

Indolent B-cell lymphomas: tests, treatment by setting, regimens and problems during treatment

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A. Diagnosis and staging tests and what they change

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).

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

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

Test	When	What it changes	Pitfalls
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
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

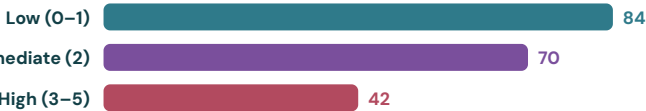
B. Treatment by setting

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).

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.

Table B. Treatment by setting

Setting	Standard choice	Key evidence	Notes
Follicular, stage I	ISRT 24 Gy	FoRT, Lowry 2011	Observe after complete excision or if RT would be morbid; add systemic only in trials (TROG 99.03)
Follicular, II–IV, no indication to treat	Watch and wait, or rituximab × 4 (± 4 more)	Ardeshna 2014	Same survival; patient preference decides
Follicular, needs treatment, clinically indolent	BR or R2; optional anti-CD20 maintenance ≤2 years	StiL, RELEVANCE, PRIMA	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, GALLIUM	Biopsy for transformation first
Transformed follicular lymphoma	As the aggressive lymphoma found; CAR-T if not in CR	Link 2013	See the aggressive B-cell module

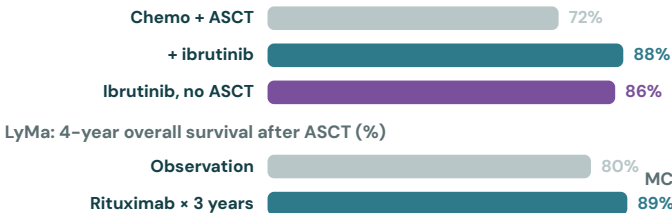
Setting	Standard choice	Key evidence	Notes
Gastric MALT, H. pylori+, stage 1–2	Eradication → endoscopy every 3–6 months	Wotherspoon 1993, Nakamura 2012	Persistent at 12–18 months, H. pylori–, or t(11;18) → ISRT 24 Gy
Non-gastric MALT, stage 1–2	ISRT 24 Gy (≤30 Gy)	UpToDate MALT review	Lung: avoid curative RT; resection or observation
Advanced MALT or nodal MZL needing treatment	Rituximab ± chemotherapy (BR or chlorambucil)	IELSG-19	One nodal region: RT
Splenic MZL	Observe → HCV antivirals → rituximab → BR; splenectomy for selected cases	Arcaini 2016	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, LyMa, TRIANGLE	TP53/blastoid: trial
MCL, older or unfit	BR (± BTK inhibitor), VR-CAP or R-lenalidomide → rituximab maintenance × 3 years	SHINE, ECHO, MCL-Elderly	BTKi: heart rhythm, bleeding, interactions
Waldenström, needs treatment	BR; BTK inhibitor if older or avoiding chemotherapy; plasmapheresis first for hyperviscosity	iNNOVATE, ASPEN	Not rituximab alone with IgM over 4000 mg/dL
CLL/SLL, no indication	Observe	iwCLL 2018	Lymphocyte count alone is not an indication
CLL, del(17p)/TP53	Continuous acalabrutinib or zanubrutinib	ELEVATE-TN, SEQUOIA	BTKi unsuitable: venetoclax-obinutuzumab
CLL, IGHV mutated / unmutated	Mutated: fixed-duration venetoclax-based; unmutated: either strategy	CLL14, GLOW, AMPLIFY, CLL13	Kidney, CYP3A drugs, lysis risk shape the choice
CLL, progression on a covalent BTKi	Venetoclax + anti-CD20, or pirtobrutinib	MURANO, BRUIN CLL-321	Intolerance only: switch BTKi
FL, late symptomatic relapse	R2 ± tafasitamab or epcoritamab; BO after R2 or rituximab alone	AUGMENT, inMIND, EPCORE FL-1, GADOLIN	Biopsy first; watch if asymptomatic
FL, early relapse (POD24) / multiply relapsed	Lenalidomide combinations; then bispecific antibodies or CAR-T	ZUMA-5, mosunetuzumab	Avoid recent bendamustine before CAR-T
MCL, relapse	BTKi-naïve: acalabrutinib or zanubrutinib; after BTKi: lenalidomide, CAR-T, pirtobrutinib	ACE-LY-004, ZUMA-2, BRUIN	Second relapse, fit: CAR-T

C. Regimens: evidence and best fit

Mantle cell lymphoma first line: the trials behind the choices

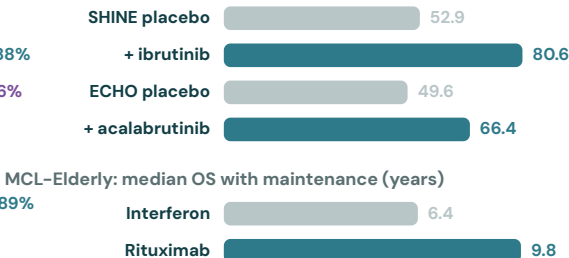
Fit, 65 or younger

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



Older or transplant-ineligible

Median PFS with BR (months)



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.

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.

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	FOLLO5: 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

Regimen or drug	Best fit	Evidence	Main toxicity
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
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

D. Managing problems during treatment

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.

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

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
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

Problem	Prevent	Recognise	Act
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