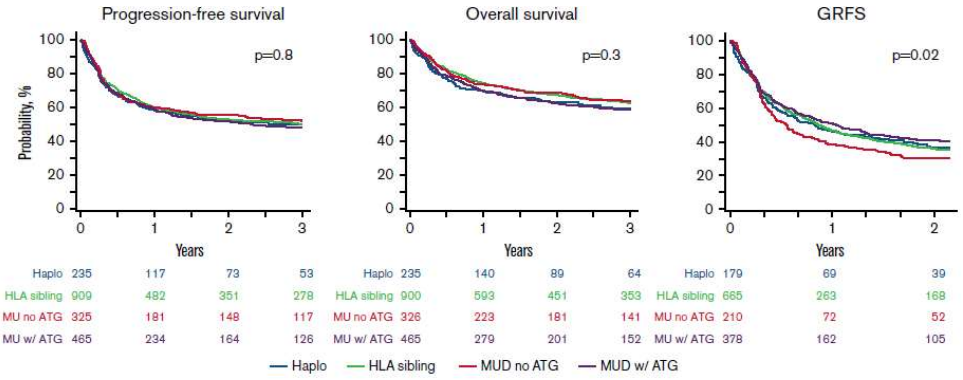






Donor source

Disease status at HCT and decreased PS



- Using univariate and multivariate comparisons, OS, PFS, RI, and NRM were not significantly different among the haplo-HCT, MSD, MUD TCD+, and MUD TCD- cohorts
- 3-year OS 60%, 63%, 59%, and 64% and PFS of 50%, 50%, 48%, and 52%

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Hamadani et al. Blood Adv 2022

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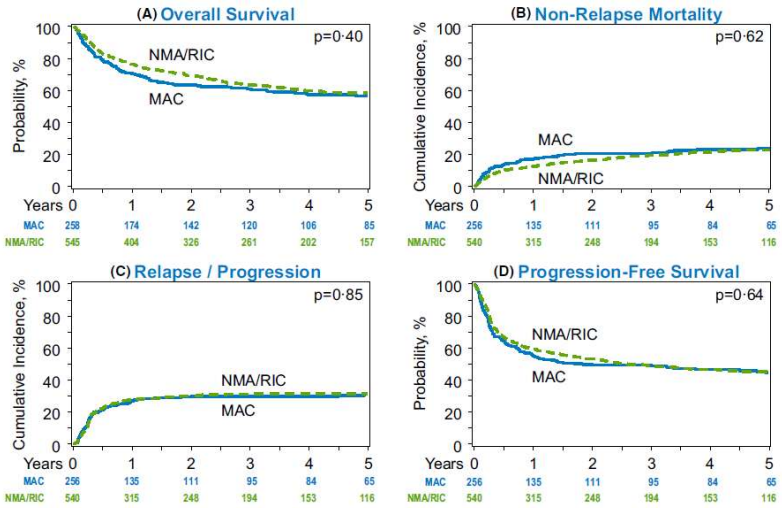
Impact of conditioning regimen intensity

Conditioning intensity (MAC vs RIC/NMA) did not impact major outcomes after allo-HCT for T-cell NHL.

RIC/NMA reduced severe acute GVHD.



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Savani et al. Br J Haematol. 2022

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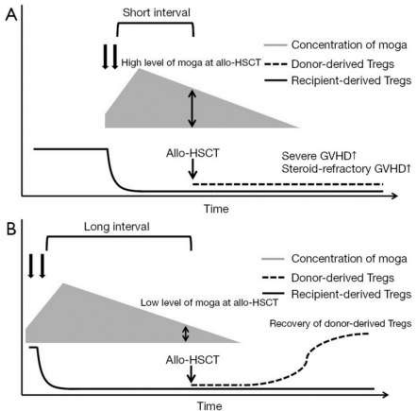
Impact of novel agents on allo HSCT

Novel Agents for TCLs		Effects on HCT Immunity	Pre-HCT Use	Post-HCT Use
Conventional salvage chemotherapy		Non-specific cytotoxic effects on both malignant and normal hematopoietic/immune cells; potential impairment of immune reconstitution.	Commonly used as salvage therapy to achieve disease control; responses are often short-lived in chemotherapy-refractory TCLs.	Limited role due to myelosuppression and cumulative toxicity; generally avoided except in selected relapse cases.
Antibody drugs	MOG	Depletes Tregs.	Increase the risk of steroid-refractory GVHD and NRM (especially with a short MOG-to-HCT interval).	·Relatively safe ≥ 3 months post-HCT. ·Effective against ATL peripheral blood lesions.
	BV	Depletes activated CD30+ T cells.	Safe as bridging therapy without affecting engraftment or GVHD.	May help reduce GVHD.
LEN		·Activates T and NK cells. ·Increases cytokine production. ·Suppresses Treg function.	Data limited.	·Early use after HCT increases the risk of GVHD. ·Delayed use or combination with AZA may reduce GVHD risk. ·Myelosuppression is a concern.
HDACis		·Suppress cytokine production. ·Stabilize Tregs ·Modulate APC and NK cell function.	Data limited.	Potential for GVHD prevention; well tolerated.
EZH1/2 inhibitors		May modulate GVHD via epigenetics.	Limited reports; no clear harm observed.	No established role; further studies needed.
Immune checkpoint inhibitors		Reduced PD-1+ T cells and Tregs.	Increased risk of GVHD; however, this may be mitigated by the use of PTCy as GVHD prophylaxis.	·May enhance the GVL effect. ·Requires monitoring for both GVHD and irAEs.



Inoue and Yasunaga. Cells 2025

Conclusions

Frontline setting

- We offer consolidative auto-HCT to eligible patients with bulky/stage III-IV/IPI ≥ 2 disease who achieve a complete remission (CR) after standard first-line therapy.
- Patients with ALK-positive ALCL or with a negative interim PET after two cycles of chemotherapy (iPET2 negativity) may not require auto-HCT.
- Any other outcome is considered treatment failure and managed accordingly.

Salvage setting – chemosensitive disease

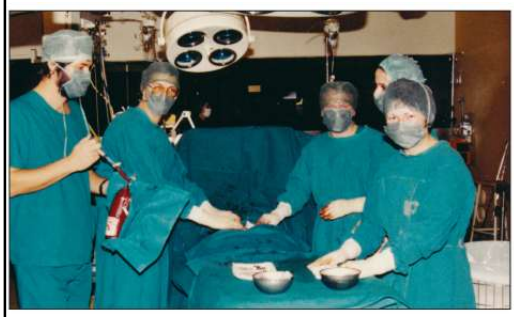
- For all transplant-eligible patients with failure of first-line therapy, we initiate a donor search immediately.
- In transplant-naïve patients who relapse from first CR (CR1) and achieve a second metabolic CR with salvage therapy, auto-HCT is discussed as an option.
- All other eligible patients are generally advised to proceed to allo-HCT.

Salvage setting – refractory disease

- If no clinical trial with a genuinely promising novel agent is available, we proceed directly to allo-HCT in salvage-refractory patients, avoiding further and largely futile attempts at inducing remission, provided the patient remains transplant-eligible.

Transplantation in CTCL

- Allo-HCT should be reserved for eligible patients with stage IIB–III disease who have failed at least one line of systemic therapy, and for those with stage IV disease.



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SREČANJE SO OMOGOČILI:

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za dosego remisije pri KLL.[2,3]

V+X*

Zdravilo VENCLYXTO® omogoča prilagojene možnosti zdravljenja za vaše bolnike s KLL.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Venclyxto 10 mg, 50 mg ali 100 mg filmsko obložene tablete **Sestava:** Ena filmsko obložena tableta vsebuje 10 mg, 50 mg oziroma 100 mg venetoklaksa. **Terapevtske indikacije:** Zdravilo Venclyxto v kombinaciji z obinutuzumabom je indicirano za zdravljenje odraslih bolnikov s predhodno nezdravljeno kronično limfocitno levkemijo (KLL). Zdravilo Venclyxto v kombinaciji z rituksimabom je indicirano za zdravljenje odraslih bolnikov s KLL, ki so predhodno prejeli vsaj eno zdravljenje. Zdravilo Venclyxto kot monoterapija je indicirano za zdravljenje KLL s prisotno delecijo 17p ali mutacijo TP53 pri odraslih bolnikih, ki niso primerni za zdravljenje z zaviralcem receptorske poti celic B oziroma pri katerih zdravljenje ni bilo uspešno, ali z odsotno delecijo 17p ali mutacijo TP53 pri odraslih bolnikih, pri katerih tako kemoimunoterapija kot zdravljenje z zaviralcem receptorske poti celic B ni bilo uspešno. Zdravilo Venclyxto v kombinaciji s hipometilacijsko učinkovino je indicirano za zdravljenje odraslih bolnikov z na novo diagnosticirano akutno mieloično levkemijo (AML), ki niso primerni za intenzivno kemoterapijo. **Odmerjanje in način uporabe**: Zdravljenje z venetoklaksom mora začeti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje raka. Pri bolnikih, zdravljenih z venetoklaksom, se lahko razvije sindrom tumorske lize (TLS). Za preprečevanje in zmanjšanje tveganja za TLS je treba upoštevati informacije, opisane v poglavju 4.2 Povzetka glavnih značilnosti zdravila. Odmerjanje: *KLL: Shema titracije odmerka:* Začetni odmerek je 20 mg venetoklaksa enkrat na dan, 7 dni. Odmerek je treba v obdobju 5 tednov postopoma povečevati do dnevnega odmerka 400 mg: prvi teden je dnevni odmerek zdravila 20 mg, drugi teden 50 mg, tretji 100 mg, četrti 200 mg in peti teden 400 mg. 5-tedenska shema titracije odmerka je načrtovana za postopno zmanjšanje tumorske obremenitve in zmanjšanje tveganja za sindrom tumorske lize. *Venetoklaks v kombinaciji z obinutuzumabom:* Venetoklaks se daje skupno 12 ciklusov, vsak ciklus traja 28 dni: 6 ciklusov v kombinaciji z obinutuzumabom, ki jim sledi 6 ciklusov monoterapije z venetoklaksom. Obinutuzumab se odmerja po 100 mg 1. dan 1. ciklusa, nato sledi 900 mg, ki jih lahko date 1. ali 2. dan. Sledijo odmerki po 1000 mg 8. in 15. dan 1. ciklusa in 1. dan vsakega naslednjega 28-dnevnega ciklusa, do skupno 6 ciklusov. 5-tedensko shemo titracije odmerka venetoklaksa (glejte preglednico 1) začnite na 22. dan 1. ciklusa in nadaljujte do 28. dne 2. ciklusa. Po zaključeni titraciji odmerka po shemi, je priporočeni odmerek venetoklaksa 400 mg enkrat na dan od 1. dne 3. ciklusa obinutuzumaba do zadnjega dne 12. ciklusa. *Odmerjanje venetoklaksa v kombinaciji z rituksimabom po titraciji:* Priporočeni odmerek venetoklaksa v kombinaciji z rituksimabom je 400 mg enkrat na dan. Rituksimab uporabite po tem, ko je bolnik zaključil s titriracijo odmerka po shemi in je 7 dni prejemal priporočeni dnevni odmerek 400 mg venetoklaksa. Venetoklaks se jemlje 24 mesecev od 1. dne 1. ciklusa rituksimaba. *Odmerjanje venetoklaksa v monoterapiji po titraciji*: Priporočeni odmerek venetoklaksa je 400 mg enkrat na dan. Z zdravljenjem se nadaljuje, dokler bolezen ne napreduje ali do tedaj, ko bolnik zdravljenja ne more več prenašati. *AML:* Priporočeni režim odmerjanja venetoklaksa (vključno s titracijo odmerka): prvi dan je odmerek zdravila 100 mg, drugi dan 200 mg, tretji dan in kasneje pa 400 mg. Azacitidin je treba dajati intravensko ali subkutano v odmerku 75 mg/m^2 od 1. do 7. dne vsakega 28-dnevnega ciklusa, in sicer od 1. dne 1. ciklusa. Decitabin je treba dajati intravensko v odmerku 20 mg/m^2 od 1. do 5. dne vsakega 28-dnevnega ciklusa, in sicer od 1. dne 1. ciklusa. Odmerjanje venetoklaksa se lahko prekine, če je to potrebno za obvladovanje hematoloških toksičnosti in normalizacijo krvne slike (glejte preglednico 4 v Povzetku glavnih značilnosti zdravila). Zdravljenje z venetoklaksom v kombinaciji s hipometilacijsko učinkovino je treba nadaljevati do opaženega napredovanja bolezni ali nesprejemljive toksičnosti. *Preprečevanje sindroma tumorske lize (TLS)*: Pri bolnikih, zdravljenih z venetoklaksom, se lahko pojavi TLS. *KLL:* Venetoklaks lahko povzroči hitro zmanjšanje tumorja in tako predstavlja tveganje za TLS v začetni 5-tedenski fazi titracije odmerka pri vseh bolnikih s KLL ne glede na tumorsko obremenitev in druge značilnosti bolnika. Za zmanjšanje tveganja za TLS je treba oceniti dejavnike za stopnjo tveganja za TLS na ravni bolnika ter bolnikom pred prvim odmerkom venetoklaksa zagotovite profilaktično hidracijo in antihiperurikemike. Priporočena profilaksa pri TLS na osnovi tumorske obremenitve pri bolnikih s KLL je naslednja: nizka tumorska obremenitev: peroralna hidracija (1,5-2 l) + alopurinol; srednja tumorska obremenitev: peroralna hidracija (1,5-2 l) ter razmislek o dodatni intravenski hidraciji + alopurinol; visoka tumorska obremenitev: peroralna (1,5-2 l) in intravenska (150–200 ml/h, kot je tolerirano) hidracija + alopurinol; pri povišanih izhodiščnih vrednostih sečne kisline razmislek o razburkazi. Za natančna priporočila in opombe glejte Povzetek glavnih značilnosti zdravila. *Prilagoditve odmerka zaradi TLS in drugih toksičnosti*: *KLL:* Morda bo potrebna prekinitev odmerjanja in/ali zmanjšanje odmerka zaradi toksičnosti. Za priporočene prilagoditve odmerka zaradi toksičnosti, povezane z venetoklaksom glejte preglednici 4 in 5 v Povzetku glavnih značilnosti zdravila. *AML:* Pri uporabi v kombinaciji z azacitidinom ali decitabinom je dnevni odmerek venetoklaksa treba titrirati 3 dni. Upoštevati je treba naslednje ukrepe za profilakso: pred začetkom zdravljenja z venetoklaksom mora biti število belih krvnih celic pri vseh bolnikih < 25 × 109/l, lahko pa je pred zdravljenjem potrebna tudi citoredukcija; vsi bolniki morajo biti pred prejemom prvega odmerka venetoklaksa in med fazo titracije odmerka ustrezno hidrirani in prejeti antihiperurikemike; pred začetkom zdravljenja z venetoklaksom ocenite rezultate krvnih preiskav in popravite obstoječe nepravilnosti; pred prvim odmerkom, 6 do 8 ur po vsakem novem odmerku med titracijo in 24 ur po prvem končnem odmerku opravite krvne preiskave za TLS. Pri bolnikih z dejavniki tveganja za TLS (npr. blasti v krvnem obtoku, visoko levkemično breme v kostnem mozgu, zvišane vrednosti laktat dehidrogenaze [LDH] pred zdravljenjem ali zmanjšano delovanje ledvic), je treba razmisliti o dodatnih ukrepih, vključno s pogostejšim laboratorijskim spremljanjem in zmanjšanjem začetnega odmerka venetoklaksa. Pogosto preverjajte krvno sliko, dokler citopenije ne izzvenijo. Prilagajanje odmerka in prekinitve zdravljenja zaradi citopenij so odvisni od stanja remisije. Za priporočene prilagoditve odmerka zaradi neželenih učinkov pri AML glejte preglednico 6 v Povzetku glavnih značilnosti zdravila. *Prilagoditve odmerka zaradi uporabe z zaviralci CYP3A*: Sočasna uporaba venetoklaksa ***z močnimi ali zmernimi zaviralci CYP3A poveča izpostavljenost venetoklaksu*** (tj. Cmax in AUC) in lahko poveča tveganje za TLS na začetku zdravljenja in med fazo titracije odmerka ter za druge toksičnosti. Pri bolnikih s KLL je sočasna uporaba venetoklaksa z močnimi zaviralci CYP3A kontraindicirana na začetku zdravljenja in med fazo titracije odmerka. ***Če je treba pri katerem koli bolniku uporabiti zaviralec CYP3A, upoštevajte priporočila za obvladovanje interakcij med zdravili, ki so povzeta v*** Povzetku glavnih značilnosti zdravila. *Izpuščeni odmerek*: Če bolnik izpusti odmerek venetoklaksa in od časa, ko ga običajno vzame, ni minilo več kot 8 ur, naj izpuščeni odmerek vzame čim prej še isti dan. Če je bolnik izpustil odmerek in od časa, ko ga običajno vzame, mine več kot 8 ur, naj ne vzame izpuščenega odmerka in naj naslednji dan nadaljuje z običajno shemo odmerjanja. *Posebne populacije*: *Starejši:* Posebna prilagoditev odmerka pri starejših bolnikih (stari ≥ 65 let) ni potrebna. *Okvara ledvic*: Venetoklaks se sme dajati bolnikom s hudo okvaro ledvic (CrCl ≥ 15 ml/min in < 30 ml/min) ali s končno ledvično odpovedjo (ESRD – end-stage renal disease), ki zahteva dializo (CrCl <15 ml/min) le, če koristi prevladajo nad tveganji. Pri bolnikih z blago, zmerno, hudo okvaro ledvic ali s končno ledvično odpovedjo, ki zahteva dializo, prilagoditev odmerka ni potrebna. *Okvara jeter:* Prilagoditev odmerka pri bolnikih z blago ali zmerno okvaro jeter ni priporočljiva. Pri bolnikih s hudo okvaro jeter se priporoča zmanjšanje odmerka za vsaj 50 % skozi celotno obdobje zdravljenja. Te bolnike je treba bolj skrbno spremljati glede znakov toksičnosti. *Pediatrična populacija*: Varnost in učinkovitost venetoklaksa pri otrocih, starih manj kot 18 let, nista bili dokazani. Način uporabe: Filmsko obložene tablete zdravila Venclyxto so za peroralno uporabo. Bolnike je treba poučiti, naj tablete pogoltnejo cele z vodo z obrokom, vsak dan ob približno istem času. Tablet se ne sme žvečiti, drobiti ali lomiti, preden se jih pogoltne. Med fazo titracije odmerka je treba venetoklaks vzeti zjutraj, da se olajša izvajanje laboratorijskih preiskav. **Kontraindikacije**: Preobčutljivost na učinkovino ali katero koli pomožno snov, navedeno v poglavju 6.1 Povzetka glavnih značilnosti zdravila. Sočasna uporaba venetoklaksa z močnimi zaviralci CYP3A na začetku zdravljenja in med fazo titracije odmerka pri bolnikih s KLL in preparatov, ki vsebujejo šentjanževko, pri vseh bolnikih. **Posebna opozorila in previdnostni ukrepi**: Sindrom tumorske lize: Do sindroma tumorske lize, vključno s smrtnimi dogodki in odpovedjo ledvic, ki je zahtevala dializo, je prišlo pri bolnikih, ki so bili zdravljeni z venetoklaksom. Venetoklaks lahko povzroči hitro zmanjšanje tumorja in tako na začetku zdravljenja in med fazo titracije sproži tveganje za TLS. Spremembe v elektrolitih, ki so skladne s TLS in zahtevajo takojšnje ukrepanje, se lahko pojavijo že v 6 do 8 urah po prvem odmerku venetoklaksa in ob vsakem povečanju odmerka. Med spremljanjem v obdobju trženja zdravila so poročali o TLS, vključno s smrtnimi dogodki, po enem 20-mg odmerku venetoklaksa. Za preprečevanje in zmanjšanje tveganja za TLS je treba upoštevati informacije, opisane v Povzetku glavnih značilnosti zdravila, vključno z oceno tveganja, profilaktičnimi ukrepi, shemo titracije odmerka in prilagoditve odmerka, laboratorijskimi preiskavami in medsebojnim delovanjem zdravil. Tveganje za TLS je stalno prisotno in temelji na več dejavnikih, vključno s pridruženimi boleznimi (še zlasti zmanjšanim delovanjem ledvic), tumorsko obremenitvijo in splenomegalijo pri KLL. Sočasna uporaba z močnimi ali zmernimi zaviralci CYP3A poveča izpostavljenost venetoklaksu in lahko poveča tveganje za TLS na začetku zdravljenja in med fazo titracije odmerka. Tudi zaviralci P-gp ali BCRP lahko povečajo izpostavljenost venetoklaksu. Nevtropenija in okužbe: Pri bolnikih s KLL, ki so se zdravili z venetoklaksom, so poročali o nevtropeniji 3. ali 4. stopnje v študiji kombinacije z rituksimabom ali obinutuzumabom in v študijah z monoterapijo. Pri bolnikih z AML je pred zdravljenjem pogosto prisotna nevtropenija 3. ali 4. stopnje. Število nevtrofilcev se lahko pri uporabi venetoklaksa v kombinaciji s hipometilacijsko učinkovino poslabša. Nevtropenija se lahko ponovno pojavi med poznejšimi ciklusi zdravljenja. Poročali so o resnih okužbah, vključno s pojavom sepse s smrtnim izidom. Potrebno je spremljanje kakršnih koli znakov in simptomov okužbe. Ob sumu na okužbo je potrebno takojšnje zdravljenje, vključno z antibiotiki, prekinitvijo ali ustreznim zmanjšanjem odmerka in uporabo rastnih faktorjev (npr. G-CSF). Imunizacija: Živih cepiv se ne sme dajati med zdravljenjem in pozneje, vse do povrnitve celic B. Induktorji CYP3A: Sočasno dajanje induktorjev CYP3A4 lahko vodi v zmanjšano izpostavljenost venetoklaksu in posledično tveganje za pomanjkanje učinkovitosti. Sočasni uporabi venetoklaksa z močnimi ali zmernimi induktorji CYP3A4 se je potrebno izogibati. Ženske v rodni dobi: Ženske v rodni dobi morajo med jemanjem venetoklaksa uporabljati visoko učinkovito metodo kontracepcije. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Venetoklaks se presnavlja predvsem s CYP3A. Učinkovine, ki lahko spremenijo plazemske koncentracije venetoklaksa: *Zaviralci CYP3A*: Pri bolnikih, pri katerih je potrebna sočasna uporaba venetoklaksa z močnimi zaviralci CYP3A (npr. itrakonazolom, ketokonazolom, posakonazolom, vorikonazolom, klaritromicinom, ritonavirjem) ali zmernimi zaviralci CYP3A (npr. ciprofloksacinom, diltiazemom, eritromicinom, flukonazolom, verapamilom), je treba venetoklaks odmerjati v skladu s preglednico 5 v Povzetku glavnih značilnosti zdravila. Bolnike je treba bolj skrbno spremljati glede znakov toksičnosti in odmerek je morda potrebno dodatno prilagoditi. Odmerek venetoklaksa, ki se je uporabljal pred začetkom zdravljenja z zaviralcem CYP3A, je treba znova uvesti 2 do 3 dni po prenehanju zdravljenja z zaviralcem. Med zdravljenjem z venetoklaksom se je treba izogibati izdelkom iz grenivke, seviljskim pomarančam in zvezdnemu sadežu (karamboli), ker vsebujejo zaviralce CYP3A. *Zaviralci Pgp in BCRP*: Venetoklaks je substrat za P-gp in BCRP. Sočasni uporabi venetoklaksa z zaviralci P-gp in BCRP na začetku in med fazo titracije odmerka se je potrebno izogibati; če je uporaba zaviralcev P-gp in BCRP nujna, je treba bolnike skrbno spremljati glede znakov toksičnosti. *Induktorji CYP3A*: Sočasni uporabi venetoklaksa z močnimi induktorji CYP3A (npr. karbamazepinom, fenitoinom, rifampicinom) ali zmernimi induktorji CYP3A (npr. bozentanom, efavirenzom, etravirinom, modafinilom, nafcilinom) se je treba izogibati. Preparati, ki vsebujejo šentjanževko, so med zdravljenjem z venetoklaksom kontraindicirani, ker je učinkovitost lahko zmanjšana. *Azitromicin*: Pri kratkotrajni uporabi azitromicina sočasno z venetoklaksom prilagajanje odmerka ni potrebno. *Učinkovine, ki zmanjšajo kislost želodčne vsebine*: Glede na analizo populacijske farmakokinetike, učinkovine, ki zmanjšajo kislost želodčne vsebine (npr. zaviralci protonske črpalke, antagonisti receptorjev H2, antacidi), ne vplivajo na biološko razpoložljivost venetoklaksa. *Izmenjevalci žolčnih kislin*: Sočasno dajanje izmenjevalcev žolčnih kislin z venetoklaksom ni priporočljivo, saj lahko zmanjša absorpcijo venetoklaksa. Učinkovine, katerih koncentracije v plazmi se lahko spremenijo zaradi venetoklaksa: *Varfarin*: Pri bolnikih, ki prejemajo varfarin, se priporoča skrbno spremljanje mednarodnega normaliziranega razmerja (INR). *Substrati P-gp, BCRP in OATP1B1:* Venetoklaks je zaviralec P-gp, BCRP in OATP1B1 *in vitro*. Sočasnemu dajanju P-gp ali BCRP substratov z ozkim terapevtskim indeksom (npr. digoksin, dabigatran, everolimus, sirolimus) z venetoklaksom se je treba izogibati. Peroralno dajan P-gp ali BCRP substrat, ki je občutljiv na inhibicijo v gastrointestinalnem traktu (npr. dabigatraneteksilat), mora biti dan kolikor se da ločeno od dajanja venetoklaksa, da se s tem zmanjša možno interakcijo. Če se statin (OATP substrat) daje sočasno z venetoklaksom, je priporočljivo skrbno spremljanje s statini povezane toksičnosti. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi/kontracepcija pri ženskah: Ženske se morajo izogniti zanositvi med jemanjem zdravila Venclyxto in še vsaj 30 dni po končanem zdravljenju in zato v tem obdobju uporabljati visoko učinkovito metodo kontracepcije. Nosečnost: Ni dovolj ustreznih in dobro preverjenih podatkov o uporabi venetoklaksa pri nosečnicah. Uporaba venetoklaksa ni priporočljiva med nosečnostjo in pri ženskah v rodni dobi, ki ne uporabljajo visoko učinkovite kontracepcije. Dojenje: Ni znano ali se venetoklaks ali njegovi presnovki izločajo v materino mleko. Med zdravljenjem z zdravilom Venclyxto je treba dojenje prekiniti. Plodnost: Podatki o vplivu venetoklaksa na plodnost pri ljudeh niso na voljo. Pred začetkom zdravljenja se je pri nekaterih moških bolnikih smiselno posvetovati o shranitvi semenske tekočine. **Vpliv na sposobnost vožnje in upravljanja strojev:** Zdravilo Venclyxto nima vpliva oziroma ima zanemarljiv vpliv na sposobnost vožnje in upravljanja strojev. **Neželeni učinki**: Pri bolnikih s KLL: Najpogostejši neželeni učinki katere koli stopnje pri bolnikih, ki so prejemali venetoklaks v študiji kombinacije z obinutuzumabom ali rituksimabom, so bili nevtropenija, driska in okužbe zgornjih dihal. V študijah z monoterapijo so bili najpogostejši neželeni učinki nevtropenija/zmanjšano število nevtrofilcev, driska, navzea, anemija, utrujenost in okužbe zgornjih dihal. Najpogosteje poročani resni neželeni učinki pri bolnikih, ki so prejemali venetoklaks v kombinaciji z obinutuzumabom ali rituksimabom, so bili pljučnica, sepsa, febrilna nevtropenija in TLS. V študijah z monoterapijo sta bila najpogosteje poročana resna neželena učinka pljučnica in febrilna nevtropenija. Pri bolnikih z AML: V študiji VIALE A so bili neželeni učinki katere koli stopnje, ki so se najpogosteje pojavljali pri bolnikih, ki so prejemali venetoklaks v kombinaciji z azacitidinom, trombocitopenija, nevtropenija, febrilna nevtropenija, navzea, driska, bruhanje, anemija, utrujenost, pljučnica, hipokaliemija in pomanjkanje apetita. Resni neželeni učinki, o katerih so najpogosteje poročali pri bolnikih, ki so prejemali venetoklaks v kombinaciji z azacitidinom, so bili febrilna nevtropenija, pljučnica, sepsa in krvavitev. V študiji M14 358 so bili neželeni učinki katere koli stopnje, ki so se najpogosteje pojavljali pri bolnikih, ki so prejemali venetoklaks v kombinaciji z decitabinom, trombocitopenija, febrilna nevtropenija, navzea, krvavitev, pljučnica, driska, utrujenost, omotica/sinkopa, bruhanje, nevtropenija, hipotenzija, hipokaliemija, pomanjkanje apetita, glavobol, bolečina v trebuhu in anemija. Resni neželeni učinki, o katerih so najpogosteje poročali, so bili febrilna nevtropenija, pljučnica, bakteriemija in sepsa. **Način in režim izdajanja:** Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Nemčija. **Pomembno opozorilo: Pred predpisovanjem in uporabo, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila. Datum revizije besedila:** 07/2025.

KLL_kronična limfocitna levkemija; V+X*_ Zdravilo VENCLYXTO® je odobreno v kombinaciji z obinutuzumabom za zdravljenje odraslih bolnikov s predhodno nezdravljeno kronično limfocitno levkemijo (KLL) in v kombinaciji z rituksimabom za zdravljenje odraslih bolnikov s KLL, ki so že prejeli vsaj eno prejšnjo terapijo. Pri vseh kombinacijah je treba vedno upoštevati podatke o zdravilih za obe kombinirani zdravili.

Reference: 1. VENCLYXTO® SmPC. **2.** Al-Sawaf O, Robrecht S, Zhang C, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study. Blood. 2024; 144(18): 1924-1935. **3.** Seymour JF, Kipps TJ, Eichhorst BF, et al. Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax- rituximab. Blood. 2022;140(8):839–850.

Samo za strokovno javnost. I Datum priprave: september 2025. I SI-VNCCLL-250003
Abbvie d .o .o., Dolenjska cesta 242c, 1000 Ljubljana

abbvie

Jaypirca je prvi in edini odobreni reverzibilni BTK inhibitor,
ki lahko ponovno vzpostavi odgovor pri odraslih bolnikih z MCL in KLL potem ko kovalentni BTK inhibitor ni več opcija[1,2]

Indikaciji

Zdravilo Jaypirca je kot monoterapija indicirano za zdravljenje odraslih bolnikov s ponovitvijo limfoma plaščnih celic (MCL – mantle cell lymphoma), ali za na zdravljenje neodzivne oblike te bolezni, po predhodnem zdravljenju z zaviralcem Brutonove tirozin kinaze (BTK).

Zdravilo Jaypirca je kot monoterapija indicirano za zdravljenje odraslih bolnikov s ponovitvijo kronične limfocitne levkemije (KLL), ali za na zdravljenje neodzivne oblike te bolezni, po predhodnem zdravljenju z zaviralcem BTK.

Skrajšan povzetek glavnih značilnosti zdravila

▽ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.
Ime zdravila Jaypirca 50 mg filmsko obložene tablete, Jaypirca 100 mg filmsko obložene tablete. **Kakovostna in količinska sestava** Ena filmsko obložena tableta vsebuje 50 mg/100 mg pirtobrutiniba. **Terapevtske indikacije** Zdravilo Jaypirca je kot monoterapija indicirano za zdravljenje odraslih bolnikov s ponovitvijo limfoma plaščnih celic (MCL – mantle cell lymphoma), ali za na zdravljenje neodzivne oblike te bolezni, po predhodnem zdravljenju z zaviralcem Brutonove tirozin kinaze (BTK). Zdravilo Jaypirca je kot monoterapija indicirano za zdravljenje odraslih bolnikov s ponovitvijo kronične limfocitne levkemije (KLL), ali za na zdravljenje neodzivne oblike te bolezni, po predhodnem zdravljenju z zaviralcem BTK. **Odmerjanje in način uporabe** Zdravljenje z zdravilom Jaypirca mora uvesti in spremljati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. Odmerjanje Priporočeni odmerek je 200 mg pirtobrutiniba enkrat dnevno. Zdravljenje se mora nadaljevati do napredovanja bolezni ali nesprejemljive toksičnosti. Prilagajanje odmerka glede na starost, pri bolnikih z blago, zmerno ali hudo okvaro ledvic ali pri bolnikih z blago, zmerno ali hudo okvaro jeter ni potrebno. Način uporabe Zdravilo Jaypirca je namenjeno za peroralno uporabo. **Kontraindikacije** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi** Pri bolnikih, zdravljenih z zdravilom Jaypirca, je prišlo do resnih okužb, vključno s smrtnimi primeri. Okužbe stopnje 3 ali višje, o katerih so najpogosteje poročali, so bile pljučnica, covidna pljučnica, covid-19 in sepsa. Pri bolnikih s povečanim tveganjem za oportunistične okužbe je treba razmisliti o profilaktičnem protimikrobnem zdravljenju. Na podlagi stopnje okužbe in morebitne pridružene nevtropenije bo morda potrebna prekinitev zdravljenja. Pri bolnikih, zdravljenih z zdravilom Jaypirca, je prišlo do krvavitev, vključno s smrtnimi primeri, s trombocitopenijo ali brez nje. Opazili so večje krvavitve stopnje 3 in višje, vključno z gastrointestinalno in intrakranialno krvavitvijo. Bolnike je treba spremljati glede znakov in simptomov krvavitve. Pri krvavitvah stopnje 3 ali 4 bo morda potrebna prekinitev zdravljenja. Pri bolnikih, zdravljenih z zdravilom Jaypirca, je prišlo do citopenij stopnje 3 ali 4, vključno z nevtropenijo, anemijo in trombocitopenijo. Med zdravljenjem je treba spremljati celotno krvno sliko, kot je medicinsko indicirano. Na podlagi stopnje citopenije bo morda potrebna prekinitev zdravljenja. Pri bolnikih, zdravljenih z zdravilom Jaypirca, so opazili atrijsko fibrilacijo in atrijsko undulacijo, zlasti pri bolnikih z atrijsko fibrilacijo v anamnezi in/ali več pridruženimi srčno-žilnimi boleznimi. Bolnike je treba spremljati glede znakov in simptomov atrijske fibrilacije in atrijske undulacije, potrebno je posneti elektrokardiogram, kot je medicinsko indicirano. Na podlagi stopnje atrijske fibrilacije/atrijske undulacije bo morda potrebna prekinitev zdravljenja. Pri bolnikih, zdravljenih z zdravilom Jaypirca, je pogosto prišlo do drugih primarnih malignih bolezni, najpogosteje nemelanomskih kožnih rakov. Med zdravljenjem z zdravilom Jaypirca so redko poročali o sindromu tumorske lize (TLS – *tumour lysis syndrome*). Bolniki z velikim tveganjem za TLS so tisti, ki imajo pred zdravljenjem veliko tumorsko breme. Bolnike je treba oceniti glede morebitnega tveganja za TLS in jih skrbno spremljati, kot je klinično indicirano. Bolniki z redko dedno intoleranco za galaktozo, odsotnostjo encima laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Pirtobrutinib se presnavlja predvsem prek CYP3A4, UGT1A8 in UGT1A9. V klinični študiji je itrakonazol, močan zaviralec CYP3A4, povečal vrednost AUC pirtobrutiniba za 48 %, vrednosti C_{max} pirtobrutiniba pa ni spremenil. V klinični študiji je rifampin, močan induktor CYP3A, zmanjšal vrednost AUC in C_{max} pirtobrutiniba za 71 % oziroma 42 %. Pirtobrutinib je zmeren zaviralec CYP2C8 in BCRP. Pirtobrutinib je šibek zaviralec P-gp,CYP2C19 in CYP3A. **Neželeni učinki** Najpogostejši neželeni učinki katere koli stopnje so: utrujenost, nevtropenija, driska in kontuzije. *Zelo pogosti:* pljučnica, okužba zgornjih dihal, nevtropenija, trombocitopenija, anemija, glavobol, krvavitev, podplutbe, kontuzije, driska, bolečine v trebuhu, navzea, izpuščaj, artralgija, utrujenost, periferni edem *Pogosti:* okužba sečil, limfocitoza, atrijska fibrilacija/atrijska undulacija, hematurija, epistaksa, hematom, vezničnа krvavitev, petehije. **Imetnik dovoljenja za promet z zdravilom** Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, Nizozemska. **Datum zadnje revizije besedila** 28.03.2025. **Režim izdaje** Rp/Spec - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Samo za strokovno javnost.**

BTK=Brutonova tirozin kinaza; MCL=mantle cell lymphoma; KLL=kronična limfocitna levkemija.

Referenci: 1. Povzetek glavnih značilnosti zdravila Jaypirca, zadnja odobrena verzija. **2.** Mato AR, Shah NN, Jurczak W, *et al.* Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 021;397(10277):892-901.

Pomembno: Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. Pred predpisovanjem zdravila Jaypirca si preberite zadnji veljavni Povzetek glavnih značilnosti zdravil. Podrobne informacije o zdravilu so objavljene na spletni strani Evropske agencije za zdravila http://www.ema.europa.eu

Eli Lilly farmacevtska družba, d.o.o., Dunajska cesta 167, 1000 Ljubljana, telefon 01 / 580 00 10, faks 01 / 569 17 05

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