

ONCOLOGY KNOWLEDGE HUB · FOR HEALTH PROFESSIONALS

Indolent B-cell Lymphomas

A mini review for clinicians

For postgraduate residents (medical, radiation and paediatric oncology, haematology, pathology, gastroenterology, nuclear medicine, general surgery, medicine), practising clinicians and medical students

Dr. Haritha Chiramana

MD (Internal Medicine), DM (Medical Oncology)

Senior Medical Oncologist & Hemato-Oncologist

C.R. Reddy Cancer Center, C.R. Reddy Superspeciality Hospital

17/406, Old Post Office Road, near Leela Mahal Road, Nellore, Andhra Pradesh 524003

Phone 0861 232 5344 · WhatsApp +91 79896 42272

info@drharitha.co.in · drharitha.co.in

Dr. Haritha teaches oncology to postgraduates and medical students. Colleges and departments may write to info@drharitha.co.in for teaching sessions.

CONTENTS

01 At a glance

02 Clinical presentation, common traps & causes

03 Diagnosis, workup & staging essentials

04 Biology and biomarkers that change treatment

05 Local therapy: radiotherapy & surgery

06 Systemic therapy: indications & options

07 Management algorithms

08 Survivorship, follow-up & late effects

09 Landmark trials

10 Practice pearls & pitfalls

11 Case vignettes: lines of management

12 References & guidelines

Cite as: Chiramana H. Indolent B-cell Lymphomas: a mini review for clinicians. Oncology Knowledge Hub [Internet]. Nellore (India): drharitha.co.in; 2026 [updated 2026 Oct 17]. Available from: <https://drharitha.co.in/professionals/indolent-b-cell-lymphomas> · Free for education with attribution (CC BY-NC-ND 4.0).

Updated 17 October 2026. Educational summary written in our own words from current guidelines and primary trials; no drug doses; not advice for an individual patient. Verify current guidelines and Indian regulatory approvals before treatment decisions. Patients and families: please see the patient guides at drharitha.co.in.

Indolent B-cell Lymphomas

Haematological cancers, part 3 · Follicular, marginal zone (MALT, splenic, nodal) and mantle cell lymphoma · CLL/SLL and lymphoplasmacytic lymphoma · Watch and wait · Radiotherapy · Anti-CD20 therapy · BTK inhibitors · Transformation · Survivorship · Key points for clinicians · Last updated 17 October 2026

01 At a glance

- **Indolent B-cell lymphomas grow over months to years:** follicular lymphoma (the commonest), marginal zone lymphomas (MALT, splenic, nodal), CLL/SLL and lymphoplasmacytic lymphoma. Mantle cell lymphoma is included by tradition but usually behaves aggressively.
- **Most are stage III–IV at diagnosis, yet most patients feel well:** painless nodes that wax and wane, a big spleen, a high lymphocyte count on a routine test, or a gastric lesion at endoscopy.
- **Diagnosis needs the right sample:** an excision biopsy for nodes, flow cytometry for blood (CLL), many endoscopic biopsies for MALT. Five markers (CD5, CD10, CD23, cyclin D1, plus a clue such as SOX11 or MYD88) sort most cases.
- **Not everyone needs treatment:** asymptomatic advanced follicular, marginal zone, indolent mantle cell and early CLL are watched; treating early delays the next treatment but does not lengthen life ([Ardeshtna 2014^{\[1\]}](#)).
- **Localised disease is often curable with low-dose radiotherapy:** 24 Gy for stage I follicular and localised MALT lymphoma ([FoRT^{\[2\]}](#)); gastric MALT with *H. pylori* usually regresses after eradication therapy alone.
- **When treatment is needed:** an anti-CD20 antibody, alone or with bendamustine, CHOP or lenalidomide, for follicular and marginal zone lymphoma ([Stil^{\[3\]}](#), [RELEVANCE^{\[4\]}](#)); cytarabine-containing induction, transplant and BTK inhibitors for fit patients with mantle cell lymphoma ([TRIANGLE^{\[5\]}](#)).
- **Two events change the outlook:** histologic transformation (about 1% a year in follicular lymphoma) and progression within 24 months of first chemoimmunotherapy ([POD24^{\[6\]}](#)). Both need a biopsy.
- **Relapse is expected and treatable:** R2-based combinations, bispecific antibodies and CAR-T in follicular lymphoma; BTK inhibitors, CAR-T and pirtobrutinib in mantle cell lymphoma; BTK inhibitors and venetoclax in CLL.
- **India traps:** these lymphomas are less common here, so nodes get weeks of anti-TB treatment first; hepatitis B and C must be checked before rituximab; *H. pylori* is common and gastric MALT can be cured with antibiotics.

Indolent B-cell lymphomas: slow-growing, usually widespread, often not cured but very treatable

Follicular

Marginal zone

CLL / SLL

Mantle cell

LPL

Widths are illustrative, not to scale. Mantle cell lymphoma is grouped here by tradition but usually behaves like an aggressive lymphoma.

What they are

- Small B cells that grow over months to years
- Most are stage III–IV at diagnosis, yet many people feel well
- Each has a fingerprint: CD5, CD10, CD23, cyclin D1, MYD88

How they are treated

- No symptoms: watch and wait is a real treatment choice
- Stage I: radiotherapy 24 Gy, often curative
- Symptoms or bulk: anti-CD20 antibody ± chemotherapy or targeted drugs

What to expect

- Follicular: median survival over 20 years
- Gastric MALT: often cured by treating H. pylori
- Transformation (about 1% a year) and early relapse change the outlook

Figure 1. Indolent B-cell lymphomas at a glance (UpToDate follicular, marginal zone, mantle cell, CLL/SLL and LPL reviews). Each entity is described in sections O2–O6.

02 Clinical presentation, common traps & causes

Where each indolent lymphoma shows up, and the clue that points to it

Follicular Painless nodes in neck, axilla or groin that wax and wane; marrow often involved; LDH usually normal	MALT (extranodal MZ) Stomach, eye adnexa, salivary gland, lung, thyroid, skin; H. pylori, Sjögren, Hashimoto	Splenic MZ Big spleen, lymphocytosis and cytopenias; few nodes; autoimmune anaemia; hepatitis C	Nodal MZ Widespread non-bulky nodes in an older adult; about 1% of NHL
Mantle cell Older man; nodes, spleen, marrow, blood; gut polyps (lymphomatous polyposis)	CLL / SLL High lymphocyte count on a routine test; smudge cells; nodes in SLL	Lymphoplasmacytic Marrow disease with an IgM spike (Waldenström); hyperviscosity, neuropathy	Transformed Rapid growth, B symptoms, high LDH or calcium; biopsy the hottest PET node

Despite widespread disease, most patients feel well: about one in five with follicular lymphoma has B symptoms and fewer than one in four a raised LDH.

In India these lymphomas are less common than in the West (Tata Memorial series: follicular 12.6%, marginal zone 8.2%, mantle cell 3.4% of NHL), so they are easily mistaken for tuberculosis or reactive nodes. A node that persists, grows or comes back needs an excision biopsy.

Figure 2. Presentation by entity (UpToDate presentation and diagnosis reviews); Indian frequencies from Naresh 2000 (2773 lymphomas, Tata Memorial Hospital).

Who gets it, and why

- **Age:** these are diseases of older adults. Median age is about 65 for follicular and splenic MZL, 68 for mantle cell lymphoma (three-quarters men) and about 70 for CLL/SLL and nodal MZL.
- **India:** in 2773 lymphomas at Tata Memorial Hospital, follicular lymphoma was 12.6% of NHL, marginal zone 8.2%, small lymphocytic 5.7% and mantle cell 3.4%, lower than in Europe and the United States ([Naresh 2000^{\[7\]}](#)). CLL is also less common in India, China and Japan than in the West, probably for genetic reasons.
- **Chronic immune stimulation drives MALT lymphoma:** H. pylori (stomach, best established), Chlamydia psittaci (eye adnexa), Campylobacter jejuni (small bowel), Borrelia (skin); and autoimmunity: Sjögren's (parotid), Hashimoto's (thyroid), lupus.
- **Hepatitis C** is linked with splenic and other marginal zone lymphomas; treating the virus can make the lymphoma regress ([Hermine 2002^{\[8\]}](#)).
- **Family:** up to 17% of first-degree relatives of people with CLL have monoclonal B-cell lymphocytosis on flow cytometry, but few develop CLL; the absolute risk of follicular lymphoma in relatives is low. Lymphoma is not contagious.
- **Children and young adults:** paediatric-type follicular lymphoma and paediatric nodal MZL are localised head-and-neck diseases with a very high cure rate after local treatment; they are not the adult disease.

Common traps

- **Months of anti-TB treatment for a node that waxes and wanes.** A node that persists, grows or keeps coming back needs an excision biopsy, even when the patient feels well.
- **FNA reported as "reactive" or "lymphoproliferative".** Follicular architecture cannot be seen on FNA; grade and transformation need the whole node.

- **A high lymphocyte count treated as an infection, or ignored.** A persistent lymphocytosis in an older adult needs a smear and blood flow cytometry.
- **CD5-positive is not always CLL.** Mantle cell lymphoma is CD5-positive too: ask for cyclin D1 and CD23 on every CD5-positive small B-cell lymphoma.
- **Starting chemotherapy for a well patient with stage IV follicular lymphoma.** Stage alone is not an indication; symptoms, bulk, organ threat and cytopenias are.
- **Gastric biopsies read as "chronic gastritis with lymphoid aggregates".** If MALT lymphoma is suspected, ask for many biopsies, immunohistochemistry and H. pylori testing off PPIs.
- **Missing hepatitis B or C.** Rituximab can reactivate hepatitis B fatally; hepatitis C may be the treatment for the lymphoma.
- **Calling a fast-growing node "just follicular".** Rapid growth, B symptoms, a high LDH or calcium suggest transformation: biopsy the most PET-avid node.

SHARE WITH PATIENTS: SWELLINGS, SYMPTOMS AND SLOW-GROWING LYMPHOMA

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

Every swollen lymph node is cancer?

A painless neck swelling is always tuberculosis?

If there is no pain, fever or weight loss, lymphoma is impossible?

A normal blood count rules out lymphoma?

Lymphoma occurs only in elderly people?

Lymphoma is contagious and can spread between family members?

Lymphoma can't occur outside the lymph nodes?

03 Diagnosis, workup & staging essentials

Making the diagnosis

- **Nodes:** excision biopsy of the largest or most PET-avid accessible node (several cores if excision is not possible). Classic follicular lymphoma can be diagnosed on morphology alone; partial involvement and variants need immunohistochemistry.
- **Blood:** CLL needs at least 5000 clonal B cells/ μ L for 3 months with the typical phenotype (CD5, CD23, dim CD20 and dim surface immunoglobulin); fewer cells with no other disease = monoclonal B-cell lymphocytosis (MBL); nodes or spleen with fewer cells = SLL.
- **Follicular grade:** the ICC counts centroblasts (grade 1–2, 3A, 3B); WHO5 calls grades 1–3A "classic follicular lymphoma" and grade 3B "follicular large B-cell lymphoma", which is treated as DLBCL ([WHO5^{\[9\]}](#), [ICC^{\[10\]}](#)).
- **Look-alikes that are not the usual disease:** in situ follicular neoplasia (BCL2-bright follicles in an otherwise normal node: usually no lymphoma on work-up); duodenal-type follicular lymphoma (small duodenal polyps, very indolent); paediatric-type follicular lymphoma (localised, BCL2-negative, cured by local treatment).
- **Mantle cell lymphoma:** cyclin D1 (nuclear), CD5, SOX11, and t(11;14) on FISH. Classic MCL vs leukaemic non-nodal MCL (spleen and blood, SOX11-negative, low Ki-67, often indolent) vs in situ mantle cell neoplasia (incidental).
- **MALT lymphoma:** biopsy of the involved organ; small cells with reactive follicles, CD5- and CD10-negative; trisomy 3 or t(11;18) in most. Gastric cases: many biopsies from every region, H. pylori on histology (then breath or stool test if negative), FISH or PCR for t(11;18).
- **Splenic MZL:** blood smear, flow cytometry and marrow biopsy are usually enough when the spleen is big; splenectomy gives the definitive answer when needed.
- **Lymphoplasmacytic lymphoma:** at least 10% marrow infiltration by small lymphocytes, plasmacytoid cells and plasma cells; MYD88 L265P supports it ([Treon 2012^{\[11\]}](#)); an IgM spike defines Waldenström macroglobulinaemia.

The small B-cell lymphoma key: five markers sort most cases

	CD5	CD10	CD23	Cyclin D1	Other clue
CLL / SLL	+	–	+	–	Dim CD20, dim surface Ig; smudge cells
Mantle cell	+	–	–	+	SOX11+; t(11;14)
Follicular	–	+	–/+	–	BCL6+, BCL2+ in >85%; t(14;18)
Marginal zone	–	–	–	–	Diagnosis of exclusion; trisomy 3, t(11;18)
Lymphoplasmacytic	–/+	–	–	–	IgM, plasma cells; MYD88 L265P
Hairy cell (mimic)	–	–	–	weak	CD103, CD25, CD11c, annexin A1

All are B cells (CD19, CD20, CD22) with light-chain restriction; the pattern above plus morphology and the clinical picture make the diagnosis. Cyclin D1-negative mantle cell lymphoma exists (cyclin D2 or D3); SOX11 positivity rescues the diagnosis. CD5-positive marginal zone lymphoma also exists.

Flow cytometry on blood is enough for CLL; every other entity needs tissue (node, spleen, marrow or the involved organ).

Figure 3. Immunophenotype key (UpToDate follicular, mantle cell, marginal zone, CLL/SLL and LPL diagnosis reviews; simplified, exceptions exist).

Before treatment

Area	What to do	Why
History and examination	B symptoms, node regions, liver and spleen, eyes and salivary glands (MALT), autoimmune disease, prior treatment, family history; performance status and comorbidities	Entity, stage, fitness, indications to treat
Blood tests	CBC and smear, chemistry, LDH, calcium, beta-2 microglobulin; serum protein electrophoresis and immunoglobulins; direct antiglobulin test if anaemic	FLIPI/FLIPI24, MIPI; paraprotein; autoimmune cytopenias
Viruses	HBsAg and anti-HBc (HBV DNA if either positive), HCV, HIV	Antiviral prophylaxis before anti-CD20 therapy; HCV-driven MZL
Imaging	PET-CT (follicular, nodal MZL, mantle cell; to find the site to biopsy if transformation is suspected); contrast CT for splenic MZL and CLL only when needed	Lugano stage; PET is poor at marrow in SMZL and low-Ki-67 MCL
Bone marrow	SMZL, LPL, MCL; follicular when it changes management (cytopenias, apparent stage I–II before RT)	True stage I is rare
Endoscopy	Gastric MALT (with endoscopic ultrasound for depth and nodes); MCL with GI symptoms or apparent early stage	Lugano GI stage; hidden gut disease
H. pylori	Off antibiotics and bismuth for 4 weeks and PPIs for 2 weeks if possible; histology at endoscopy, breath or stool test if negative	Avoid false negatives
CLL genetics	FISH for del(17p) and TP53 mutation; IGHV mutation status; before treatment, not at diagnosis of early disease	Chooses the first treatment
Fertility and pregnancy	Pregnancy test; discuss fertility before chemotherapy or transplant	Timing and options

Staging and prognosis

- Lugano staging ([Cheson 2014](#)^[12]) for nodal disease; the Lugano staging system for gastrointestinal lymphoma for gastric MALT (stage 1–2 confined to the gut ± regional nodes; no stage 3; stage 4 disseminated); Rai or Binet clinical staging for CLL (examination and blood count only).
- Follicular: FLIPI ([Solal-Céligny 2004](#)^[13]), still valid with rituximab ([Nooka 2013](#)^[14]); FLIPI24 predicts early progression better ([Maurer 2026](#)^[15]).
- Mantle cell: MIPI ([Hoster 2008](#)^[16]) plus Ki-67, morphology and TP53. MALT: MALT-IPI (age 70 or more, stage 3–4, raised LDH; [Thieblemont 2017](#)^[17]). Splenic MZL: the Italian ILL index ([Arcaini 2006](#)^[18]).

Follicular lymphoma: who does well and who does not**FLIPI: one point each**

- Age over 60
- Stage III or IV
- Haemoglobin below 12 g/dL
- More than 4 nodal areas
- LDH above normal

Median progression-free survival (months), rituximab era**2-year overall survival (%)**

FLIPI24 (age, beta-2 microglobulin, LDH, haemoglobin, white count) predicts progression within 24 months better: 5-year OS 96–97% (low) vs 77–83% (high).

POD24: progression within 24 months of first chemoimmunotherapy (about one in five) is the strongest bad sign; biopsy to look for transformation.

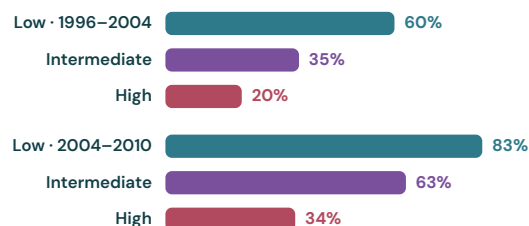
Grade 3B (WHO5: follicular large B-cell lymphoma) behaves like DLBCL and is treated like it. Grades 1–3A are one disease (classic FL).

Figure 4. Follicular lymphoma prognosis (Solal-Céligny 2004; Nooka 2013, National LymphoCare Study; Maurer 2026, FLIPI24; Casulo 2015, POD24), as quoted in the UpToDate follicular lymphoma reviews.

Mantle cell lymphoma: the MIPI and the biology that overrides it

Points	Age	ECOG	LDH/ULN	WBC $\times 10^9/L$
0	under 50	0–1	under 0.67	under 6.7
1	50–59	–	0.67–0.99	6.7–9.9
2	60–69	2–4	1.00–1.49	10.0–14.9
3	70 or more	–	1.50 or more	15.0 or more

Low 0–3 · intermediate 4–5 · high 6 or more points

5-year overall survival (%)

Worse whatever the MIPI: blastoid or pleomorphic cells, Ki-67 30% or more, TP53 mutation or strong p53 staining, complex karyotype.

Better: leukaemic non-nodal MCL (spleen and blood, SOX11-negative, low Ki-67) and gut-only disease, which can often be watched. TP53-mutated, blastoid or CNS disease does poorly with standard chemoimmunotherapy: refer for a trial or BTK-inhibitor-based treatment.

Figure 5. Mantle cell lymphoma prognosis (Hoster 2008, MIPI; later validation in 958 trial patients; UpToDate mantle cell diagnosis and pathobiology reviews).

SHARE WITH PATIENTS: SCANS, BIOPSIES AND THE TYPE OF LYMPHOMA

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

FNAC alone can reliably diagnose every lymphoma?

All lymphomas are the same cancer?

A lymph node that lights up on PET always means cancer?

Stage IV lymphoma means the disease is incurable?

04 Biology and biomarkers that change treatment

Genetic fingerprints and what each one changes

t(14;18) · BCL2

Follicular lymphoma, about 85%. BCL2 blocks cell death. Not specific for follicular lymphoma: read it with the morphology.

t(11;14) · cyclin D1

Mantle cell lymphoma, nearly all. Drives the cell cycle. Also seen in myeloma: interpret with morphology.

t(11;18) · MALT1

Up to one-third of gastric MALT. Predicts no response to H. pylori treatment (continuous CR 30% vs 77%).

MYD88 L265P

Lymphoplasmacytic lymphoma / Waldenström in most cases. Supports, but does not prove, the diagnosis.

TP53 / del(17p)

CLL and mantle cell: poor response to chemotherapy. In CLL it steers to continuous BTK inhibitors.

IGHV mutation (CLL)

Mutated IGHV: long remissions after fixed-duration treatment. Unmutated: shorter, BTK inhibitor favoured.

SOX11 marks most mantle cell lymphomas (including cyclin D1-negative ones); its absence suggests the indolent non-nodal form. Trisomy 3 and t(11;18) are common in MALT lymphoma; the MALT1 translocation is checked by FISH or PCR in every gastric case.

Figure 6. Biology that changes management (UpToDate pathobiology reviews of follicular and mantle cell lymphoma; MALT treatment review; Treon 2012 for MYD88).

Marker or feature	What it tells you	What it changes
t(14;18) / BCL2 protein	Follicular lymphoma (about 85%); BCL2-negative cases are mostly grade 3B or paediatric-type	Supports the diagnosis; not specific on its own
Follicular grade 3B (follicular large B-cell lymphoma)	Sheets of centroblasts; behaves like DLBCL	Treat as DLBCL (aggressive B-cell module)
t(11;14) / cyclin D1; SOX11	Mantle cell lymphoma; SOX11 identifies cyclin D1-negative cases	Separates MCL from CLL and MZL
Ki-67, blastoid or pleomorphic morphology, TP53 / p53	High-risk MCL (Eskelund 2017 ^[19])	Trial or BTK-inhibitor-based treatment; intensive chemotherapy alone works poorly
t(11;18) (MALT1)	Up to one-third of gastric MALT; resistant to eradication therapy (Liu 2001 ^[20])	Radiotherapy rather than waiting if eradication fails
H. pylori; hepatitis C	Antigen drive in gastric MALT; HCV in splenic and other MZL	Antibiotics or antivirals can be the lymphoma treatment
MYD88 L265P	Most lymphoplasmacytic lymphomas	Supports LPL over MZL; not specific
del(17p) / TP53 mutation (CLL)	Chemotherapy-resistant CLL	Continuous BTK inhibitor preferred
IGHV mutation status (CLL)	Mutated: long remissions after fixed-duration treatment	Fixed-duration venetoclax-based treatment favoured
End-of-treatment PET (follicular)	Positive PET: 3.9-fold risk of progression (Trotman 2014 ^[21])	Watch closely; low threshold to biopsy; no proven intervention

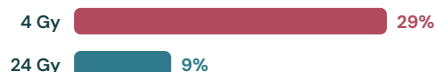
05 Local therapy: radiotherapy & surgery

Radiotherapy

- **Stage I follicular lymphoma:** involved-site RT 24 Gy in 2 Gy fractions is preferred over observation or systemic treatment; about half are cured (10-year overall survival 60–80% in older series, better with PET staging). Observation is reasonable after complete excision or when RT would be morbid.
- **Dose:** 24 Gy was as good as 40–45 Gy ([Lowry 2011](#)^[22]); 4 Gy (2 × 2 Gy) was less toxic but local progression was higher (29% vs 9%), mostly in tumours over 5 cm ([FoRT](#)^[2]). Low dose is for palliation or selected small, frail cases.
- **Adding systemic treatment to RT** in stage I–II follicular lymphoma improved 10-year PFS (59% vs 41%) but not survival ([TROG 99.03](#)^[23]). Stage II is usually managed like advanced disease; RT is still an option when one field covers it.
- **MALT lymphoma:** ISRT 24 Gy in 12 fractions for stage 1–2 non-gastric disease and for *H. pylori*-negative or eradication-resistant gastric disease; complete response and local control above 90%; doses should not exceed 30 Gy. Avoid curative doses to the lung. An ultra-low-dose (4 Gy) response-adapted approach for gastric MALT is still experimental ([Gunther 2024](#)^[24]).
- **Nodal MZL confined to one region:** RT with curative intent (24 Gy), as for stage I follicular lymphoma.
- **Palliation:** 2 × 2 Gy shrinks most bulky, painful or obstructing sites in relapsed or frail patients and can be repeated.

Radiotherapy: low doses, high cure rates in localised indolent lymphoma

Local progression after 4 Gy vs 24 Gy (FoRT, 614 sites)



Stage I–II FL: 10-year PFS (TROG 99.03)



Follicular stage I

- ISRT 24 Gy in 12 fractions
- About half are cured; 10-year OS 60–80%
- Stage II: often treated like advanced disease

MALT and nodal MZ

- 24 Gy in 12 fractions; never more than 30 Gy
- CR and local control above 90%
- Lung: avoid curative doses; consider surgery or watching

Palliation

- 2 × 2 Gy shrinks most bulky or painful sites
- Can be repeated
- Useful for frail patients and in relapse

24 Gy is as good as 40–45 Gy (UK randomised trial). Adding chemotherapy to RT in early FL improved PFS but not survival (over 85% alive at 10 years in both arms).

Figure 7. Radiotherapy (Hoskin 2014, FoRT; Lowry 2011; MacManus 2018, TROG 99.03; UpToDate stage I follicular and MALT treatment reviews).

Surgery

- **Diagnosis:** excision biopsy is the surgeon's main role. Avoid inguinal nodes when another site is available.
- **Splenectomy in splenic MZL:** for suspected transformation in the spleen, or an isolated, symptomatic huge spleen without disease beyond the splenic hilum. It is not useful when marrow infiltration causes the cytopenias. About a quarter have perioperative complications; vaccinate beforehand.
- **No gastrectomy for gastric MALT:** more morbidity and more relapses than RT.

- **Selected sites:** resection is acceptable for some lung MALT lymphomas; surgery for bowel obstruction or bleeding from lymphomatous polyposis in mantle cell lymphoma.

SHARE WITH PATIENTS: RADIOTHERAPY AND SURGERY

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[Radiotherapy has no role in lymphoma?](#)

[Every lymphoma needs surgery to remove the affected lymph nodes?](#)

o6 Systemic therapy: indications & options

Follicular lymphoma, stage II–IV

Watch and wait is treatment: what the trials show

Start treatment when there is

- Symptoms from nodes or bulk
- Organ compromise (ureter, airway, bowel)
- B symptoms
- Symptomatic effusions or extranodal disease
- Cytopenias from marrow infiltration or hypersplenism
- A clear increase in tempo

Rituximab vs watch and wait, asymptomatic stage II–IV FL

Still not needing new treatment at 15 years (%)



15-year overall survival (%)



Immediate treatment of asymptomatic disease delays the next treatment but does not lengthen life. Both choices are correct; the patient decides.

During watch and wait: visit every 3 months in year 1, then every 3–6 months; blood counts and LDH; scans only for new symptoms. Spontaneous partial remissions happen in about one in five; a node that suddenly grows is biopsied, not just measured.

Figure 8. Watch and wait (Ardeshna 2014, 15-year results as quoted in the UpToDate stage II–IV follicular lymphoma review; GELF and BNLI criteria).

- **No symptoms, no threat:** watch and wait or single-agent rituximab (four weekly doses, with or without four more every two months) are equally acceptable. Rituximab postponed chemotherapy (median time to next treatment 5.6 years with watching vs 14.8 years with rituximab) without changing survival ([Ardeshna 2014](#)^[1], [Ardeshna 2003](#)^[25]). An extended schedule gave more complete responses ([FLIRT](#)^[26]).
- **Symptomatic, high tumour burden, clinically indolent:** bendamustine–rituximab (BR) or lenalidomide–rituximab (R2) rather than R–CHOP. BR gave longer PFS and less toxicity than R–CHOP, with no hair loss or anthracycline ([Stil](#)^[3]; [BRIGHT](#)^[27], [5-year update](#)^[28]). R2 matched chemoimmunotherapy for PFS (median 111 vs 103 months) and 10-year survival (82% vs 81%) with a different toxicity profile ([RELEVANCE](#)^[4], [10-year update](#)^[29]).
- **Choosing between BR and R2:** BR is six months; R2 is 18 months (more rash and diarrhoea, less cytopenia and neuropathy). Bendamustine causes long T-cell depletion and may blunt later CAR-T or bispecific therapy; standard-dose BR caused excess deaths in patients over 70, so reduce or shorten it, or use obinutuzumab–CVP.
- **Aggressive clinical picture** (B symptoms, high LDH, rapid growth) even without proven transformation: R–CHOP or obinutuzumab–CHOP, so that hidden transformation is treated. R–CVP gave shorter PFS than R–CHOP but similar survival ([FOLLO5](#)^[30]).
- **Rituximab or obinutuzumab:** obinutuzumab–based induction and maintenance gave better 7-year PFS (63% vs 56%) with more toxicity and the same survival ([GALLIUM](#)^[31], [final analysis](#)^[32]). Rituximab remains the usual choice; obinutuzumab suits patients who value PFS and accept more toxicity.
- **Maintenance is optional:** rituximab every two months for two years after induction improved 3-year PFS (75% vs 58%), with more infections and no survival gain ([PRIMA](#)^[33]). Never longer than two years; after bendamustine, weigh the excess non-relapse deaths.

- **Low tumour burden, frail or comorbid:** rituximab alone.
- **Hepatitis C:** antiviral treatment first if the lymphoma does not otherwise need treatment.
- **Outlook:** median survival now exceeds 20 years. After CHOP-based chemoimmunotherapy, lymphoma-related events plateaued after about 15 years and a cure fraction of about 42% was modelled ([SOO16^{\[34\]}](#)). Progression within 24 months (POD24) identifies the minority at high risk of death ([Casulo 2015^{\[6\]}](#)).
- **After treatment:** end-of-treatment PET-CT; a positive scan predicts progression ([Trotman 2014^{\[21\]}](#)) but no extra treatment has been shown to help: watch closely and biopsy early.

Histologic transformation

Transformation: when an indolent lymphoma turns aggressive

How often

- Follicular: about 1% a year
- Splenic MZL: up to 10% overall
- CLL: Richter (DLBCL or Hodgkin)

Clues

- A node growing faster than the rest
- B symptoms, high LDH, high calcium
- New extranodal site; a much hotter PET spot

What to do

- Biopsy the most PET-avid node
- Grade 1 → 3A is not transformation
- Treat as the aggressive lymphoma found

Little or no prior treatment: R-CHOP or Pola-R-CHP (double-hit: DA-EPOCH-R); complete response → observe; partial → CAR-T. After prior R-CHOP: salvage like refractory DLBCL; CR → autologous transplant or CAR-T; less than CR → CAR-T. Bispecifics if CAR-T is not possible.

Transformation is the leading cause of death in follicular lymphoma: a low threshold to biopsy saves lives.

Figure 9. Histologic transformation (Link 2013; Sarkozy 2016; UpToDate transformation review). The aggressive B-cell lymphoma module covers treatment in detail.

- Transformation is the leading cause of death in follicular lymphoma. Biopsy at every progression where feasible, choosing the node with the highest PET uptake ([Link 2013^{\[35\]}](#); [Sarkozy 2016^{\[36\]}](#)).
- Little or no prior therapy → treat as the aggressive lymphoma found (R-CHOP, O-CHOP or Pola-R-CHP; DA-EPOCH-R for double-hit or high-grade morphology); complete response → observe; partial or no response → CAR-T.
- Prior R-CHOP → second-line therapy as for refractory DLBCL; complete response → autologous transplant or CAR-T consolidation; less than complete response → CAR-T. Bispecific antibodies when CAR-T is not possible (details in the aggressive B-cell lymphoma module).

Marginal zone lymphomas

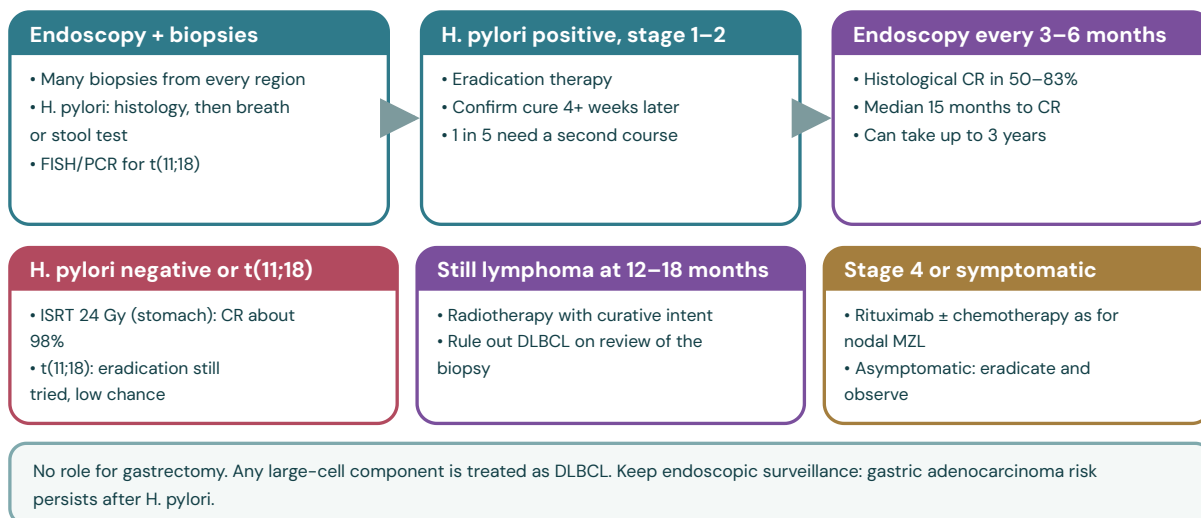
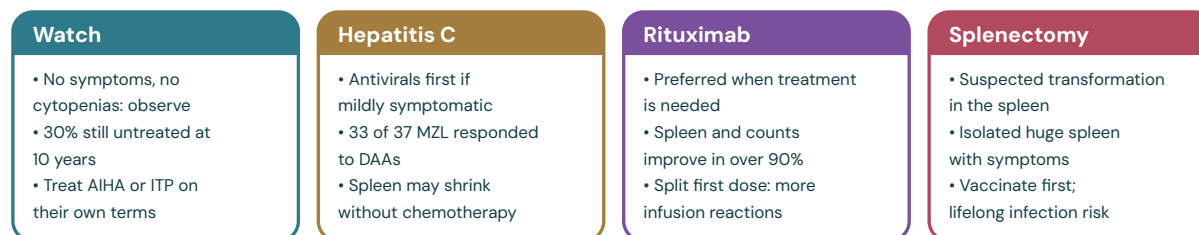
Gastric MALT lymphoma: treat the infection first, then be patient

Figure 10. Gastric MALT lymphoma (Lugano GI staging; UpToDate MALT treatment review; Wotherspoon 1993; Stathis 2009; Nakamura 2012; Liu 2001 for t(11;18)).

- **Gastric MALT, H. pylori positive, stage 1–2:** eradication therapy, then surveillance endoscopy ([Wotherspoon 1993](#)^[37]). Histological complete response in 50–83%, median 15 months, sometimes up to 3 years; about one in five relapsed over a median of 6.8 years in one series ([Stathis 2009](#)^[38]; [Nakamura 2012](#)^[39]). Adjuvant chlorambucil after a response did not help ([LY03](#)^[40]).
- **Confirm cure of the infection** at least 4 weeks after treatment (off PPIs for 2 weeks); up to one in five need a second regimen. Endoscopy every 3–6 months until complete response, then every 6–12 months for at least 2 years.
- **H. pylori negative, t(11;18), or lymphoma still present at 12–18 months:** ISRT 24 Gy to the stomach. Asymptomatic stage 4: eradicate (if positive) and observe. Any large-cell component: treat as DLBCL.
- **Non-gastric MALT, stage 1–2:** ISRT 24 Gy; observation for some stage 1; resection for selected lung lesions; treat an underlying infection where relevant. Ocular adnexal disease: look carefully for bilateral or multifocal involvement.
- **Advanced MALT or nodal MZL needing treatment:** rituximab alone or with chemotherapy. In MALT lymphoma, rituximab plus chlorambucil gave better 5-year EFS (68%) than either drug alone (51% and 50%), with about 90% alive at 5 years in all arms ([IELSG-19](#)^[41]). Bendamustine-rituximab is widely used, extrapolated from follicular lymphoma.
- **Nodal MZL:** one region → RT; advanced asymptomatic → watch; symptomatic → anti-CD20 antibody with or without chemotherapy (deeper, longer responses with chemotherapy, same survival). Response to rituximab alone is lower than in follicular lymphoma.

Splenic marginal zone lymphoma: spleen, blood and sometimes hepatitis C



5-year cause-specific survival by the Italian (IIL) index: haemoglobin under 12, LDH high, albumin under 3.5



PET is poor at showing marrow disease in SMZL (sensitivity about 31%); the marrow biopsy is the staging test. About 10% transform.

Figure 11. Splenic MZL (Arcaini 2006, IIL index; Arcaini 2016, antivirals; UpToDate SMZL review).

- Splenic MZL:** observe if there are no symptoms and no cytopenias; manage autoimmune haemolysis or thrombocytopenia directly. Hepatitis C → direct-acting antivirals first ([Arcaini 2016](#)^[42]; [BArT](#)^[43]).
- Symptomatic without HCV → rituximab (four weekly doses, maintenance optional): over 90% improve within weeks and responses last years. Splenectomy for suspected transformation or an isolated, symptomatic spleen. After rituximab fails: bendamustine-rituximab before targeted drugs.
- Relapsed MZL: serial anti-CD20-based treatments, BTK inhibitors and lenalidomide; CAR-T is kept for refractory or multiply relapsed disease with short remissions.

Mantle cell lymphoma

Mantle cell lymphoma first line: the trials behind the choices

Fit, 65 or younger

TRIANGLE: 3-year failure-free survival (%)



LyMa: 4-year overall survival after ASCT (%)



Older or transplant-ineligible

Median PFS with BR (months)



MCL-Elderly: median OS with maintenance (years)



In older patients BTK inhibitors added to BR prolong remissions without a clear overall survival gain so far (SHINE, ECHO); ibrutinib adds heart rhythm and bleeding risks. Cytarabine-containing induction (R-CHOP/R-DHAP, Nordic) beat R-CHOP alone before transplant (MCL Younger). R-HyperCVAD is too toxic (S1106).

India: zanubrutinib is DCGI-approved for mantle cell lymphoma (June 2025); check availability and cost of the others locally.

Figure 12. First-line MCL (Dreyling 2024, TRIANGLE; Le Gouill 2017, LyMa; Wang 2022, SHINE; Wang 2025, ECHO; Kluin-Nelemans 2020, MCL-Elderly). TRIANGLE, SHINE and ECHO web-verified 17 Oct 2026; the UpToDate MCL review (Feb 2025) predates them.

- Indolent MCL can be watched:** about one in five (leukaemic non-nodal, gut-only, or low-burden nodal with normal LDH and low Ki-67). In retrospective series, starting with observation did not appear to worsen outcomes.

- **Every patient who is treated gets rituximab** with the chemotherapy: it reduced mortality in a meta-analysis that included MCL.
- **Fit, about 65 or younger** (UpToDate, Feb 2025): induction with BR or a high-dose cytarabine regimen (R-CHOP/R-DHAP, Nordic, R-B/R-HiDac), not R-CHOP alone or R-HyperCVAD ([MCL Younger](#)^[44], [long-term](#)^[45], [S1106](#)^[46], [Nordic MCL2](#)^[47]). Complete response → autologous transplant ([Dreyling 2005](#)^[48]) → rituximab maintenance for 3 years ([LyMa](#)^[49]: 4-year OS 89% vs 80%).
- **Since then: TRIANGLE** (web-verified): adding ibrutinib to R-CHOP/R-DHAP induction and 2 years of ibrutinib maintenance raised 3-year failure-free survival from 72% to 88% with transplant, and reached 86% without transplant; the investigators concluded that ibrutinib in induction and maintenance should be part of first-line treatment, and that the need for transplant is unresolved ([Dreyling 2024](#)^[5]). The UpToDate review predates its publication: an expert decision for Dr. Haritha (review point).
- **Older or transplant-ineligible**: BR, VR-CAP (bortezomib replacing vincristine: median OS 91 vs 56 months over R-CHOP; [LYM-3002](#)^[50]) or rituximab-lenalidomide; responders get rituximab maintenance for 3 years (median OS 9.8 vs 6.4 years vs interferon, the benefit greatest after R-CHOP induction; [MCL-Elderly](#)^[51], [long-term](#)^[52]).
- **BTK inhibitor + BR** in patients 65 or older (web-verified): ibrutinib prolonged median PFS to 80.6 vs 52.9 months without an overall survival gain ([SHINE](#)^[53]); acalabrutinib gave 66.4 vs 49.6 months with a favourable survival trend and is FDA-approved for this use since January 2025 ([ECHO](#)^[54]).
- **TP53-mutated, blastoid or CNS disease**: poor results with standard treatment; a trial or BTK-inhibitor-based strategy. True stage I MCL is very rare: look for hidden gut and marrow disease before treating it as localised.

CLL and small lymphocytic lymphoma

CLL and SLL: one disease, three labels, and when to treat

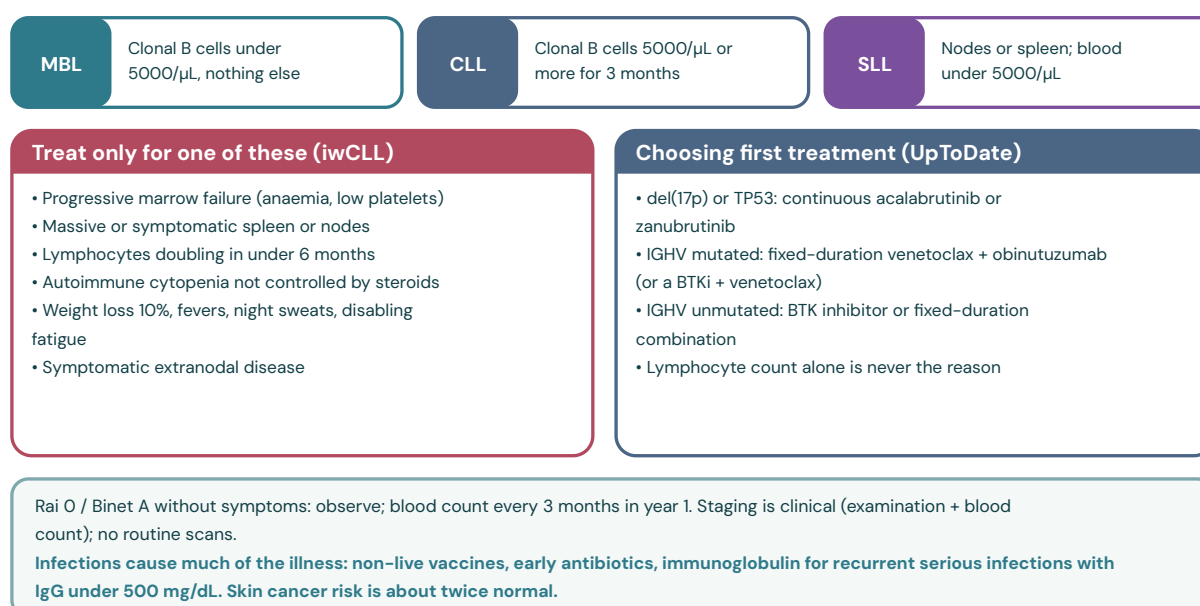


Figure 13. CLL/SLL (Hallek 2018, iwCLL; UpToDate CLL diagnosis, initial-therapy and infection-prevention reviews).

- **Most patients do not need treatment for years**: median survival is about 10–15 years. Early-stage CLL without symptoms is observed (blood count every 3 months in the first year, then less often).

Lymphocytosis, low immunoglobulins or a small paraprotein alone are not reasons to treat ([iwCLL 2018](#)^[55]).

- **Before treatment:** FISH for del(17p) and TP53 mutation (again at every progression: clonal evolution), IGHV mutation status, comorbidities, interacting drugs (anticoagulants, CYP3A inhibitors), kidney function, HBV. The CLL-IPI combines these with age and stage ([CLL-IPI](#)^[56]).
- **Two strategies, chosen by genetics, comorbidity and preference:** continuous acalabrutinib or zanubrutinib until progression, or fixed-duration targeted therapy (venetoclax-obinutuzumab for 12 months; ibrutinib-venetoclax; acalabrutinib-venetoclax ± obinutuzumab). Chemoimmunotherapy (FCR, BR, chlorambucil-obinutuzumab) has been beaten in every comparison.
- **del(17p) or TP53 mutation:** continuous acalabrutinib or zanubrutinib; BTK-inhibitor-containing fixed-duration combinations are alternatives; venetoclax-obinutuzumab if a BTK inhibitor is unsuitable (atrial fibrillation, bleeding, warfarin).
- **IGHV mutated:** fixed-duration targeted therapy for a long treatment-free interval. **IGHV unmutated:** either strategy.
- **The evidence:** acalabrutinib ± obinutuzumab vs chlorambucil-obinutuzumab, 6-year PFS 78% and 62% vs 17% ([ELEVATE-TN](#)^[57]); zanubrutinib vs BR, 5-year PFS 76% vs 40% ([SEQUOIA](#)^[58]); venetoclax-obinutuzumab vs chlorambucil-obinutuzumab, median PFS 76 vs 35 months ([CLL14](#)^[59]); ibrutinib-venetoclax vs chlorambucil-obinutuzumab, 3.5-year PFS 75% vs 25% and better survival ([GLOW](#)^[60]); acalabrutinib-venetoclax vs FCR/BR, 3-year PFS 77% vs 67% and OS 94% vs 86% ([AMPLIFY](#)^[61]); in young fit patients venetoclax-obinutuzumab-ibrutinib vs FCR/BR, 5-year PFS 76% vs 34% ([CLL13](#)^[62]). Ibrutinib-based treatment also beat FCR ([E1912](#)^[63], [FLAIR](#)^[64]) and BR ([A041202](#)^[65]).
- **Choosing a BTK inhibitor:** acalabrutinib and zanubrutinib are at least as effective as ibrutinib and better tolerated: zanubrutinib beat ibrutinib for PFS (3-year 65% vs 54%; [ALPINE](#)^[66]); acalabrutinib matched ibrutinib with less bleeding ([ELEVATE-RR](#)^[67]).
- **Relapse:** re-confirm CLL and look for Richter transformation; treat only active disease. Progression on a covalent BTK inhibitor → venetoclax plus an anti-CD20 antibody (venetoclax-rituximab vs BR: median PFS 55 vs 17 months, 5-year OS 82% vs 62%; [MURANO](#)^[68]) or pirtobrutinib (median PFS 14 vs 8.7 months; [BRUIN CLL-321](#)^[69]). Intolerance (not progression) → another BTK inhibitor. Young patients with a donor: allogeneic transplant after response.
- **Infections are the main threat:** CLL itself causes hypogammaglobulinaemia and T-cell defects. No routine antimicrobial prophylaxis off treatment or with BTK inhibitors, venetoclax or alkylators alone; Pneumocystis and herpesvirus prophylaxis when anti-CD20 antibodies are combined with high-dose steroids. Intravenous immunoglobulin for recurrent infections needing IV antibiotics or admission with IgG under 500 mg/dL. Non-live vaccines, ideally before treatment.
- **Other complications:** autoimmune haemolysis and thrombocytopenia (treat the cause), tumour lysis with venetoclax (follow the ramp-up schedule), second cancers (skin cancer 10-year risk 13.5%, about twice that of controls; age- and sex-appropriate screening), leukaemia cutis (under 5%) and Richter transformation (rapid node growth, B symptoms, high LDH: biopsy).

CLL: targeted drugs replaced chemoimmunotherapy (experimental vs control)**ELEVATE-TN · older/unfit**

Acalabrutinib + obinutuzumab vs chlorambucil + obinutuzumab · 6-year PFS

**SEQUOIA · no del(17p)**

Zanubrutinib vs BR · 5-year PFS

**CLL13 · young, fit**

Venetoclax + obinutuzumab + ibrutinib vs FCR/BR · 5-year PFS

**GLOW · older/unfit**

Ibrutinib + venetoclax vs chlorambucil + obinutuzumab · 3.5-year PFS

**AMPLIFY · no del(17p)/TP53**

Acalabrutinib + venetoclax vs FCR/BR · 3-year PFS

**MURANO · relapsed**

Venetoclax + rituximab vs BR · 5-year OS

**ALPINE · relapsed**

Zanubrutinib vs ibrutinib · 3-year PFS



CLL14 (fixed 12 months of venetoclax + obinutuzumab vs chlorambucil + obinutuzumab): median PFS 76 vs 35 months. Acalabrutinib vs ibrutinib (ELEVATE-RR): same PFS, less bleeding. After a covalent BTK inhibitor: pirtobrutinib (BRUIN CLL-321: median PFS 14 vs 8.7 months) or venetoclax-based treatment.

Figure 14. CLL trials as reported in the UpToDate CLL initial-therapy and relapsed CLL reviews (Sharman 2020; Tam 2022; Eichhorst 2023; Kater 2022; Brown 2025; Seymour 2018; Brown 2023; Byrd 2021; Sharman 2025).

Lymphoplasmacytic lymphoma and Waldenström macroglobulinaemia**Waldenström macroglobulinaemia: IgM, marrow and when to treat****Diagnosis**

- IgM paraprotein on immunofixation
- Marrow: ≥10% lymphoplasmacytic infiltrate
- MYD88 L265P in over 90%

Treat only for

- Symptoms with nodes, spleen or cytopenias (Hb ≤10, platelets ≤100,000)
- Hyperviscosity
- Severe neuropathy

Hyperviscosity

- Bleeding nose or gums, blurred vision, headache, confusion
- Plasmapheresis at once; no transfusion before it
- Then treat the clone

Randomised evidence (experimental vs control)

BR vs R-CHOP (StiL, WM) · median PFS, months



Ibrutinib-rituximab vs rituximab (iNNOVATE) · 54-month PFS, %



Zanubrutinib vs ibrutinib (ASPEN) · 42-month PFS, %



First line (UpToDate): BR for most; a BTK inhibitor for older patients or those who do not want chemotherapy. Rituximab alone is no longer routine, especially with IgM over 4000 mg/dL: the IgM flare can trigger hyperviscosity. Relapse after BR → zanubrutinib (or BR again after a remission over 5 years).

Figure 15. Waldenström macroglobulinaemia (UpToDate WM diagnosis and treatment reviews; Rummel 2013, StiL; Dimopoulos 2018 and Buske 2022, iNNOVATE; Tam 2020, ASPEN).

- **Diagnosis:** an IgM paraprotein on immunofixation plus at least 10% lymphoplasmacytic infiltration of the marrow with a typical phenotype (surface IgM, CD19, CD20, CD22, CD25, CD27; usually CD5, CD10, CD23 and CD103 negative); MYD88 L265P in over 90% ([Treon 2012^{\[11\]}](#)). Median age at presentation is in the seventh decade. The revised IPSS-WM grades prognosis ([Kastritis 2019^{\[70\]}](#)).

- **Most patients can be watched** ("smouldering" WM): blood counts and IgM periodically; early treatment has no clear advantage. Treat for symptoms with nodes, liver or spleen enlargement or cytopenias (haemoglobin 10 g/dL or less, platelets 100,000/μL or less), hyperviscosity, or severe neuropathy.
- **Hyperviscosity is an emergency**: oronasal bleeding, blurred vision, headache, dizziness, retinal vein engorgement, confusion. Start plasmapheresis at once (chemotherapy acts too slowly) and avoid red-cell transfusion before it, then treat the clone.
- **First line**: bendamustine–rituximab for most (four to six months; in StIL, BR gave median PFS 70 vs 28 months over R-CHOP with less toxicity; [StIL](#) ^[3]); a BTK inhibitor for older patients or those who prefer to avoid chemotherapy. Ibrutinib–rituximab beat rituximab (54-month PFS 68% vs 25%; [INNOVATE](#) ^[71], [final analysis](#) ^[72]); zanubrutinib gave deeper responses and fewer discontinuations than ibrutinib (42-month PFS 78% vs 70%; [ASPEN](#) ^[73]). Rituximab alone is no longer routine, especially with IgM over 4000 mg/dL (IgM flare).
- **Relapse**: after BR → zanubrutinib (BR again if the first remission lasted over 5 years); after a BTK inhibitor → BR; then venetoclax or pirtobrutinib (limited data). Autologous transplant only for selected patients with no other options.

Relapsed follicular and mantle cell lymphoma

Relapsed follicular lymphoma: biopsy first, then choose by timing and prior treatment

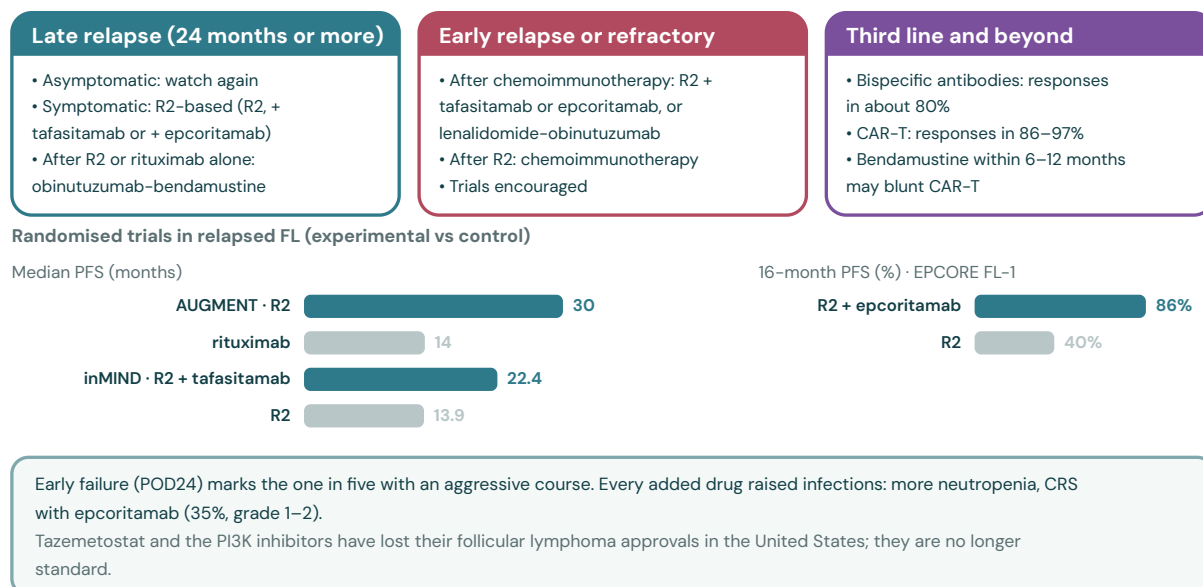


Figure 16. Relapsed follicular lymphoma (Leonard 2019, AUGMENT; Sehn 2026, inMIND; Falchi 2026, EPCORE FL-1; UpToDate relapsed follicular lymphoma review).

- **Biopsy before re-treatment** whenever feasible, to confirm relapse and exclude transformation. About one in five patients with follicular lymphoma has an aggressive course, flagged by early failure: progression within 24 months of BR, R2, R-CHOP or R-CVP, or within 12 months of rituximab alone or RT.
- **Relapse after RT alone**: treat as stage II–IV disease. **Late, asymptomatic relapse**: watch again.
- **Late symptomatic relapse**: an R2-based regimen. R2 beat rituximab alone (median PFS 30 vs 14 months; [AUGMENT](#) ^[74]); adding tafasitamab (median PFS 22.4 vs 13.9 months; [inMIND](#) ^[75]) or epcoritamab (16-month PFS 86% vs 40%, complete response 83% vs 50%; [EPCORE FL-1](#) ^[76]) improves PFS at the cost of more infections. Obinutuzumab–bendamustine after R2 or rituximab alone (overall survival benefit in rituximab–

refractory disease; [GADOLIN](#)^[77], [update](#)^[78]); an anthracycline regimen for an aggressive late relapse; antibody alone for frail patients after a long rituximab remission.

- **Early relapse or refractory disease:** after chemoimmunotherapy → lenalidomide–obinutuzumab, R2–tafasitamab or R2–epcoritamab; after R2 → chemoimmunotherapy. Clinical trials whenever possible.
- **Multiply relapsed:** CD20xCD3 bispecific antibodies (mosunetuzumab, epcoritamab, odronextamab; responses in about 80%, CRS in 44–66%; [Budde 2022](#)^[79], [Linton 2024](#)^[80]) or CD19 CAR–T (axi-cel, tisa-cel, liso-cel; responses in 86–97%; [ZUMA-5](#)^[81], [ELARA](#)^[82], [TRANSCEND FL](#)^[83]). Zanubrutinib plus obinutuzumab is another option (median PFS 28 vs 10.4 months; [ROSEWOOD](#)^[84]). Bendamustine within 6–12 months may blunt CAR–T. Tazemetostat and the PI3K inhibitors have lost their US follicular lymphoma approvals.

Relapsed mantle cell lymphoma: the BTK inhibitor decides the path

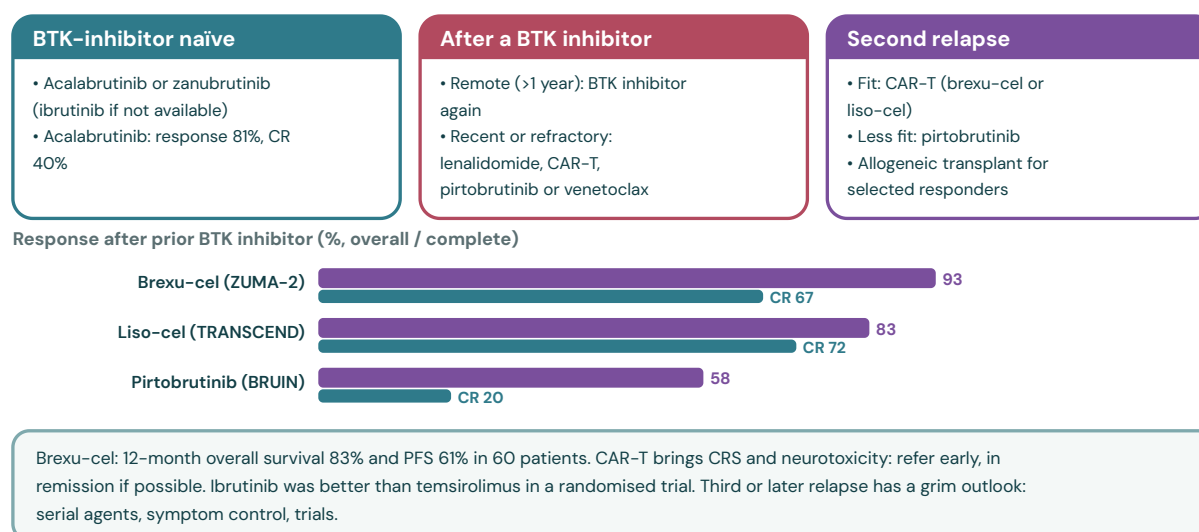


Figure 17. Relapsed MCL (Wang 2018, ACE–LY–004; Wang 2020, ZUMA–2; Wang 2024, TRANSCEND MCL; Wang 2023, BRUIN; Dreyling 2016; UpToDate relapsed MCL review).

- **Confirm** first relapse and primary refractory MCL with a biopsy; reassess fitness, Ki-67, morphology and TP53.
- **No prior BTK inhibitor:** acalabrutinib or zanubrutinib (ibrutinib if they are unavailable); acalabrutinib gave responses in 81% (complete 40%) ([ACE–LY–004](#)^[85], [Tam 2021](#)^[86]). Ibrutinib beat temsirolimus ([Dreyling 2016](#)^[87]). Watch kidney function, bleeding and atrial fibrillation.
- **After a BTK inhibitor:** remote exposure (more than a year) → a BTK inhibitor again; recent or refractory → lenalidomide, with CAR–T, pirtobrutinib or venetoclax as alternatives.
- **Second relapse:** fit → CD19 CAR–T: brexucabtagene autoleucel (responses 93%, complete 67%, 12-month OS 83%; [ZUMA-2](#)^[88]) or lisocabtagene maraleucel (83%, complete 72%; [TRANSCEND](#)^[89]); less fit → pirtobrutinib (responses 58%; [BRUIN](#)^[90]). Allogeneic transplant can consolidate a good response in selected patients.

India now (October 2026)

- Zanubrutinib received DCGI approval in June 2025 for five B–cell cancers: CLL/SLL, Waldenström macroglobulinaemia, mantle cell, marginal zone and follicular lymphoma (marketed in India by Glenmark; web-verified 17 Oct 2026).

- H. pylori eradication is an inexpensive oral treatment that can cure early gastric MALT lymphoma: test every patient, confirm eradication, and keep up endoscopic follow-up.
- Availability and cost of obinutuzumab, lenalidomide, bendamustine, acalabrutinib, ibrutinib, venetoclax, pirtobrutinib and the bispecific antibodies to be confirmed by the treating team. Indian CD19 CAR-T products (NexCAR19, Qartemi) are described in the aggressive B-cell module; their use in follicular and mantle cell lymphoma is to be confirmed.

SHARE WITH PATIENTS: TREATMENT CHOICES

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

Chemotherapy is needed immediately for every lymphoma?

Aggressive lymphoma is always harder to cure than slow-growing lymphoma?

Immunotherapy and targeted therapy are the same as chemotherapy?

If lymphoma returns after chemotherapy, no effective treatment remains?

Quick reference (also as a printable PDF on the Printable Teaching Resources page)

Table A. Diagnosis and staging tests and what they change

Test	When	What it changes	Pitfalls
Excision biopsy of a node (several cores if not feasible)	Every suspected nodal lymphoma; again at progression	Entity, grade, transformation	FNA cannot grade or exclude lymphoma; choose the most PET-avid node at relapse
Flow cytometry of blood	Lymphocytosis; splenomegaly	CLL vs MBL vs leukaemic MCL, MZL or hairy cell	CD5-positive is not always CLL: check cyclin D1 and CD23
IHC: CD20, CD5, CD10, CD23, cyclin D1, SOX11, BCL2, BCL6, Ki-67	Every tissue diagnosis	Sorts FL, MCL, MZL, SLL, LPL	Cyclin D1-negative MCL (SOX11+); CD5-positive MZL
FISH: t(14;18), t(11;14), t(11;18); CLL: del(17p) and TP53 mutation, IGHV status	As the case needs; CLL genetics before treatment	Entity; gastric MALT response to antibiotics; CLL first-line choice	t(14;18) is not specific for follicular lymphoma
PET-CT	Staging FL, nodal MZL, MCL; end of chemoimmunotherapy; suspected transformation	Stage; biopsy target; end-of-treatment response	Poor for marrow in SMZL and low-Ki-67 MCL; no interim PET
Bone marrow aspirate and biopsy	SMZL, LPL, MCL; FL before RT for apparent stage I–II or with cytopenias	True stage; cause of cytopenias	Often not needed in advanced FL
Endoscopy (± EUS) with many biopsies	Gastric MALT; MCL with GI symptoms or apparent early stage	Lugano GI stage; hidden gut disease	One or two biopsies can miss MALT lymphoma
H. pylori: histology, then breath or stool test	Every gastric MALT	Eradication therapy as first treatment	Off antibiotics 4 weeks and PPIs 2 weeks, if possible, to avoid false negatives

Test	When	What it changes	Pitfalls
HBsAg, anti-HBc (HBV DNA if positive), HCV, HIV	Before any anti-CD20 therapy; HCV in all MZL	Antiviral prophylaxis; HCV antivirals as lymphoma treatment	Anti-HBc alone still carries reactivation risk
Serum protein electrophoresis, immunoglobulins, beta-2 microglobulin, DAT	Baseline	IgM (Waldenström), hypogammaglobulinaemia, FLIPI24, autoimmune haemolysis	Beta-2 microglobulin rises with kidney impairment

Table B. Treatment by setting

Setting	Standard choice	Key evidence	Notes
Follicular, stage I	ISRT 24 Gy	FoRT ^[2] , Lowry 2011 ^[22]	Observe after complete excision or if RT would be morbid; add systemic only in trials (TROG 99.03 ^[23])
Follicular, II–IV, no indication to treat	Watch and wait, or rituximab × 4 (± 4 more)	Ardeshna 2014 ^[1]	Same survival; patient preference decides
Follicular, needs treatment, clinically indolent	BR or R2; optional anti-CD20 maintenance ≤2 years	Stil ^[3] , RELEVANCE ^[4] , PRIMA ^[33]	Over 70: reduce or shorten bendamustine, or O-CVP
Follicular, aggressive clinical picture or grade 3B	R-CHOP or O-CHOP (grade 3B: as DLBCL)	FOLLO5 ^[30] , GALLIUM ^[31]	Biopsy for transformation first
Transformed follicular lymphoma	As the aggressive lymphoma found; CAR-T if not in CR	Link 2013 ^[35]	See the aggressive B-cell module
Gastric MALT, H. pylori+, stage 1–2	Eradication → endoscopy every 3–6 months	Wotherspoon 1993 ^[37] , Nakamura 2012 ^[39]	Persistent at 12–18 months, H. pylori-, or t(11;18) → ISRT 24 Gy
Non-gastric MALT, stage 1–2	ISRT 24 Gy (≤30 Gy)	UpToDate MALT review	Lung: avoid curative RT; resection or observation
Advanced MALT or nodal MZL needing treatment	Rituximab ± chemotherapy (BR or chlorambucil)	IELSG-19 ^[41]	One nodal region: RT
Splenic MZL	Observe → HCV antivirals → rituximab → BR; splenectomy for selected cases	Arcaini 2016 ^[42]	Split the first rituximab dose
MCL, indolent (non-nodal, gut-only, low burden)	Observe	UpToDate MCL review (series)	Treat at symptoms or progression
MCL, fit ≤65	Cytarabine-containing induction (or BR) → ASCT → rituximab × 3 years; ibrutinib in induction and maintenance (TRIANGLE)	MCL Younger ^[44] , LyMa ^[49] , TRIANGLE ^[5]	TP53/blastoid: trial
MCL, older or unfit	BR (± BTK inhibitor), VR-CAP or R-lenalidomide → rituximab maintenance × 3 years	SHINE ^[53] , ECHO ^[54] , MCL-Elderly ^[51]	BTKi: heart rhythm, bleeding, interactions
Waldenström, needs treatment	BR; BTK inhibitor if older or avoiding chemotherapy; plasmapheresis first for hyperviscosity	INNOVATE ^[71] , ASPEN ^[73]	Not rituximab alone with IgM over 4000 mg/dL

Setting	Standard choice	Key evidence	Notes
CLL/SLL, no indication	Observe	iwCLL 2018 ^[55]	Lymphocyte count alone is not an indication
CLL, del(17p)/TP53	Continuous acalabrutinib or zanubrutinib	ELEVATE-TN ^[57] , SEQUOIA ^[58]	BTKi unsuitable: venetoclax-obinutuzumab
CLL, IGHV mutated / unmutated	Mutated: fixed-duration venetoclax-based; unmutated: either strategy	CLL14 ^[59] , GLOW ^[60] , AMPLIFY ^[61] , CLL13 ^[62]	Kidney, CYP3A drugs, lysis risk shape the choice
CLL, progression on a covalent BTKi	Venetoclax + anti-CD20, or pirtobrutinib	MURANO ^[68] , BRUIN CLL-321 ^[69]	Intolerance only: switch BTKi
FL, late symptomatic relapse	R2 ± tafasitamab or epcoritamab; BO after R2 or rituximab alone	AUGMENT ^[74] , inMIND ^[75] , EPCORE FL-1 ^[76] , GADOLIN ^[77]	Biopsy first; watch if asymptomatic
FL, early relapse (POD24) / multiply relapsed	Lenalidomide combinations; then bispecific antibodies or CAR-T	ZUMA-5 ^[81] , mosunetuzumab ^[79]	Avoid recent bendamustine before CAR-T
MCL, relapse	BTKi-naïve: acalabrutinib or zanubrutinib; after BTKi: lenalidomide, CAR-T, pirtobrutinib	ACE-LY-004 ^[85] , ZUMA-2 ^[88] , BRUIN ^[90]	Second relapse, fit: CAR-T

Table C. Regimens and drugs: evidence and best fit

Regimen or drug	Best fit	Evidence	Main toxicity
Rituximab alone	Low-burden FL, MZL, SMZL; frail patients	Ardeshta 2014: delays chemotherapy, same survival; SMZL: >90% improve	Infusion reactions (split dose in SMZL), HBV reactivation, infections
Bendamustine-rituximab (BR)	Symptomatic FL, MZL, older MCL	StiL and BRIGHT: PFS at least as good as R-CHOP, less toxic	Long T-cell depletion and infections; excess deaths over 70 at full dose
Lenalidomide-rituximab (R2)	Symptomatic FL (also MCL in older patients)	RELEVANCE: PFS 111 vs 103 months; 10-year OS 82% vs 81%	Rash, diarrhoea, neutropenia, clots; 18 months of treatment
R-CHOP / O-CHOP	FL with aggressive features; grade 3B	FOLL05: better PFS than R-CVP; same OS	Alopecia, neuropathy, cardiotoxicity
Obinutuzumab-based chemoimmunotherapy	FL when PFS is the priority	GALLIUM: 7-year PFS 63% vs 56%; same OS	More infusion reactions, infections, cytopenias
Anti-CD20 maintenance (≤2 years)	FL responders who value PFS	PRIMA: 3-year PFS 75% vs 58%; no OS gain	Infections (39% vs 24%); low immunoglobulins
Rituximab-chlorambucil	MALT lymphoma needing treatment, frail	IELSG-19: 5-year EFS 68% vs 51%	Cytopenias (mild)
R-CHOP/R-DHAP, Nordic, R-B/R-HiDAc → ASCT	Fit MCL ≤65	MCL Younger: longer TTF than R-CHOP; Nordic MCL2: median OS 12.7 years	Myelosuppression, kidney (platinum), infections
Ibrutinib with induction and as maintenance	Fit MCL ≤65 (TRIANGLE)	3-year FFS 88% vs 72%	Atrial fibrillation, bleeding, infections; more toxicity after ASCT

Regimen or drug	Best fit	Evidence	Main toxicity
BTK inhibitor + BR	MCL ≥65	SHINE: median PFS 80.6 vs 52.9 months; ECHO: 66.4 vs 49.6	Atrial fibrillation, bleeding, infections (ECHO: AF 6.1% vs 4.4%)
VR-CAP	Older MCL	LYM-3002: median OS 91 vs 56 months vs R-CHOP	Neuropathy, thrombocytopenia
Rituximab maintenance (MCL, 3 years)	After ASCT; after R-CHOP in older patients	LyMa: 4-year OS 89% vs 80%; MCL-Elderly: OS 9.8 vs 6.4 years	Infections, HBV
Acalabrutinib or zanubrutinib (continuous)	CLL with del(17p)/TP53; IGHV-unmutated CLL	UpToDate first-line algorithm	Hypertension, arrhythmia, bleeding, infections
Venetoclax-obinutuzumab (fixed duration)	IGHV-mutated CLL; BTKi unsuitable	CLL14: median PFS 76 vs 35 months	Tumour lysis (ramp-up), neutropenia
Venetoclax-rituximab	Relapsed CLL	MURANO: 5-year OS 82% vs 62% vs BR	Tumour lysis, neutropenia
Zanubrutinib (Waldenström)	WM, first line or after BR	ASPEN: 42-month PFS 78% vs 70% vs ibrutinib; fewer discontinuations	Neutropenia; less AF and diarrhoea than ibrutinib
Pirtobrutinib (non-covalent BTKi)	CLL and MCL after a covalent BTKi	BRUIN CLL-321: median PFS 14 vs 8.7 months; MCL responses 58%	Neutropenia, bleeding (less AF)
Lenalidomide-based (R2 ± tafasitamab or epcoritamab)	Relapsed FL	AUGMENT: PFS 30 vs 14 months; EPCORE FL-1: 16-month PFS 86% vs 40%	Neutropenia, infections, rash; CRS with epcoritamab
CD20xCD3 bispecific antibodies	Multiply relapsed FL	Responses in about 80%	CRS (44–66%), infections; PJP and herpes prophylaxis
CD19 CAR-T (axi-cel, tisa-cel, liso-cel; brexu-cel in MCL)	Multiply relapsed FL; MCL after a BTKi	FL responses 86–97%; ZUMA-2 MCL 93% (CR 67%)	CRS, neurotoxicity, prolonged cytopenias

Table D. Managing problems during treatment

Problem	Prevent	Recognise	Act
Hepatitis B reactivation	Screen HBsAg and anti-HBc; entecavir or tenofovir from before anti-CD20 therapy until at least 12 months after the last dose	Rising ALT, HBV DNA	Hold the antibody; hepatology
Infusion reactions	Premedication; slow first infusion; split first rituximab dose in SMZL or high counts	Fever, rigors, low blood pressure in the first infusion	Stop, treat, restart slowly
Infections and low immunoglobulins	Vaccinate before treatment (no live vaccines); antimicrobial prophylaxis by local policy, especially after bendamustine	Recurrent chest infections; zoster	Check IgG; treat early; consider immunoglobulin replacement
Tumour lysis	Hydration ± allopurinol; follow the venetoclax ramp-up and monitoring schedule	Potassium, phosphate, uric acid up; creatinine rising	Admit high-risk patients for ramp-up
BTK-inhibitor effects	Check blood pressure, heart rhythm, anticoagulants and interacting drugs before starting	Palpitations, bleeding, hypertension, infections	Cardiology; hold around procedures; consider switching agent

Problem	Prevent	Recognise	Act
Lenalidomide effects	Check kidney function and clot risk before starting	Rash, diarrhoea, low counts, leg swelling	Hold and resume; check for clots
CRS with bispecific antibodies	Step-up dosing; hydration; monitoring after the first full doses	Fever, low blood pressure, low oxygen	Supportive care, tocilizumab and steroids by grade; specialist unit
Recurrent infections in CLL	Non-live vaccines; prophylaxis by regimen (PJP and herpes with anti-CD20 + high-dose steroids)	IV antibiotics or admissions; IgG under 500 mg/dL	Intravenous immunoglobulin replacement
Autoimmune cytopenias (CLL, SMZL)	Check DAT at baseline	Falling haemoglobin with haemolysis; sudden low platelets	Steroids; treat the lymphoma if refractory
Hyperviscosity (Waldenström)	Avoid rituximab alone with high IgM (flare)	Bleeding nose or gums, blurred vision, headache, confusion	Plasmapheresis at once; no transfusion before it; then treat the clone

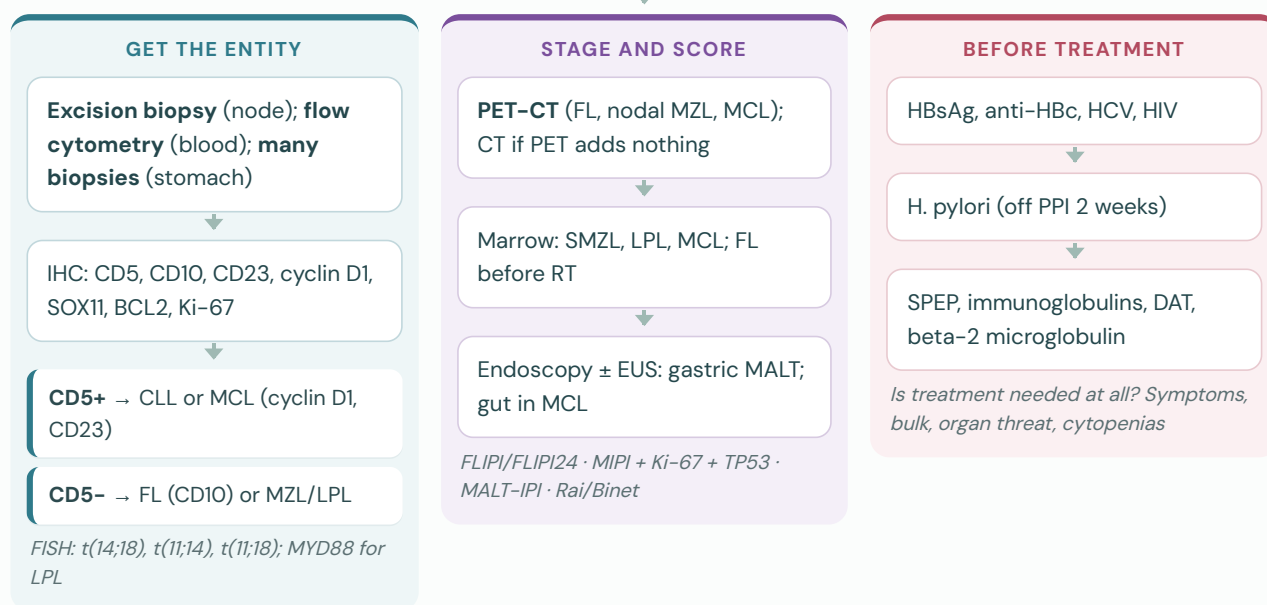
07 Management algorithms

Five decision paths pull together sections 02–06. Colours: teal for standard or favourable paths, purple for intermediate settings, rose for higher-risk or treatment paths.

ALGORITHM 1

Suspected indolent B-cell lymphoma: from a finding to an entity and a plan

Node that persists or waxes and wanes, lymphocytosis, big spleen, gastric or ocular lesion, IgM spike → tissue or blood flow cytometry before any steroid or anti-TB trial

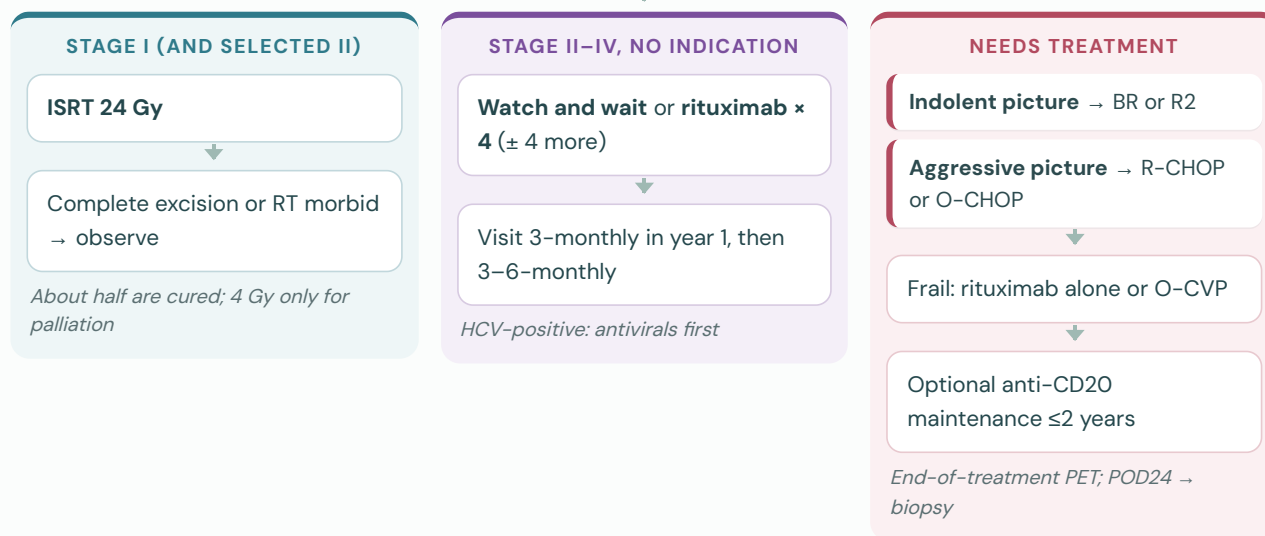


All patients: lymphoma multidisciplinary team · grade 3B follicular or any large-cell component → treat as DLBCL · biopsy any node that grows faster than the rest.

ALGORITHM 2

Follicular lymphoma (grade 1–3A) by stage and need for treatment

Classic follicular lymphoma → stage with PET-CT (marrow if apparent stage I–II) → FLIPI, symptoms, bulk, organ function

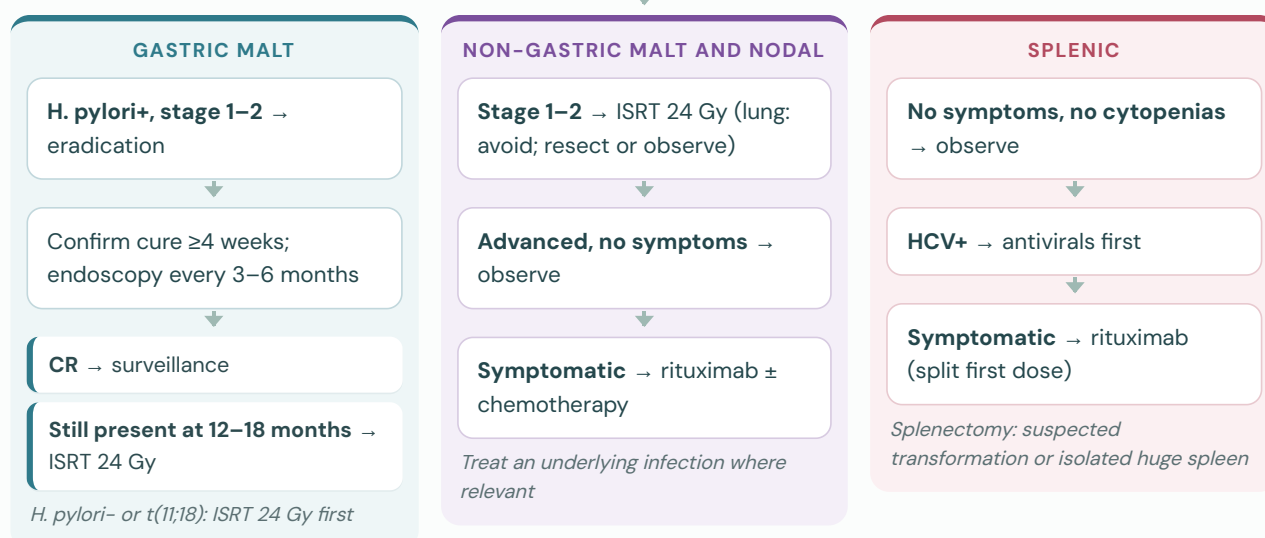


All: HBV prophylaxis with anti-CD20 therapy · over 70: reduce or shorten bendamustine · relapse: biopsy, then choose a regimen not used before.

ALGORITHM 3

Marginal zone lymphoma by site

Marginal zone lymphoma confirmed → site, stage, H. pylori, HCV, t(11;18) → any large-cell component treated as DLBCL



All: HBV and HCV before rituximab · autoimmune cytopenias treated on their own terms · endoscopic surveillance after gastric MALT.

ALGORITHM 4

Mantle cell lymphoma first line

Mantle cell lymphoma → MIPI, Ki-67, morphology, TP53, presentation (nodal vs non-nodal, gut-only) → fitness

INDOLENT PRESENTATION

Leukaemic non-nodal, gut-only or low-burden nodal

Normal LDH, low Ki-67, no TP53/blastoid

Observe; treat at symptoms

About one in five patients

FIT, ABOUT 65 OR YOUNGER

Cytarabine-containing induction (or BR) + rituximab

Ibrutinib in induction and maintenance (TRIANGLE)

CR → ASCT (role debated with ibrutinib)

Less than CR → treat as refractory

Rituximab maintenance × 3 years

OLDER OR UNFIT

BR (± ibrutinib or acalabrutinib), **VR-CAP** or **R-lenalidomide**

CR or PR → rituximab maintenance × 3 years

Avoid R-HyperCVAD; check heart and drugs before a BTKi

All: TP53-mutated, blastoid or CNS disease → trial or BTK-inhibitor-based treatment · true stage I is rare: look for gut and marrow disease · HBV prophylaxis.

ALGORITHM 5

CLL/SLL: when and how to treat

CLL confirmed (flow cytometry) → Rai/Binet → is there an iwCLL indication (marrow failure, symptomatic nodes or spleen, rapid doubling, uncontrolled autoimmune cytopenia, B symptoms)?

NO INDICATION

Observe

CBC every 3 months in year 1, then less often

Non-live vaccines; skin checks; treat infections early

Lymphocyte count alone is never the trigger

NEEDS TREATMENT: GENETICS FIRST

FISH del(17p), TP53 mutation, IGHV status; comorbidities and drugs

del(17p)/TP53 → continuous acalabrutinib or zanubrutinib

IGHV mutated → fixed-duration venetoclax-based

IGHV unmutated → either strategy

BTKi unsuitable (AF, bleeding, warfarin) → venetoclax-obinutuzumab

RELAPSE

Re-confirm CLL; exclude Richter (biopsy)

Progressed on covalent BTKi → venetoclax + anti-CD20 or pirtobrutinib

Intolerance → switch BTKi or venetoclax

Young with a donor: allogeneic transplant after response

All: HBV before anti-CD20 · tumour lysis ramp-up with venetoclax · IVIG for recurrent serious infections with IgG under 500 mg/dL · repeat TP53 testing at each progression.

o8 Survivorship, follow-up & late effects

A simple follow-up rhythm for indolent B-cell lymphomas

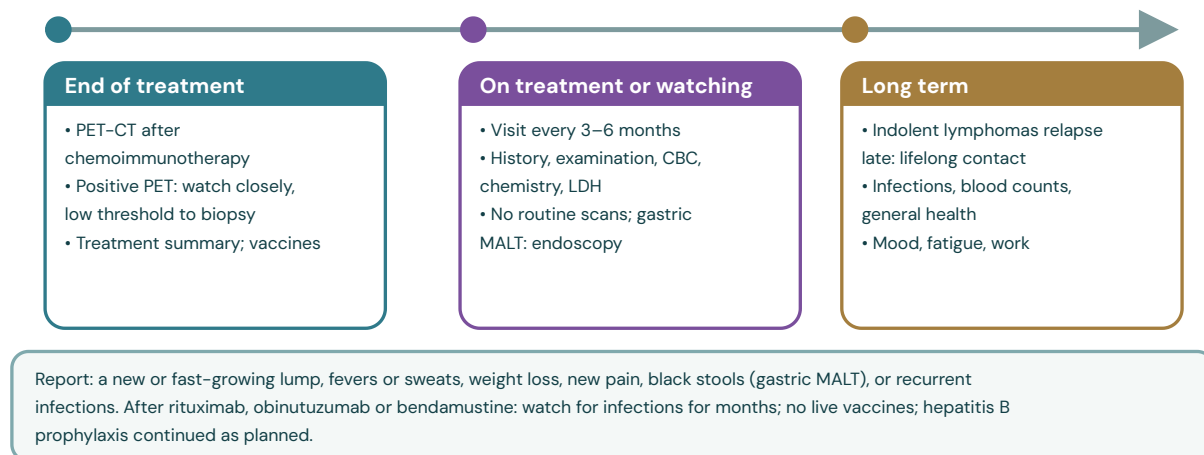


Figure 18. A simple follow-up rhythm, adapted from the UpToDate follicular, MALT, splenic MZL and mantle cell reviews. Individualise by entity and treatment.

- **After chemoimmunotherapy:** PET-CT to document response; follow up every 3–6 months with history, examination, blood count, chemistry and LDH. Routine surveillance scans are not needed; image for symptoms.
- **During watch and wait:** every 3 months in the first year, then every 3–6 months; explain clearly that watching is a treatment decision and what should prompt an earlier visit.
- **Gastric MALT:** endoscopy with biopsies every 3–6 months until complete response, then every 6–12 months for at least 2 years; surveillance can stop after two consecutive normal endoscopies in an asymptomatic patient, but the risk of gastric adenocarcinoma remains.
- **Infections:** anti-CD20 antibodies, bendamustine, bispecific antibodies and CLL itself lower immunity for months to years: non-live vaccines (influenza, pneumococcal), no live vaccines during and after treatment, treat infections early; in CLL, immunoglobulin replacement for recurrent serious infections with IgG under 500 mg/dL.
- **Hepatitis B:** continue antiviral prophylaxis for at least 12 months after the last anti-CD20 dose; do not stop early.
- **Transformation awareness:** teach patients to report a fast-growing lump, fevers, sweats or weight loss; biopsy rather than restage.

When relapses happen: indolent lymphomas come back, often more than once

Early (within 2 years)

- POD24 in follicular lymphoma: biopsy for transformation
- Mantle cell after short remission: BTK inhibitor era

Late (years later)

- The usual pattern in follicular and MZL
- Often still indolent: watch, rituximab, RT or chemo again

Very late (10+ years)

- Possible; some never relapse (functional cure)
- Always biopsy: may be a new lymphoma

A relapse is not the end: most patients get years of further control with the next treatment.

Figure 19. When relapses happen (Casulo 2015; Shadman 2026, SOO16 15-year results; UpToDate follicular, relapsed follicular and relapsed mantle cell reviews).

Late effects and long-term care

Infections

- Low immunoglobulins after anti-CD20 therapy and in CLL
- Bendamustine: long-lasting T-cell depletion
- Non-live vaccines (influenza, pneumococcal); no live vaccines

Keep watching for

- Transformation: a fast-growing node, B symptoms
- Autoimmune cytopenias (CLL, splenic MZL)
- Skin cancer in CLL: 10-year risk 13.5%, twice normal
- Gastric cancer after gastric MALT

Everyday life

- Living with a chronic, relapsing illness
- Anxiety during watch and wait is common
- Rituximab lessened anxiety in one trial

Hepatitis B: HBsAg and anti-HBc before every anti-CD20 course; prophylaxis for 12 months or more after the last dose. Never stop it early.
BTK inhibitors: blood pressure, atrial fibrillation, bleeding with anticoagulants; check interactions before adding any new drug.

Figure 20. Late effects (UpToDate follicular, mantle cell and CLL reviews; Marzolini 2025 for quality of life during watch and wait).

SHARE WITH PATIENTS: LIFE AFTER TREATMENT

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

Lymphoma survivors can't return to normal life?

.....

If the PET scan becomes negative, treatment can always be stopped immediately?

.....

Stage IV lymphoma means the disease is incurable?

.....

09 Landmark trials

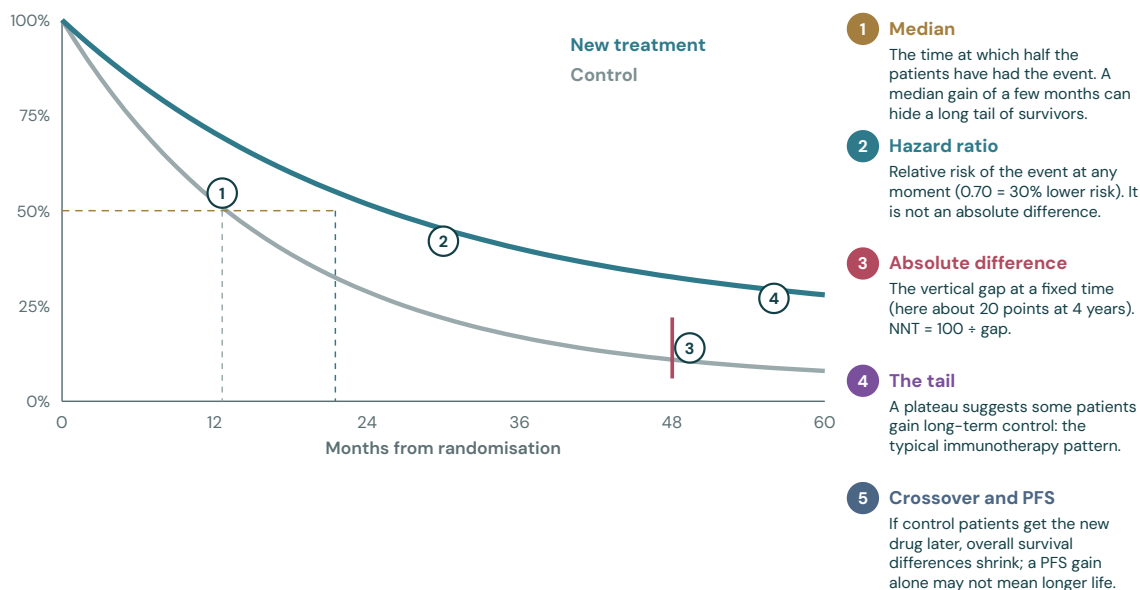
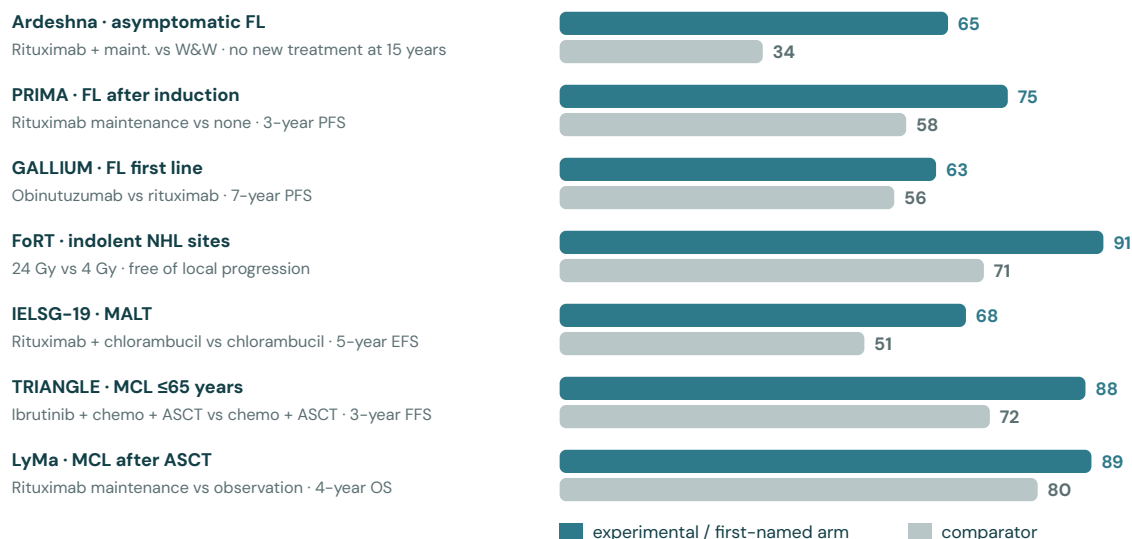


Figure 21. How to read a survival curve (illustrative). Use the absolute gap at a fixed time and overall survival, not the median or PFS alone, when weighing benefit against toxicity and cost.

The trials behind today's choices (experimental arm vs control, %)



Endpoints and time points differ: compare arms within a trial, not across trials. None of these showed a large overall survival difference except LyMa.

Figure 22. Landmark results as reported in the UpToDate reviews (FoRT shown as freedom from local progression, 100 minus 9% and 29%); TRIANGLE web-verified.

- **Ardeshna 2014**^[1]: asymptomatic advanced FL → rituximab delayed new treatment (65% free of it at 15 years with maintenance vs 34%), same survival → watching remains a valid choice.
- **StiL**^[3] and **BRIGHT**^[27]: BR vs R-CHOP/R-CVP → at least as effective, less toxic → BR a standard for FL, MZL and older MCL.
- **RELEVANCE**^[4]: R2 vs chemoimmunotherapy → similar PFS and 10-year survival → a chemotherapy-free first-line option.

- **PRIMA**^[33]: rituximab maintenance → longer PFS, no survival gain → maintenance optional, two years at most.
- **GALLIUM**^[31]: obinutuzumab vs rituximab → better PFS, more toxicity, same survival.
- **FoRT**^[2] and **Lowry 2011**^[22]: 24 Gy is the curative dose; 4 Gy for palliation.
- **IELSG-19**^[41]: MALT lymphoma → rituximab plus chlorambucil gave the best EFS; survival about 90% at 5 years in all arms.
- **MCL Younger**^[44]: adding high-dose cytarabine before transplant → longer time to treatment failure.
- **LyMa**^[49]: rituximab maintenance after transplant in MCL → better overall survival.
- **TRIANGLE**^[5], **SHINE**^[53], **ECHO**^[54]: BTK inhibitors move into first-line MCL treatment for young and old.
- **ZUMA-2**^[88]: CAR-T after a BTK inhibitor in MCL → responses in 93%.
- **AUGMENT**^[74] and **EPCORE FL-1**^[76]: R2, then R2 plus epcoritamab, set the standard for relapsed follicular lymphoma.
- **ELEVATE-TN**^[57], **SEQUOIA**^[58], **CLL14**^[59], **CLL13**^[62]: targeted drugs (continuous or fixed-duration) replace chemoimmunotherapy in CLL.
- **MURANO**^[68]: fixed-duration venetoclax-rituximab improves survival in relapsed CLL.

10 Practice pearls & pitfalls

- A node that waxes and wanes for months is a reason for an excision biopsy, not for another course of anti-TB treatment.
- Stage IV follicular lymphoma in a well patient is not an emergency: decide on watch and wait, rituximab or treatment by symptoms and bulk, not by stage.
- Every CD5-positive small B-cell lymphoma gets cyclin D1: mantle cell lymphoma must not be treated as CLL.
- Grade 3B follicular lymphoma (follicular large B-cell lymphoma) is treated as DLBCL; grades 1–3A are one disease.
- Stage I follicular or localised MALT lymphoma: 24 Gy cures many patients; do not give chemotherapy instead.
- Gastric MALT: test for *H. pylori* off PPIs, treat it, confirm cure, and wait up to 12–18 months for the lymphoma to regress before giving RT.
- Splenic MZL: always test for hepatitis C; antivirals can be the only treatment needed. Split the first rituximab dose.
- Before any anti-CD20 antibody: HBsAg and anti-HBc; prophylaxis for at least 12 months after the last dose.
- Bendamustine in patients over 70: reduce or shorten it; it also depletes T cells for a long time, which may matter for later CAR-T or bispecifics.
- Progression within 24 months of first chemoimmunotherapy (POD24) or a node that outgrows the rest: biopsy for transformation.
- In CLL, the lymphocyte count alone is never an indication to treat; check del(17p)/TP53 and IGHV before choosing the first treatment.
- Mantle cell lymphoma with TP53 mutation or blastoid morphology does poorly with chemotherapy alone: refer for a trial or BTK-inhibitor-based treatment.
- Relapsed follicular lymphoma: biopsy first; early failure after chemoimmunotherapy calls for a lenalidomide-based combination, not the same chemotherapy again.
- Think about CAR-T early in relapsed follicular or mantle cell lymphoma: avoid bendamustine in the 6–12 months before T-cell collection when possible.
- In CLL, retest del(17p)/TP53 at every progression; clonal evolution changes the choice of treatment.

11 Case vignettes: lines of management

Eleven cases from the clinic. Read the presentation, decide, then open the line of management.

CASE 1 Follicular · stage III · no symptoms

Groin and neck nodes for two years and two courses of anti-TB treatment

58 years, man

Stage III

FLIPI 2

A 58-year-old farmer has had painless neck and groin nodes for two years; they shrink and come back. He received two courses of anti-TB treatment elsewhere. He feels well, works full days and has no fevers or weight loss. Blood counts and LDH are normal.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

DIAGNOSE

Excision of the largest groin node: classic follicular lymphoma, grade 2 (CD20+, CD10+, BCL6+, BCL2+, CD5-); t(14;18) present.

2

STAGE AND SCORE

PET-CT: nodes above and below the diaphragm, none over 5 cm; spleen normal. Stage III. FLIPI 2 (stage, more than 4 nodal areas).

3

DECIDE WHETHER TO TREAT

No symptoms, no bulk, no organ threat, normal counts: no indication. Options discussed: watch and wait, or four weekly doses of rituximab (delays chemotherapy, same survival). He chooses to watch.

4

FOLLOW

Visits every 3 months in year 1 with blood count and LDH; no routine scans. HBsAg and anti-HBc checked now so that rituximab can start promptly when needed. Told to report fast-growing nodes, fevers or weight loss.

TEACHING POINTS

- Waxing and waning nodes for years: think follicular lymphoma, not TB.
- Stage is not an indication to treat; symptoms, bulk, organ threat and cytopenias are.
- Watching is an active, evidence-based treatment choice.

See: Sections 02, 03 and 06, Algorithm 2.

CASE 2 Follicular · stage I · radiotherapy

A single lump under the jaw

46 years, woman

Stage IA

Curative intent

A 46-year-old teacher has a 3 cm painless submandibular node that has slowly grown over 6 months. No other complaints.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

DIAGNOSE

Excision: follicular lymphoma, grade 1–2; Ki-67 low.

2

STAGE

PET-CT: no other disease. Marrow biopsy (apparent stage I before RT): negative. Stage IA.

3

TREAT

Involved-site RT 24 Gy in 12 fractions with parotid sparing; no chemotherapy (TROG 99.03: better PFS but no survival gain with added systemic treatment).

4

FOLLOW

Clinical follow-up every 3–6 months; dental and salivary care; scans only for symptoms. About half of such patients are cured.

TEACHING POINTS

- Stage I follicular lymphoma is potentially curable with 24 Gy.
- Stage carefully (PET, marrow) before calling it stage I.
- 4 Gy is for palliation, not cure.

See: Section O5, Algorithm 2.

CASE 3 Follicular · high tumour burden · hepatitis B**Abdominal fullness and swollen legs**

63 years, woman

Stage IV, bulky

FLIPI 4

A 63-year-old woman has 3 months of abdominal fullness and leg swelling. She has a 9 cm mesenteric mass, hydronephrosis on the right and a haemoglobin of 10.5 g/dL. LDH is normal. Her husband had hepatitis B.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

DIAGNOSE

CT-guided cores of the mesenteric mass: follicular lymphoma grade 2; no large-cell sheets. PET: hottest node SUV similar to the rest.

2

INDICATIONS

Bulk with ureteric obstruction and anaemia: treatment needed. Stent for the obstruction.

3

BEFORE TREATMENT

HBsAg negative, anti-HBc positive, HBV DNA undetectable: entecavir from before the first rituximab dose until at least 12 months after the last.

4

TREAT

Bendamustine-rituximab × 6 (clinically indolent picture; no anthracycline needed). End-of-treatment PET Deauville 2. Maintenance discussed (PRIMA: longer PFS, more infections, no survival gain); she declines.

TEACHING POINTS

- Organ compromise is a clear indication to treat.
- BR or R2 for symptomatic indolent disease; R-CHOP if the picture looks aggressive.
- Anti-HBc alone needs antiviral prophylaxis with rituximab.

See: Sections O3 and O6, Algorithm 2, Table D.

CASE 4 Follicular · POD24 · transformation**Fourteen months after BR, one node grows fast**

55 years, man

POD24

High LDH

A 55-year-old man treated with BR for stage IV follicular lymphoma 14 months ago develops night sweats and a rapidly enlarging left axillary node. LDH is now twice normal.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

SUSPECT

Progression within 24 months, B symptoms, high LDH and one node outgrowing the rest: transformation until proven otherwise.

2

DIAGNOSE

PET-CT: axillary node SUVmax 21, others 5–6. Excision of the axillary node: DLBCL arising from follicular lymphoma; MYC FISH negative.

3

TREAT

Little prior therapy (no anthracycline): R-CHOP (or Pola-R-CHP), as for de novo DLBCL. Complete response → observe; partial response → CAR-T referral.

4

PLAN AHEAD

Discuss CAR-T early; record that bendamustine was given (T-cell depletion may affect cell collection).

TEACHING POINTS

- POD24 and a discordant hot spot mean biopsy, not another regimen chosen blind.
- Treat transformation as the aggressive lymphoma found.
- Transformation is the leading cause of death in follicular lymphoma.

See: Section O6 (transformation), Figure on transformation, aggressive B-cell module.

CASE 5 Gastric MALT · *H. pylori***Dyspepsia and an ulcerated gastric fold**

49 years, man

Lugano stage 1

H. pylori positive

A 49-year-old bank manager has 6 months of dyspepsia. Endoscopy shows thickened, ulcerated folds in the gastric body. He has been taking a PPI for 5 months.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

DIAGNOSE

Repeat endoscopy off PPI for 2 weeks with many biopsies from every region: extranodal MZL (MALT); *H. pylori* on histology; FISH negative for t(11;18). EUS: mucosa and submucosa, no nodes. CT: no other disease. Lugano stage 1.

2

TREAT

H. pylori eradication therapy. Urea breath test 4 weeks after finishing, off PPI for 2 weeks: eradicated.

3

FOLLOW

Endoscopy with biopsies every 3–6 months: residual lymphoma at 6 months, histological complete response at 15 months. Then endoscopy every 6–12 months for at least 2 years.

4

IF IT HAD FAILED

Lymphoma still present at 12–18 months, or t(11;18) positive with no response → ISRT 24 Gy to the stomach. No gastrectomy.

TEACHING POINTS

- Test for *H. pylori* off PPIs and antibiotics, with histology and a non-invasive test if histology is negative.
- Responses are slow: median 15 months, sometimes 3 years.
- t(11;18) predicts failure of eradication therapy.

See: Sections 03, 05 and 06, Algorithm 3.

CASE 6 Splenic MZL · hepatitis C**A big spleen found during a check-up**

61 years, woman

Spleen 18 cm

HCV RNA positive

A 61-year-old woman has a spleen palpable 8 cm below the costal margin, lymphocytes 9000/ μ L with villous projections on the smear, haemoglobin 11.2 g/dL and platelets 110,000/ μ L. She feels early fullness after meals.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**DIAGNOSE**

Flow cytometry: clonal B cells CD20+, CD5-, CD10-, CD103-, CD23-. Marrow: intrasinusoidal infiltrate. Splenic MZL. Small IgM paraprotein. HCV RNA positive; HBV negative.

2**TREAT THE VIRUS FIRST**

Mild symptoms: direct-acting antivirals with hepatology. Spleen shrinks and counts improve over the following months.

3**IF NOT ENOUGH**

Rituximab (split first dose: infusion reactions are commoner in SMZL); splenectomy only for suspected transformation or an isolated, symptomatic spleen.

4**FOLLOW**

Every 3 months in year 1; watch for autoimmune haemolysis and transformation (rapid spleen growth, nodes, high LDH).

TEACHING POINTS

- Every marginal zone lymphoma: test for hepatitis C.
- Antivirals alone can control HCV-associated SMZL.
- Rituximab is the usual first systemic treatment; splenectomy is now selective.

See: Sections 02 and 06, Algorithm 3.

CASE 7 Mantle cell · fit · first line**A CD5-positive lymphoma that is not CLL**

57 years, man

Stage IV

MIPI intermediate

A 57-year-old engineer has generalised nodes, a palpable spleen and lymphocytes 14,000/ μ L. A haematologist elsewhere labelled it CLL because the cells were CD5-positive.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**DIAGNOSE**

Node excision: cyclin D1+, SOX11+, CD5+, CD23-; Ki-67 20%; classic morphology; TP53 not mutated; t(11;14) on FISH. Mantle cell lymphoma, not CLL.

2

STAGE AND SCORE

PET-CT: nodes, spleen, marrow positive; colonoscopy shows small polyps (MCL). MIPI intermediate.

3

TREAT

Fit, under 65: rituximab with a cytarabine-containing induction (R-CHOP/R-DHAP) with ibrutinib in induction and maintenance as in TRIANGLE, then autologous transplant (role debated with ibrutinib) and rituximab maintenance for 3 years (LyMa). Cost and access decide part of this plan in India.

4

BEFORE TREATMENT

HBV, HCV, HIV; echo; ECG and blood pressure before ibrutinib; review interacting drugs; sperm banking.

TEACHING POINTS

- CD5-positive small B-cell lymphoma: always check cyclin D1 and CD23.
- Fit younger patients: cytarabine-based induction, transplant consolidation and rituximab maintenance; ibrutinib adds benefit.
- TP53 and blastoid morphology change the plan.

See: Sections 03, 04 and 06, Algorithm 4.

CASE 8 CLL · Rai 0 · observation**A lymphocyte count of 18,000 on a routine test**

67 years, woman

Rai 0 / Binet A

No symptoms

A 67-year-old retired nurse has a white count of 22,000/ μ L with 18,000 lymphocytes on a pre-operative test for cataract surgery. She has no nodes, no spleen, normal haemoglobin and platelets, and no symptoms.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

DIAGNOSE

Smear: small mature lymphocytes with smudge cells. Flow cytometry: CD19+, CD5+, CD23+, dim CD20 and dim surface light chain (kappa). CLL. Repeat in 3 months confirms it is sustained.

2

STAGE

Rai 0, Binet A: no imaging needed.

3

DECIDE

No iwCLL indication: observe. Del(17p)/TP53 and IGHV testing deferred until treatment is needed. Cataract surgery goes ahead.

4

FOLLOW

Blood count every 3 months in year 1, then less often if stable; non-live vaccines; report infections, nodes, sweats or weight loss.

TEACHING POINTS

- A high lymphocyte count alone is not a reason to treat CLL.
- Staging is clinical (examination and blood count).
- Watch for infections, autoimmune haemolysis and Richter transformation, not the count.

See: Sections 03 and 06 (CLL).

CASE 9 Follicular · late relapse**Lumps again, five years after BR**

66 years, man

Relapse at 62 months

Symptomatic

A 66-year-old retired clerk treated with BR and 2 years of rituximab maintenance for follicular lymphoma 5 years ago has new groin and axillary nodes, the largest 6 cm, causing leg swelling. LDH is normal.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**BIOPSY**

Excision of an accessible groin node: follicular lymphoma grade 2; no large-cell sheets. PET: hottest node similar to the rest.

2**CLASSIFY**

Late relapse (more than 24 months after chemoimmunotherapy), symptomatic: needs treatment.

3**TREAT**

R2-based regimen: R2 (AUGMENT), or R2 plus tafasitamab or epcoritamab (inMIND, EPCORE FL-1) if available and he accepts more infections. HBV prophylaxis continued; clot risk and kidney function checked before lenalidomide.

4**PLAN AHEAD**

If he relapses early after this, discuss bispecific antibodies or CAR-T; avoid bendamustine before T-cell collection.

TEACHING POINTS

- Biopsy every relapse when feasible.
- Late relapse: R2-based treatment; early relapse after chemoimmunotherapy: lenalidomide-based combinations.
- Plan the third line before you need it.

See: Section O6 (relapse), Figure on relapsed follicular lymphoma.

CASE 10 CLL · treatment · del(17p)**Falling platelets and drenching sweats**

72 years, man

Rai IV

del(17p)

A 72-year-old man with CLL watched for 4 years now has night sweats for 2 months, a spleen 8 cm below the costal margin, haemoglobin 10.2 g/dL and platelets 78,000/μL. He takes aspirin after a coronary stent; no atrial fibrillation.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**INDICATION**

Marrow failure, symptomatic spleen and B symptoms: active disease by iwCLL criteria. Node sizes stable; LDH normal: no clue to Richter transformation.

2**GENETICS**

FISH: del(17p) present (not seen at diagnosis: clonal evolution); IGHV unmutated.

3**TREAT**

Continuous acalabrutinib or zanubrutinib (del(17p): BTK inhibitor preferred). Cardiology review of aspirin and blood pressure; no anticoagulant; check interacting drugs. HBV checked.

4**SUPPORTIVE CARE**

Non-live vaccines; early antibiotics for fever; immunoglobulin only if recurrent serious infections with IgG under 500 mg/dL; skin examination at visits.

TEACHING POINTS

- Treat CLL for an iwCLL indication, not a number.
- Retest TP53/del(17p) before every treatment.
- Choose the BTK inhibitor around the heart and the drug list.

See: Section 06 (CLL), Algorithm 5.

CASE 11 Waldenström · hyperviscosity**Bleeding gums and blurred vision**

69 years, man

IgM 5200 mg/dL

MYD88 L265P

A 69-year-old retired teacher has 2 weeks of gum bleeding, blurred vision and headache. Haemoglobin 8.9 g/dL; total protein high. Fundoscopy shows engorged retinal veins with flame haemorrhages.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**EMERGENCY**

Symptomatic hyperviscosity: plasmapheresis the same day; no red-cell transfusion before it.

2**DIAGNOSE**

Immunofixation: IgM kappa, 5200 mg/dL. Marrow: 40% lymphoplasmacytic infiltrate, CD20+, CD5-, CD10-, CD23-; MYD88 L265P positive. Waldenström macroglobulinaemia.

3**TREAT THE CLONE**

BR for four to six cycles (or a BTK inhibitor if he prefers no chemotherapy); not rituximab alone (IgM flare). HBV checked first.

4**FOLLOW**

IgM and blood counts during and after treatment; at relapse after BR, zanubrutinib.

TEACHING POINTS

- Hyperviscosity: plasmapheresis first, treatment second.
- Avoid rituximab alone with high IgM.
- Most Waldenström patients are watched, not treated.

See: Section 06 (Waldenström), Figure on Waldenström macroglobulinaemia.

12 References & guidelines

- NCCN Guidelines: B-Cell Lymphomas and CLL/SLL (current versions); ESMO clinical practice guideline on lymphomas (2025); British Society for Haematology guideline on follicular lymphoma (2020); ILROG radiotherapy guidelines for nodal and extranodal lymphoma; iwCLL 2018; [Lugano 2014](#)^[12]; WHO Classification, 5th edition, and the International Consensus Classification (2022); management of lymphomas: consensus document by an Indian expert group (2018).
- Cross-checked in October 2026 against 20 UpToDate topic reviews: follicular lymphoma presentation, diagnosis and prognosis; pathobiology of follicular lymphoma; initial treatment of stage I and of stage II–IV follicular lymphoma; histologic transformation of follicular lymphoma; society guideline links for follicular lymphoma; mantle cell lymphoma epidemiology, diagnosis and prognosis; pathobiology of mantle cell lymphoma; mantle cell lymphoma initial management; MALT lymphoma diagnosis; MALT lymphoma treatment; diagnosis of H. pylori infection; nodal MZL; splenic MZL; lymphoplasmacytic lymphoma; CLL/SLL clinical features and diagnosis; B-cell prolymphocytic leukaemia; primary cutaneous follicle centre and marginal zone lymphoma (detail kept for the cutaneous lymphoma module); Burkitt lymphoma diagnosis. Second batch the same day: treatment of relapsed or refractory follicular lymphoma; treatment of relapsed or refractory mantle cell lymphoma; CLL selection of initial therapy, overview of treatment, relapsed or refractory CLL, staging and prognosis, overview of complications, prevention of infections, evaluating response, pathobiology (plus Waldenström diagnosis and treatment: 34 topics in all; the two secondary CNS lymphoma topics in that batch were already used for the aggressive module).
- Citations were taken from the UpToDate reference lists (journal, volume and first page). Web-verified on 17 October 2026: TRIANGLE (*Lancet* 2024;403:2293), SHINE (*N Engl J Med* 2022;386:2482) and ECHO (*J Clin Oncol* 2025; FDA approval 16 January 2025), which postdate the UpToDate mantle cell review; the Tata Memorial subtype study; zanubrutinib DCGI approval (June 2025). Reviewed and approved by Dr. Haritha Chiramana, 17 October 2026.

Core trials and papers cited on this page (91)

Journal, year, volume and first page (or a PubMed search); each links to the PubMed record by exact citation.

NUMBERED IN ORDER OF FIRST CITATION IN THE TEXT

1. **Rituximab vs watch and wait (Ardeshna 2014)**: Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in advanced-stage, asymptomatic, non-bulky follicular lymphoma. *Lancet Oncol* 2014;15:424. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
2. **ForT**: Hoskin PJ, Kirkwood AA, Popova B, et al. 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. *Lancet Oncol* 2014;15:457. [PubMed](#) Follicular lymphoma: radiotherapy and first-line treatment
3. **StiL NHL1 (Rummel 2013)**: Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for indolent and mantle-cell lymphomas. *Lancet* 2013;381:1203. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
4. **RELEVANCE**: Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma (RELEVANCE). *N Engl J Med* 2018;379:934. [PubMed](#) Follicular lymphoma: radiotherapy and first-line treatment
5. **TRIANGLE (Dreyling 2024)**: Dreyling M, Doorduijn J, Giné E, et al. Ibrutinib combined with immunochemotherapy with or without ASCT versus immunochemotherapy and ASCT in previously untreated MCL (TRIANGLE). *Lancet* 2024;403:2293. [PubMed](#)
Mantle cell lymphoma
6. **POD24 (Casulo 2015)**: Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after R-CHOP defines patients at high risk for death. *J Clin Oncol* 2015;33:2516. [PubMed](#) Classification, diagnosis and prognosis
7. **Lymphoma subtypes in India (Naresh 2000)**: Naresh KN, Srinivas V, Soman CS. Distribution of various subtypes of non-Hodgkin's lymphoma in India: a study of 2773 lymphomas using R.E.A.L. and WHO classifications. *Ann Oncol* 11 Suppl 1:S63. 2000. [PubMed](#) India

8. **HCV treatment and splenic lymphoma (Hermine 2002):** Hermine O, Lefrère F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. *N Engl J Med* 2002;347:89. [PubMed](#)
Marginal zone lymphomas
9. **WHO 5th edition lymphoid (Alaggio 2022):** Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the WHO Classification of Haematolymphoid Tumours: lymphoid neoplasms. *Leukemia* 2022;36:1720. [PubMed](#)
Classification, diagnosis and prognosis
10. **International Consensus Classification (Campo 2022):** Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of mature lymphoid neoplasms. *Blood* 2022;140:1229. [PubMed](#) Classification, diagnosis and prognosis
11. **MYD88 L265P (Treon 2012):** Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *N Engl J Med* 2012;367:826. [PubMed](#) Classification, diagnosis and prognosis
12. **Lugano classification (Cheson 2014):** Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014;32:3059. [PubMed](#) Classification, diagnosis and prognosis
13. **FLIPI (Solal-Céligny 2004):** Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood* 2004;104:1258. [PubMed](#) Classification, diagnosis and prognosis
14. **FLIPI in the LymphoCare Study (Nooka 2013):** Nooka AK, Nabhan C, Zhou X, et al. Examination of the FLIPI in the National LymphoCare Study. *Ann Oncol* 2013;24:441. [PubMed](#) Classification, diagnosis and prognosis
15. **FLIPI24 (Maurer 2026):** Maurer MJ, Prochazka VK, El-Galaly TC, et al. FLIPI24: a modern prognostic model and clinical trial enrichment tool for newly diagnosed follicular lymphoma. *J Clin Oncol* 2026;44:117. [PubMed](#) Classification, diagnosis and prognosis
16. **MIPI (Hoster 2008):** Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood* 2008;111:558. [PubMed](#) Classification, diagnosis and prognosis
17. **MALT-IPI (Thieblemont 2017):** Thieblemont C, Cascione L, Conconi A, et al. A MALT lymphoma prognostic index. *Blood* 2017;130:1409. [PubMed](#) Classification, diagnosis and prognosis
18. **SMZL IIL index (Arcaini 2006):** Arcaini L, Lazzarino M, Colombo N, et al. Splenic marginal zone lymphoma: a prognostic model for clinical use. *Blood* 2006;107:4643. [PubMed](#) Classification, diagnosis and prognosis
19. **TP53 in younger MCL (Eskelund 2017):** Eskelund CW, Dahl C, Hansen JW, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. *Blood* 2017;130:1903. [PubMed](#)
Classification, diagnosis and prognosis
20. **t(11;18) and eradication failure (Liu 2001):** Liu H, Ruskoné-Fourmestreaux A, Lavergne-Slove A, et al. Resistance of t(11;18) positive gastric MALT lymphoma to *Helicobacter pylori* eradication therapy. *Lancet* 2001;357:39. [PubMed](#)
Classification, diagnosis and prognosis
21. **PET after first-line FL (Trotman 2014):** Trotman J, Luminari S, Boussetta S, et al. Prognostic value of PET-CT after first-line therapy in follicular lymphoma: a pooled analysis. *Lancet Haematol* 2014;1:e17. [PubMed](#) Classification, diagnosis and prognosis
22. **UK radiotherapy dose trial (Lowry 2011):** Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. *Radiother Oncol* 2011;100:86. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
23. **TROG 99.03:** MacManus M, Fisher R, Roos D, et al. Randomized trial of systemic therapy after involved-field radiotherapy in early-stage follicular lymphoma: TROG 99.03. *J Clin Oncol* 2018;36:2918. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
24. **Ultra-low-dose 4 Gy for gastric MALT (Gunther 2024):** Gunther JR, Xu J, Bhutani MS, et al. Response-adapted ultra-low-dose 4 Gy radiation as definitive therapy of gastric MALT lymphoma: a single-centre pilot trial. *Lancet Haematol* 2024;11:e521. [PubMed](#)
Marginal zone lymphomas
25. **Watch and wait vs chlorambucil (Ardeshtna 2003):** Ardeshtna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma. *Lancet* 2003;362:516. [PubMed](#) Follicular lymphoma: radiotherapy and first-line treatment
26. **FLIRT (Cartron 2023):** Cartron G, Bachy E, Tilly H, et al. Randomized phase III trial evaluating subcutaneous rituximab for first-line treatment of low-tumor-burden follicular lymphoma (FLIRT). *J Clin Oncol* 2023;41:3523. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
27. **BRIGHT (Flinn 2014):** Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood* 2014;123:2944. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
28. **BRIGHT five-year (Flinn 2019):** Flinn IW, van der Jagt R, Kahl B, et al. First-line treatment of indolent NHL or MCL with BR versus R-CHOP or R-CVP: BRIGHT 5-year follow-up. *J Clin Oncol* 2019;37:984. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment

29. **RELEVANCE ten-year (2026)**: Gower N, Feugier P, Westin J, et al. Lenalidomide plus rituximab for previously untreated advanced follicular lymphoma: the 10-year RELEVANCE analysis. *Blood* 2026;147:3061. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
30. **FOLLO5**: Federico M, Luminari S, Dondi A, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of advanced-stage follicular lymphoma (FOLLO5). *J Clin Oncol* 2013;31:1506. [PubMed](#) Follicular lymphoma: radiotherapy and first-line treatment
31. **GALLIUM**: Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med* 2017;377:1331. [PubMed](#) Follicular lymphoma: radiotherapy and first-line treatment
32. **GALLIUM final (Townsend 2023)**: Townsend W, Hiddemann W, Buske C, et al. Obinutuzumab versus rituximab immunochemotherapy in previously untreated iNHL: final results from the GALLIUM study. *Hemasphere* 2023;7:e919. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
33. **PRIMA**: Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA). *Lancet* 2011;377:42. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
34. **S0016 fifteen-year (Shadman 2026)**: Shadman M, LeBlanc M, Rimsza L, et al. Treatment of follicular lymphoma with CHOP and anti-CD20 therapy: 15-year follow-up of the SWOG S0016 trial. *JAMA Oncol* 2026;12:394. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
35. **FL transformation rates (Link 2013)**: Link BK, Maurer MJ, Nowakowski GS, et al. Rates and outcomes of follicular lymphoma transformation in the immunochemotherapy era. *J Clin Oncol* 2013;31:3272. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
36. **Transformation in PRIMA (Sarkozy 2016)**: Sarkozy C, Trneny M, Xerri L, et al. Risk factors and outcomes for follicular lymphoma with histologic transformation after first-line immunochemotherapy in the PRIMA trial. *J Clin Oncol* 2016;34:2575. [PubMed](#)
Follicular lymphoma: radiotherapy and first-line treatment
37. **MALT regression after H. pylori eradication (Wotherspoon 1993)**: Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of MALT type after eradication of Helicobacter pylori. *Lancet* 1993;342:575. [PubMed](#)
Marginal zone lymphomas
38. **Gastric MALT after eradication (Stathis 2009)**: Stathis A, Chini C, Bertoni F, et al. Long-term outcome following H. pylori eradication in 105 patients with localized gastric MALT lymphoma. *Ann Oncol* 2009;20:1086. [PubMed](#) Marginal zone lymphomas
39. **Gastric MALT in Japan (Nakamura 2012)**: Nakamura S, Sugiyama T, Matsumoto T, et al. Long-term clinical outcome of gastric MALT lymphoma after eradication of H. pylori: a multicentre cohort follow-up study of 420 patients in Japan. *Gut* 2012;61:507. [PubMed](#) Marginal zone lymphomas
40. **LY03 (Hancock 2009)**: Hancock BW, Qian W, Linch D, et al. Chlorambucil versus observation after anti-Helicobacter therapy in gastric MALT lymphomas: the international randomised LY03 trial. *Br J Haematol* 2009;144:367. [PubMed](#) Marginal zone lymphomas
41. **IELSG-19**: Zucca E, Conconi A, Martinelli G, et al. Final results of the IELSG-19 randomized trial of MALT lymphoma: rituximab plus chlorambucil versus either drug alone. *J Clin Oncol* 2017;35:1905. [PubMed](#) Marginal zone lymphomas
42. **Antivirals in HCV-associated lymphoma (Arcaini 2016)**: Arcaini L, Besson C, Frigeni M, et al. Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. *Blood* 2016;128:2527. [PubMed](#)
Marginal zone lymphomas
43. **BArT (Merli 2022)**: Merli M, Rattotti S, Spina M, et al. Direct-acting antivirals as primary treatment for HCV-associated indolent non-Hodgkin lymphomas: the BArT study. *J Clin Oncol* 2022;40:4060. [PubMed](#) Marginal zone lymphomas
44. **MCL Younger (Hermine 2016)**: Hermine O, Hoster E, Walewski J, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous transplantation in patients aged 65 or younger with MCL (MCL Younger). *Lancet* 2016;388:565. [PubMed](#) Mantle cell lymphoma
45. **MCL Younger long-term (Hermine 2023)**: Hermine O, Jiang L, Walewski J, et al. High-dose cytarabine and autologous transplantation in MCL: long-term follow-up of the MCL Younger trial. *J Clin Oncol* 2023;41:479. [PubMed](#) Mantle cell lymphoma
46. **S1106 (Chen 2017)**: Chen RW, Li H, Bernstein SH, et al. RB but not R-HCVAD is a feasible induction regimen prior to auto-HCT in frontline MCL (SWOG S1106). *Br J Haematol* 2017;176:759. [PubMed](#) Mantle cell lymphoma
47. **Nordic MCL2 fifteen-year (Eskelund 2016)**: Eskelund CW, Kolstad A, Jerkeman M, et al. 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2). *Br J Haematol* 2016;175:410. [PubMed](#) Mantle cell lymphoma
48. **European MCL Network ASCT (Dreyling 2005)**: Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy and autologous transplantation in first remission prolongs PFS in mantle-cell lymphoma. *Blood* 2005;105:2677. [PubMed](#) Mantle cell lymphoma
49. **LyMa (Le Gouill 2017)**: Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *N Engl J Med* 2017;377:1250. [PubMed](#) Mantle cell lymphoma

50. **LYM-3002 VR-CAP (Robak 2015)**: Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. *N Engl J Med* 2015;372:944. [PubMed](#) Mantle cell lymphoma
51. **MCL-Elderly (Kluin-Nelemans 2012)**: Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med* 2012;367:520. [PubMed](#) Mantle cell lymphoma
52. **MCL-Elderly long-term (Kluin-Nelemans 2020)**: Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with MCL: long-term follow-up of the European MCL Elderly trial. *J Clin Oncol* 2020;38:248. [PubMed](#) Mantle cell lymphoma
53. **SHINE (Wang 2022)**: Wang ML, Jurczak W, Jerkeman M, et al. Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma (SHINE). *N Engl J Med* 2022;386:2482. [PubMed](#) Mantle cell lymphoma
54. **ECHO (Wang 2025)**: Wang M, et al. Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma: the phase 3 ECHO trial. *J Clin Oncol* 43. 2025. [PubMed](#) Mantle cell lymphoma
55. **iwCLL guidelines (Hallek 2018)**: Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood* 2018;131:2745. [PubMed](#) Classification, diagnosis and prognosis
56. **CLL-IPI (2016)**: International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI). *Lancet Oncol* 2016;17:779. [PubMed](#) CLL/SLL treatment
57. **ELEVATE-TN**: Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve CLL (ELEVATE TN). *Lancet* 2020;395:1278. [PubMed](#) CLL/SLL treatment
58. **SEQUOIA**: Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated CLL and SLL (SEQUOIA). *Lancet Oncol* 2022;23:1031. [PubMed](#) CLL/SLL treatment
59. **CLL14**: Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med* 2019;380:2225. [PubMed](#) CLL/SLL treatment
60. **GLOW**: Kater AP, Owen C, Moreno C, et al. Fixed-duration ibrutinib-venetoclax in patients with CLL and comorbidities. *NEJM Evid* 1. 2022. [PubMed](#) CLL/SLL treatment
61. **AMPLIFY**: Brown JR, Seymour JF, Jurczak W, et al. Fixed-duration acalabrutinib combinations in untreated CLL (AMPLIFY). *N Engl J Med* 2025;392:748. [PubMed](#) CLL/SLL treatment
62. **CLL13**: Eichhorst B, Niemann CU, Kater AP, et al. First-line venetoclax combinations in CLL (CLL13). *N Engl J Med* 2023;388:1739. [PubMed](#) CLL/SLL treatment
63. **E1912**: Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for CLL (E1912). *N Engl J Med* 2019;381:432. [PubMed](#) CLL/SLL treatment
64. **FLAIR MRD-guided (Munir 2024)**: Munir T, Cairns DA, Bloor A, et al. CLL therapy guided by measurable residual disease (FLAIR). *N Engl J Med* 2024;390:326. [PubMed](#) CLL/SLL treatment
65. **AO41202**: Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL (AO41202). *N Engl J Med* 2018;379:2517. [PubMed](#) CLL/SLL treatment
66. **ALPINE**: Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory CLL (ALPINE). *N Engl J Med* 2023;388:319. [PubMed](#) CLL/SLL treatment
67. **ELEVATE-RR**: Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated CLL: the first randomized phase III trial (ELEVATE-RR). *J Clin Oncol* 2021;39:3441. [PubMed](#) CLL/SLL treatment
68. **MURANO**: Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory CLL (MURANO). *N Engl J Med* 2018;378:1107. [PubMed](#) CLL/SLL treatment
69. **BRUIN CLL-321**: Sharman JP, Munir T, Grosicki S, et al. Pirtobrutinib versus idelalisib/rituximab or bendamustine/rituximab in covalent BTK inhibitor-pretreated CLL/SLL (BRUIN CLL-321). *J Clin Oncol* 2025;43:2538. [PubMed](#) CLL/SLL treatment
70. **Revised IPSS-WM (Kastritis 2019)**: Kastritis E, Morel P, Duhamel A, et al. A revised international prognostic score system for Waldenström's macroglobulinemia. *Leukemia* 2019;33:2654. [PubMed](#) Waldenström macroglobulinaemia
71. **INNOVATE**: Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. *N Engl J Med* 2018;378:2399. [PubMed](#) Waldenström macroglobulinaemia
72. **INNOVATE final (Buske 2022)**: Buske C, Tedeschi A, Trotman J, et al. Ibrutinib plus rituximab versus placebo plus rituximab for Waldenström's macroglobulinemia: final analysis of INNOVATE. *J Clin Oncol* 2022;40:52. [PubMed](#) Waldenström macroglobulinaemia
73. **ASPEN**: Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood* 2020;136:2038. [PubMed](#) Waldenström macroglobulinaemia
74. **AUGMENT**: Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol* 2019;37:1188. [PubMed](#) Relapsed follicular and mantle cell lymphoma
75. **inMIND**: Sehn LH, Hübel K, Luminari S, et al. Tafasitamab, lenalidomide, and rituximab in relapsed or refractory follicular lymphoma (inMIND). *Lancet* 2026;407:133. [PubMed](#) Relapsed follicular and mantle cell lymphoma

76. **EPCORE FL-1:** Falchi L, Nijland M, Huang H, et al. Epcoritamab, lenalidomide, and rituximab versus lenalidomide and rituximab for relapsed or refractory follicular lymphoma (EPCORE FL-1). *Lancet* 2026;407:161. [PubMed](#)
Relapsed follicular and mantle cell lymphoma
77. **GADOLIN:** Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in rituximab-refractory indolent NHL (GADOLIN). *Lancet Oncol* 2016;17:1081. [PubMed](#) Relapsed follicular and mantle cell lymphoma
78. **GADOLIN overall survival (Cheson 2018):** Cheson BD, Chua N, Mayer J, et al. Overall survival benefit with obinutuzumab plus bendamustine induction and obinutuzumab maintenance in GADOLIN. *J Clin Oncol* 2018;36:2259. [PubMed](#)
Relapsed follicular and mantle cell lymphoma
79. **Mosunetuzumab in FL (Budde 2022):** Budde LE, Sehn LH, Matasar M, et al. Mosunetuzumab in relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Oncol* 2022;23:1055. [PubMed](#)
Relapsed follicular and mantle cell lymphoma
80. **Epcoritamab in FL, EPCORE NHL-1 (Linton 2024):** Linton KM, Vitolo U, Jurczak W, et al. Epcoritamab monotherapy in relapsed or refractory follicular lymphoma (EPCORE NHL-1). *Lancet Haematol* 2024;11:e593. [PubMed](#)
Relapsed follicular and mantle cell lymphoma
81. **ZUMA-5:** Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5). *Lancet Oncol* 2022;23:91. [PubMed](#) Relapsed follicular and mantle cell lymphoma
82. **ELARA:** Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med* 2022;28:325. [PubMed](#) Relapsed follicular and mantle cell lymphoma
83. **TRANSCEND FL:** Morschhauser F, Dahiya S, Palomba ML, et al. Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study. *Nat Med* 2024;30:2199. [PubMed](#) Relapsed follicular and mantle cell lymphoma
84. **ROSEWOOD:** Zinzani PL, Mayer J, Flowers CR, et al. ROSEWOOD: zanubrutinib plus obinutuzumab versus obinutuzumab in relapsed or refractory follicular lymphoma. *J Clin Oncol* 2023;41:5107. [PubMed](#) Relapsed follicular and mantle cell lymphoma
85. **ACE-LY-004 (Wang 2018):** Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004). *Lancet* 2018;391:659. [PubMed](#) Relapsed follicular and mantle cell lymphoma
86. **Zanubrutinib in relapsed MCL (Tam 2021):** Tam CS, Opat S, Simpson D, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. *Blood Adv* 2021;5:2577. [PubMed](#) Relapsed follicular and mantle cell lymphoma
87. **Ibrutinib vs temsirolimus (Dreyling 2016):** Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in relapsed or refractory mantle-cell lymphoma. *Lancet* 2016;387:770. [PubMed](#) Relapsed follicular and mantle cell lymphoma
88. **ZUMA-2 (Wang 2020):** Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2020;382:1331. [PubMed](#) Relapsed follicular and mantle cell lymphoma
89. **TRANSCEND MCL (Wang 2024):** Wang M, Siddiqi T, Gordon LI, et al. Lisocabtagene maraleucel in relapsed/refractory mantle cell lymphoma: TRANSCEND NHL 001. *J Clin Oncol* 2024;42:1146. [PubMed](#) Relapsed follicular and mantle cell lymphoma
90. **BRUIN MCL (Wang 2023):** Wang ML, Jurczak W, Zinzani PL, et al. Pirtobrutinib in covalent BTK inhibitor pretreated mantle-cell lymphoma. *J Clin Oncol* 2023;41:3988. [PubMed](#) Relapsed follicular and mantle cell lymphoma

FURTHER READING (NOT CITED IN THE TEXT ABOVE)

- **Quality of life, rituximab vs watch and wait (Marzolini 2025):** Marzolini MAV, Qian W, Clifton-Hadley L, et al. Quality of life in advanced-stage, asymptomatic, non-bulky follicular lymphoma treated with rituximab versus watchful waiting. *Br J Haematol* 2025;206:876. [PubMed](#) Follicular lymphoma: radiotherapy and first-line treatment

Educational summary for health professionals, written in our own words from current guidelines and primary trials. No drug doses are given. Hodgkin lymphoma is covered in part 1 and aggressive B-cell lymphomas in part 2; T-cell and cutaneous lymphomas are parts 4 and 5; leukaemias will follow as a separate module in the haematological cancers series. Verify current guidelines, Indian regulatory approvals and individual patient factors before treatment decisions.