Follicular Lymphoma Treatment Landscape Overview

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Epidemiology

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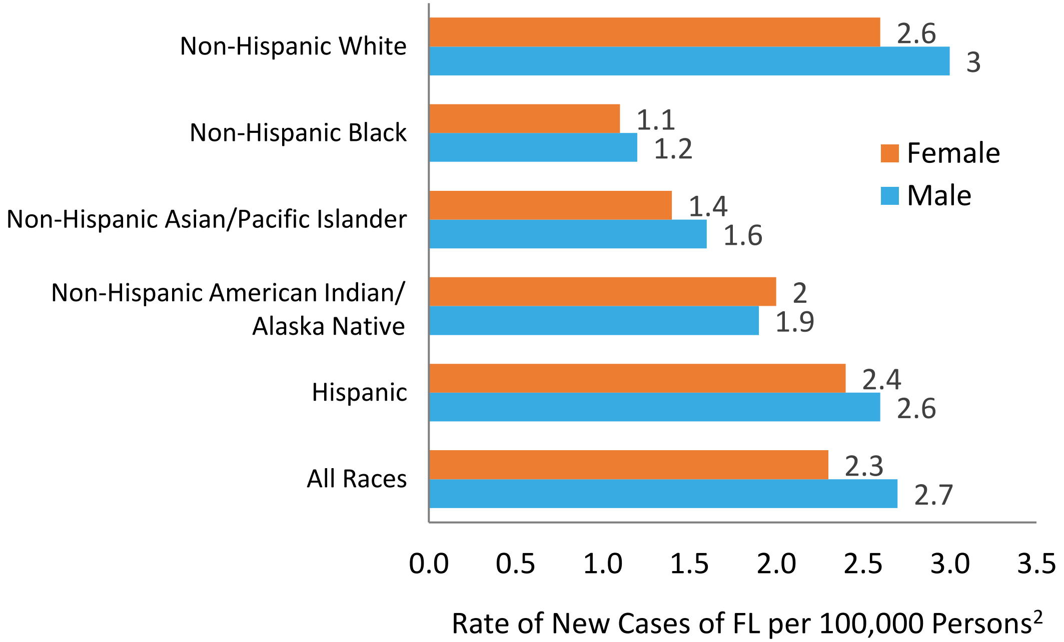
Follicular Lymphoma Is the Second Most Common Lymphoma in the US and Western Europe[1]

Epidemiology

- In the US, the estimated incidence of FL is 2.5 cases per 100,000 persons per year[2,a]
- In Europe, the estimated incidence of FL is 2.18 cases per 100,000 persons per year[3,b]

New Cases of FL by Race/Ethnicity



New Cases of FL by Age

Median age of diagnosis[2]

64 years

The percent of new FL cases by age group[2]

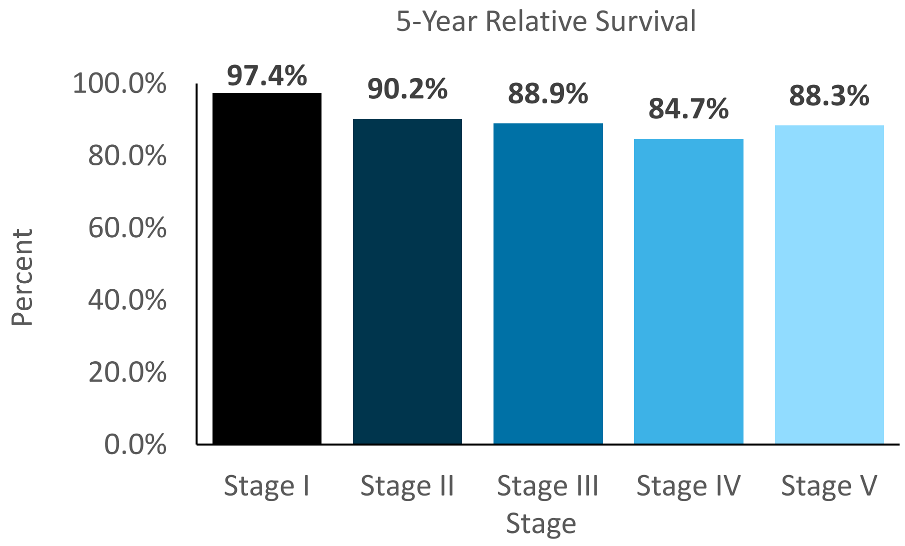
- Age <55 years: 24.4%
- Age 55-64 years: 27.0%
- Age 65-74 years: 28.1%
- Age >75: 20.4%

[a]Age-adjusted rate on the basis of cases occurring from 2017-2021.
[b]On the basis of European cancer registry data from 2000-2002.
FL, follicular lymphoma; US, United States.

1. Jacobsen E. *Am J Hematol*. 2022;97(12):1638-1651. 2. National Cancer Institute. Cancer Stat Facts: NHL Follicular Lymphoma. Accessed November 22, 2024. https://seer.cancer.gov/statfacts/html/follicular.html 3. Sant M, et al. *Blood*. 2010 Nov 11;116(19):3724-34.

Follicular Lymphoma Survival Rates Are High Overall, but Subsets of Patients Continue to Have Poor Prognosis

Survival



Ann Arbor Stage for All Races and Both Sexes from SEER 17 2014-2020

Unmet Needs

While a majority of patients have long-term survival, a subset of patients with aggressive disease have poor outcomes[2]

- Approximately 20% of patients with FL have progressive disease within 2 years (POD24) of initial treatment and a 5-year survival rate of 50%[2]
- For the majority of patients who initially respond to treatment, relapses occur repeatedly, with increasing refractoriness[3]
- Histologic transformation explains 40% of treatment failures during the first year following initiation of treatment[3]

An unmet need remains for FL patients with POD24, multiple relapses, and histologic transformation

FL, follicular lymphoma; POD24, progression of disease within 24 months; SEER, Surveillance, Epidemiology, and End Results.

1. National Cancer Institute. Cancer Stat Facts: NHL Follicular Lymphoma. Accessed November 22, 2024. https://seer.cancer.gov/statfacts/html/follicular.html 2. Cahill KE, Smith SM. *Oncology (Williston Park).* 2022;36(2):97-106. 3. Milpied P, et al. *Adv Immunol*. 2021;150:43-103.

Diagnosis and Treatment

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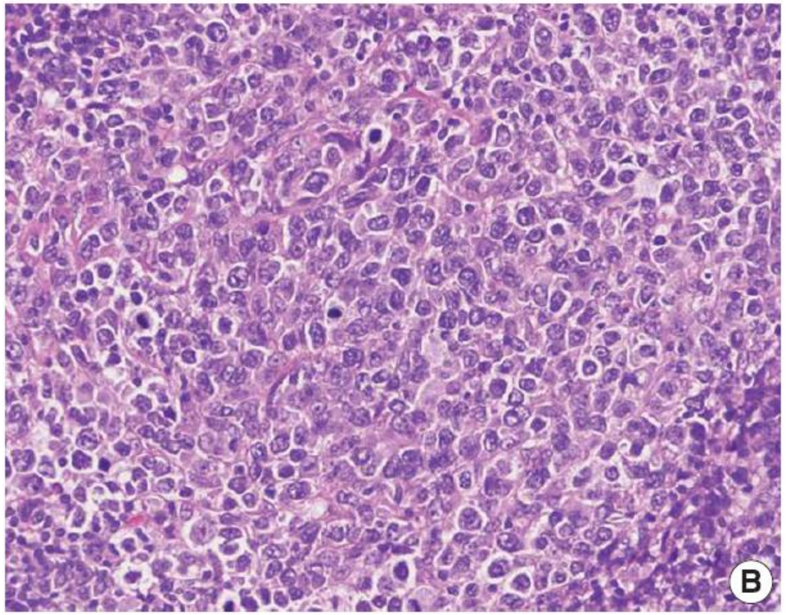
Pathology and Grading of Follicular Lymphoma

Diagnosis of FL is made histologically on the basis of surgically excised lymph nodes or needle biopsies[1]

WHO grading for FL[1]

- Grade 1: 0-5 centroblasts/high power field with a follicular or diffuse pattern
- Grade 2: 6-15 centroblasts/high power field with follicular or diffuse pattern
- Grade 3A: >15 centroblasts/high power field (centrocytes present) with follicular pattern[a]
- Grade 3B: >15 centroblasts/high power field (lacking centrocytes) with follicular pattern[a]



H&E stained high-grade (grade 3B) follicular lymphoma excisional biopsy at high power magnification. Most cells in this follicle are large centroblasts without intervening centrocytes.
Image from Khanlari M, Chapman JR. Follicular lymphoma: updates for pathologists. *J Pathol Transl Med*. 2022;(1):1-15. Copyright © 2022 The Korean Society of Pathologists/The Korean Society for Cytopathology.

IHC is positive in almost all cases for cell surface CD19, CD20, CD10, and monoclonal immunoglobulin; the majority of cases have the characteristic t(14;18) translocation involving the IgH/BCL-2 genes[2]

FL, follicular lymphoma; H&E, hematoxylin and eosin; IHC, immunohistochemistry; WHO, World Health Organization.

1. Khanlari M, Chapman JR. *J Pathol Transl Med*. 2022 Jan;56(1):1-15.
2. Jacobsen E. *Am J Hematol*. 2022;97(12):1638-1651.

[a]If there is a diffuse component, it will be reported as diffuse large B cell lymphoma and follicular lymphoma.

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Imaging for Follicular Lymphoma

PET/CT is the standard approach for staging, restaging, and evaluation of response for lymphomas, including FL

Diagnostic Workup[1]

Evaluation of FL should include history, physical examination, laboratory studies, and imaging (including CT, MRI, and FDG PET/CT)

Treatment Decision Making[2]

^{18}F-FDG-PET is required for optimal disease staging

- It may show FDG-avid lesions not easily found by an initial CT scan; CT scans are indicated for nonavid histology
- PET scans may indicate an increase in the disease stage for 10%-60% of patients with early-stage FL

Response Assessment[2]

PET/CT scans are employed to guide biopsy in patients with a suspected lack of response to therapy

PET scan evaluation of response can provide guidance for treatment de-escalation for patients with early complete metabolic response

Post-treatment Surveillance[2,3]

In FL, the clinical benefit of routine surveillance imaging has not been demonstrated

- Surveillance with ^{18}F-FDG-PET/CT is not routinely recommended

Ann Arbor Staging of Non-Hodgkin Lymphoma[1]	
Stage I	Single lymph node group or single extra lymphatic organ involved without lymph node involvement
Stage II	Two or more lymph node regions involved on the same side of the diaphragm with or without the involvement of an extra lymphatic organ
Stage III	Lymph nodes on both sides of the diaphragm involved
Stage IV	One or more extra lymphoid organs diffusely involved with or without lymph node involvement

FDG PET/CT, combined fluorodeoxyglucose positron emission tomography with computed tomography; FL, follicular lymphoma; MRI, magnetic resonance imaging.

1. Kaseb H, et al. Follicular Lymphoma. *StatPearls.* StatPearls Publishing; 2024. Accessed March 7, 2024. https://www.ncbi.nlm.nih.gov/books/NBK538206/ 2. Zanoni L, et al. *Semin Nucl Med*. 2023;53(3):320-351. 3. Goldman ML, et al. *Cancer*. 2021;127(18):3390-3402.

Treatment of Follicular Lymphoma

Treatment Selection

Choice of therapy for FL is highly dependent on patient and disease characteristics, including the following:[1,2]

- Stage of disease (Ann Arbor staging)
- Prognostic indices such as FLIPI
- Early progression of disease or POD24

Treatment Paradigm

- Patients with FL are observed clinically until there is an indication to treat, typically assessed by GELF or NCCN criteria, which identify patients with high tumor burden[1,2]
- First-line treatment for patients with stage I-II FL includes observation, rituximab, chemoimmunotherapy, or radiation[2]
- First-line treatment of high tumor burden and symptomatic advanced FL often includes chemotherapy and/or an antiCD20 antibody[2]
- Treatment of relapsed/refractory FL has no standard treatment or recommended sequence of treatments[2]

Approved Therapies for FL Include[2,3]

- Monoclonal antibodies ± chemotherapy
- Immunomodulators
- BTK inhibitors
- EZH2 inhibitors
- CAR-T cell therapies
- Bispecific antibodies

BTK, Bruton's tyrosine kinase; CAR-T, chimeric antigen receptor T cell; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; NCCN, National Comprehensive Cancer Network.

1. Luminari S, et al. *Cancer J*. 2020;26(3):231-240. 2. Cahill KE, Smith SM. *Oncology (Williston Park)*. 2022;36(2):97-106. 3. Radhakrishnan VS, Davies AJ. *Front Immunol*. 2024;14:1295599.

Approved Therapies for FL: CD20 mAbs With Chemotherapy, Immunomodulators, and BTK Inhibitors

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Treatment	Indication	Mechanism of action
Obinutuzumab + chemotherapy[1]	• Previously untreated stage II bulky, stage III, or stage IV FL	• Obinutuzumab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes • Upon binding to CD20, obinutuzumab mediates B-cell lysis through (1) engagement of immune effector cells, (2) by directly activating intracellular death signaling pathways (direct cell death), and/or (3) activation of the complement cascade
Obinutuzumab + bendamustine[1]	• FL relapsed after, or refractory to, a rituximab-containing regimen	
Rituximab[2]	• R/R, low grade or follicular, $CD20^+$ B-cell NHL as a single agent	• Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes • Upon binding to CD20, rituximab mediates B-cell lysis
Rituximab + chemotherapy[2]	• Previously untreated follicular, $CD20^+$ B-cell NHL in combination with 1L chemotherapy and as a single-agent maintenance therapy in patients achieving a CR or PR to rituximab + chemotherapy	
Lenalidomide + rituximab[3]	• Previously treated FL in combination with rituximab	• Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties • Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells in vitro
Zanubrutinib + obinutuzumab[4]	• R/R FL as 3L+	• Zanubrutinib is a small-molecule inhibitor of BTK • In nonclinical studies, zanubritinib inhibited malignant B-cell proliferation and reduced tumor growth

REFERENCES

[a]Patients who achieve stable disease, complete response, or partial response to the initial 6 cycles should continue obinutuzumab 1000 mg as monotherapy for up to two years.

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Approved Therapies for FL: CD20 mAbs With Chemotherapy and Immunomodulators

Treatment	Indication	Mechanism of action
Obinutuzumab + chemotherapy[1]	• Previously untreated stage II bulky, stage III, or stage IV FL	• Obinutuzumab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes • Upon binding to CD20, obinutuzumab mediates B-cell lysis through (1) engagement of immune effector cells, (2) by directly activating intracellular death signaling pathways (direct cell death), and/or (3) activation of the complement cascade
Obinutuzumab + bendamustine[1]	• FL relapsed after, or refractory to, a rituximab-containing regimen	
Rituximab[2]	• R/R, low grade or follicular, $CD20^+$ B-cell NHL as a single agent	• Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes • Upon binding to CD20, rituximab mediates B-cell lysis
Rituximab + chemotherapy[2]	• Previously untreated follicular, $CD20^+$ B-cell NHL in combination with 1L chemotherapy and as a single-agent maintenance therapy in patients achieving a CR or PR to rituximab + chemotherapy	
Lenalidomide + rituximab[3]	• Previously treated FL in combination with rituximab	• Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties • Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells in vitro
Zanubrutinib + obinutuzumab[4]	• R/R FL as 3L+	• Zanubrutinib is a small-molecule inhibitor of BTK • In nonclinical studies, zanubritinib inhibited malignant B-cell proliferation and reduced tumor growth

1L, first line; 2L, second line; 3L, third line; CR, complete response; FL, follicular lymphoma; IV, intravenous; mAbs, monoclonal antibodies; NHL, non-Hodgkin lymphoma; PR, partial response; R/R, relapsed/refractory.

1. GAZYVA®. Prescribing information. Genentech; 2023. Accessed March 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125486s029lbl.pdf
2. RITUXAN®. Prescribing information. Genentech; 2021. Accessed March 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103705s5464lbl.pdf
3. REVLIMID®. Prescribing information. Bristol Myers Squibb; 2023. Accessed March 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021880s067lbl.pdf

Approved Therapies for FL: BTK Inhibitors and EZH2 Inhibitors

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Treatment	Indication	Mechanism of action
Zanubrutinib + obinutuzumab[1]	• R/R FL as 3L+	• Zanubrutinib is a small-molecule inhibitor of BTK • In nonclinical studies, zanubritinib inhibited malignant B-cell proliferation and reduced tumor growth
Tazemetostat[2]	• R/R FL with EZH2 mutation as 3L+ • R/R FL for adults with no satisfactory alternative treatment option	• Tazemetostat is an inhibitor of the methyltransferase, EZH2, and some EZH2 gain-of-function mutations, including Y646X, A682G, and A692V • Tazemetostat suppressed proliferation of B-cell lymphoma cell lines in vitro and demonstrated antitumor activity in a mouse xenograft model of B-cell lymphoma with or without EZH2 gain-of-function mutations

Idelalisib and duvelisib are no longer indicated for FL; umbralisib and copanlisib were previously approved but have been withdrawn from the market.[3-6]

3L, third line; BTK, Bruton's tyrosine kinase; FL, follicular lymphoma; IV, intravenous; R/R, relapsed/refractory.

1. BRUKINSA®. Prescribing information. BeiGene; 2024. Accessed March 11, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213217s011lbl.pdf
2. TAZVERIK®. Prescribing information. Epizyme, Inc; 2023. Accessed March 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213400s000lbl.pdf
3. ZYDELIG®. Prescribing information. Gilead Sciences, Inc; 2022. Accessed March 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/205858s016lbl.pdf
4. COPIKTRA®. Prescribing information. Secura Bio, Inc; 2021. Accessed March 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211155s005lbl.pdf
5. TG Therapeutics announces voluntary withdrawal of the BLA/sNDA for U2 to treat patients with CLL and SLL. 2022. Accessed February 15, 2024. https://ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-announces-voluntary-withdrawal-blasnda-u2-treat.
6. Bayer provides update on Aliqopa® (copanlisib). 2023. Accessed February 26, 2024. https://www.bayer.com/en/us/news-stories/update-on-aliqopar.

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Approved Therapies for FL: T-cell Mediated Therapy

Treatment	Indication	Mechanism of action	
Axi-cel[1]	• R/R FL as 3L+	CD28 and CD3-zeta costimulatory domains	• CD19-directed genetically modified autologous CAR-T therapies • CAR binding to CD19 expressed on the surface of tumor and normal B cell, induces activation and proliferation of CAR-positive T cells, the release of pro-inflammatory cytokines, and cytotoxic killing of target tumor cells
Liso-cel[2]	• R/R FL 2L (FL grade 3B with relapse within 12 months or not eligible for HSCT) or R/R FL 3L+ (all grades)	CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain	
Tisa-cel[3]	• R/R FL as 3L+	Intracellular signaling domains from 4-1BB (CD137) and CD3 zeta	
Mosunetuzumab[4]	• R/R FL as 3L+	• Mosunetuzumab is a T-cell–engaging bispecific antibody that binds to the CD3 receptor expressed on the surface of T cells and CD20 expressed on the surface of lymphoma cells and some healthy B-lineage cells • In vitro, mosunetuzumab activated T cells, caused the release of proinflammatory cytokines, and induced lysis of B cells	
Epcoritamab[5]	• R/R FL as 3L+	• Epcoritamab is a T-cell engaging bispecific antibody that binds to both the CD3 receptor expressed on the surface of T cells and CD20 expressed on the surface of lymphoma cells and healthy B-lineage cells • In vitro, epcoritamab activated T cells, caused the release of proinflammatory cytokines, and induced lysis of B cells	

2L, second line; 3L, third line; CAR-T, chimeric antigen receptor T cell; FL, follicular lymphoma; R/R, relapsed/refractory.

1. YESCARTA®. Prescribing information. Kita Pharma, Inc; 2022. Accessed March https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf
2. BREYANZI®. Prescribing information. Genentech, Inc; 2023. Accessed November 22, 2024. https://packageinserts.bms.com/pi/pi_breyanzi.pdf
3. KYMRIAH®. Prescribing information. Novartis Pharmaceuticals; 2022. Accessed March 7, 2024. https://www.fda.gov/media/107296/download?attachment
4. LUNSUMIO®. Prescribing information. Genentech, Inc; 2022. Accessed March 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761263s000lbl.pdf
5. EPKINLY®. Prescribing information. Genmab US, Inc; 2024. Accessed November 22, 2024 https://www.genmab-pi.com/prescribing-information/epkinly-pi.pdf

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Hematopoietic Cell Transplant for FL

In the relapsed/refractory FL setting, allo-SCT and auto-SCT are treatment options

- Allo-SCT has curative potential in FL but is best reserved for patients who are medically fit with heavily pretreated disease, have persistent marrow involvement, and have refractory but low-bulk disease[1,2]
- Auto-SCT appears to improve overall survival in patients who are transplant-eligible with chemosensitive disease to first salvage therapy, particularly in high-risk patients with early relapse of chemoimmunotherapy (<2 years)[1,2]

Factors for deciding between allo-SCT and auto-SCT for patients in 2L+ relapse/progression[2]

Auto-SCT	Allo-SCT
• Older patients (age 60-75 years) • Medical comorbidities • ≤2-3 prior lines of therapy • PET-negative remission • No marrow involvement	• Age ≤60-65 years • Few or no comorbidities • Available matched donor • Heavily pretreated disease • Chemorefractory relapse • Marrow involvement • Failed stem cell mobilization • Relapse after prior auto-SCT

However, with the increase in number of therapeutic options for FL, including CAR-T, the use of auto- and allo-SCT has decreased in recent years[1-3]

- Safety concerns including treatment-related mortality and graft versus host disease with allo-SCT and the development of secondary malignancies with both auto- and allo-SCT are also a consideration

allo, allogeneic; auto, autologous; CAR-T, chimeric antigen receptor T cell; FL, follicular lymphoma; PET, positron emission tomography; SCT, stem cell transplant.

1. Cahill KE, Smith SM. *Oncology (Williston Park)*. 2022;36(2):97-106. 2. Hamadani M, Horowitz MM. *J Oncol Pract*. 2017;13(12):798-806.
3. Jacobsen E. *Am J Hematol*. 2022;97(12):1638-1651.

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Investigational Therapies for FL as of December 2024

Class	Agents	Population	Trial phase
Antibody–drug conjugates	**Lonca**[1]	**R/R FL (≥1 prior therapies)**	**Phase 2, NCT04998669**
	Brentuximab vedotin + bendamustine[2]	R/R FL (≥1 prior therapies)	Phase 2, NCT04587687
Monoclonal antibodies	Tafasitamab + lenalidomide + rituximab[3]	R/R FL (≥1 prior therapies)	Phase 3, NCT04680052 (InMIND)
	MIL62 + lenalidomide[4]	R/R FL (refractory to rituximab), CD20+	Phase 3, NCT04834024
	Tiselizumab[5]	FL (previously untreated bulky disease)	Phase 2, NCT06704555
CAR-T	Lisocabtagene maraleucel[6]	R/R FL	Phase 3, NCT06313996

Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; R/R, relapsed/refractory.
On the basis of a search of ClinicalTrials.gov (through 12/2/24) limited to phase 2 or 3 trials in follicular lymphoma that are "not yet recruiting," "recruiting," or "active, not recruiting."
References in Notes.

Investigational Therapies for FL as of December 2024

Class	Agents	Population	Trial phase
BsAbs (CD20×CD3)	Mosunetuzumab + lenalidomide[1,2]	R/R FL (≥1 prior therapies), CD20+	Phase 3, NCT04712097 (Celestimo) Phase 1/2, NCT04246086
	Mosunetuzumab + pola (CD79b)[3]	Previously untreated FL	Phase 2, NCT05410418
	Mosunetuzumab + tazemetostat[4]	Previously untreated FL	Phase 2, NCT05994235
	Mosunetuzumab + lenalidomide[5]	Previously untreated FL	Phase 3, NCT06284122 (MorningLyte)
	Mosunetuzumab[6]	FL (low tumor burden or unusual cytological features)	Phase 3, NCT06337318
	Mosunetuzumab + zanubrutinib[7]	R/R FL	Phase 2, NCT06492837 (MOZART)
	Mosunetuzumab + pola (CD79b)[8]	R/R FL (grades 1-3a)	Phase 2, NCT06453044
	Mosunetuzumab[9]	FL (grade 1-3a)	Phase 2, NCT06442475
	Glofitamab + obinutuzumab[10]	Previously untreated FL	Phase 2, NCT05783596
	Epcoritamab + rituximab[11]	Previously untreated FL, CD20+	Phase 2, NCT05783609
	Epcoritamab + lenalidomide[12]	Previously untreated FL	Phase 2, NCT06112847
	Epcoritamab + rituximab + lenalidomide[13]	Previously untreated FL, CD20+	Phase 3, NCT06191744 (EPCORE FL-2)
	Epcoritamab + tazemetostat[14]	R/R GL (Grade 1-3a)	Phase 2, NCT06575686
	Epcoritamab[15]	FL (not accomplishing CR with 1L chemotherapy)	Phase 2, NCT06510361
	Epcoritamab + ibrutinib[16]	R/R FL (Grade 3b)	Phase 1/2, NCT06536049
	Epcoritamab + ASCT [17]	Relapsed FL (Grade 3b)	Phase 2, NCT06287398
	Odronextamab[18]	Previously untreated FL, CD20+	Phase 3, NCT06091254 (OLYMPIA-1)
	Odronextamab + chemotherapy[19]	Previously untreated FL, CD20+	Phase 3, NCT06097364 (OLYMPIA-2)
	Odronextamab + lenalidomide[20]	R/R FL (≥2 prior therapies)	Phase 3, NCT06149286 (OLYMPIA-5)
	AZD5492[21]	R/R FL (≥2 prior therapies)	Phase 1/2, NCT06542250 (TITANium)
BsAbs (CD19×CD3)	AZD0486[22]	R/R FL (≥2 prior therapies)	Phase 2, NCT06526793
	AZD0486 + rituximab[23]	Previously untreated FL	Phase 3, NCT06549595

1L, first-line; ASCT, autologous stem-cell transplantation; BsAb, bispecific antibody; FL, follicular lymphoma; pola, polatuzumab vedotin; R/R, relapsed/refractory. On the basis of a search of ClinicalTrials.gov (through 12/2/24) limited to phase 2 or 3 trials in follicular lymphoma that are "not yet recruiting," "recruiting," or "active, not recruiting." *References in Notes.*

Investigational Therapies for FL as of December 2024 (cont'd)

Class	Agents	Population	Trial Phase
Checkpoint inhibitors	Atezolizumab + obinutuzumab[1]	Previously untreated FL, CD20+	Phase 2, NCT04962126 (FLUORO)
	Pembrolizumab + rituximab[2]	Relapsed FL (≥1 prior therapies)	Phase 2, NCT02446457
BCL-2 inhibitors	Venetoclax + lenalidomide + obinutuzumab[3]	Previously untreated FL	Phase 1/2, NCT03980171 (LEVERAGE)
	Venetoclax + ibrutinib[4]	R/R FL (≥2 prior therapies)	Phase 1/2, NCT02956382
	Venetoclax + ibrutinib + obinutuzumab[5]	Previously untreated FL	Phase 2, NCT04450173
BTK inhibitors	Acalabrutinib + obinutuzumab[6]	Previously untreated FL	Phase 2, NCT04883437
	Acalabrutinib + lenalidomide + rituximab[7]	Previously untreated FL, CD20+	Phase 2, NCT04404088
	Ibrutinib[8]	R/R FL (≥1 prior therapies)	Phase 2, NCT01849263
	Ibrutinib + rituximab[9]	Previously untreated FL	Phase 3, NCT02947347
	Zanubrutinib + antiCD20[10]	R/R FL (≥1 prior therapies)	Phase 3, NCT05100862 (MAHOGANY)
	Zanubrutinib + obinutuzumab + lenalidomide[11]	Previously untreated FL	Phase 2, NCT06549335
	Zanubrutinib + rituximab + venetoclax[12]	Previously untreated FL	Phase 2, NCT06471738
	Zanubrutinib + obinutuzumab[13]	Previously untreated FL	Phase 2, NCT06553352
	Zanubrutinib + rituximab + epcoritamab[14]	R/R FL	Phase 2, NCT06563596
	Zanubrutinib + rituximab[15]	Previously untreated FL	Phase 2, NCT06350318
	Zanubrutinib + G-CHOP[16]	Previously untreated FL	Phase 2, NCT06474481

BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; FL, follicular lymphoma; G-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory.
On the basis of a search of ClinicalTrials.gov (through 12/2/24) limited to phase 2 or 3 trials in follicular lymphoma that are "not yet recruiting", "recruiting", or "active, not recruiting".
References in Notes.

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Investigational Therapies for FL as of December 2024 (cont'd)

Class	Agents	Population	Trial Phase
EZH2 and HDAC inhibitors	Tazemetostat + rituximab + bendamustine[1]	Previously untreated FL	Phase 1/2, NCT05551936
	Tazemetostat + rituximab + lenalidomide[2]	R/R FL (≥1 prior therapies)	Phase 3, NCT04224493
	Abexinostat[3,4]	R/R FL (≥2 prior therapies)	Phase 2, NCT03934567 Phase 2, NCT03600441 (FORERUNNER)
	Valemetostat + rituximab + lenalidomide[5]	R/R FL (≥1 prior therapies)	Phase 1/2, NCT05683171
	SHR2554[6]	R/R FL	Phase 2, NCT06368167
PI3K Inhibitors	Copanlisib + obinutuzumab[7]	Previously untreated FL	Phase 2, NCT05387616
Immunomodulators	Golcadomide + rituximab ± nivolumab[8]	Previously untreated FL	Phase 2, NCT05788081 (TOP-FLOR)
	Golcadomide + obinutuzumab[9]	Previously untreated FL	Phase 2, NCT06108232
	Golcadomide + rituximab[10]	Previously untreated FL	Phase 2, NCT06425302 (GOLSEEK-2)

FL, follicular lymphoma; HDAC, histone deacetylases; PI3K, phosphoinositide 3-kinases; R/R, relapsed/refractory.
On the basis of a search of ClinicalTrials.gov (through 12/2/24) limited to phase 2 or 3 trials in follicular lymphoma that are "not yet recruiting", "recruiting", or "active, not recruiting".
References in Notes.

Lonca Clinical Data: Investigator Initiated Trial in FL

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LOTIS-1: Phase 1 Dose-Escalation and Dose-Expansion Study of Lonca in R/R B-NHL (Including R/R FL)

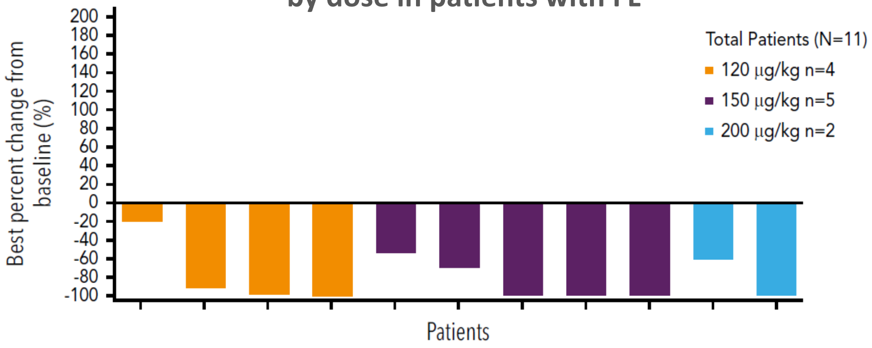
Objective: To determine the maximum tolerated dose and recommended dose(s) for expansion and evaluate safety, clinical activity, pharmacokinetics, and immunogenicity of Lonca

LOTIS-1: Patient demographics[1]	(N = 183)
Age, median (range), years	63.0 (20-87)
Male, n (%)	114 (62.3)
ECOG PS, n (%)	
0-1	160 (87.4)
2-3	23 (12.6)
B-NHL subtype, n (%)	
DLBCL	139 (76.0)
MCL	15 (8.2)
FL[a]	14 (7.7)
CLL	6 (3.3)
Number of lines of prior systemic therapy, median (range)	3 (1-13)
Prior HCT, n (%)	42 (23.0)
Prior CAR-T, n (%)	3 (1.6)
Prior systemic therapy response	
Primary refractory	43 (23.5)
Refractory to most recent therapy	109 (59.6)

[a]One patient with FL also had CLL/small lymphocytic lymphoma recurrence.

LOTIS-1: Outcomes with Lonca[1]	FL (n = 14)	Total (N = 180)
ORR, n (%)	11 (78.6)	82 (45.6)
95% CI	49.2-95.3	38.1-53.1
CR	9 (64.3)	48 (26.7)
PR	2 (14.3)	34 (18.9)
mDOR, months	NR	5.4
mPFS, months	NR	3.1
mOS, months	NR	8.3

LOTIS-1: Best percent change in tumor volume size by dose in patients with FL



LOTIS-1: Grade ≥3 TEAEs reported in ≥5% of patients[1]	(N = 183)
Any	141 (77.0)
Neutrophil count decreased[b]	71 (39.7)
Platelet count decreased[b]	48 (26.7)
GGT increased	39 (21.3)
Anemia	28 (15.3)
Blood ALP increased	12 (6.6)
Lymphocyte count decreased	12 (6.6)
PD	11 (6.0)
Febrile neutropenia	10 (5.5)
Hypokalemia	10 (5.5)

[b]Platelet count decrease and neutrophil count decrease are based on laboratory abnormality reporting; data for 4 patients (1 at 120 µg/kg, 2 at 150 µg/kg, and 1 at 200 µg/kg) were missing for neutrophil count decrease, and data for 3 patients (1 each at 120, 150, and 200 µg/kg) were missing for platelet count decrease.

ALP, alkaline phosphatase; B-NHL, B-cell non-Hodgkin lymphoma; CAR-T, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GGT, gamma-glutamyltransferase; HCT, hematopoietic cell transplantation; MCL, mantle cell lymphoma; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; R, rituximab; R/R, relapsed or refractory; TEAE, treatment emergent adverse events. Hamadani M, et al. Blood. 2021; 137(19):2634-2645.

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Study Rationale: Phase 2 Investigator Initiated Trial of Lonca with Rituximab in R/R FL

Rationale for

Lonca in R/R FL

- In the phase 1 LOTIS-1 study, Lonca demonstrated an ORR of 78.6% and a complete response rate of 64.3% in a subset of 14 patients with R/R FL[1]

Lonca Combined with Rituximab

- Preclinical data have demonstrated durable synergistic activity between Lonca and rituximab-induced cytotoxicity[2]
- Preliminary data from the LOTIS-5 safety run-in demonstrated encouraging antitumor activity (ORR: 80%; CR: 50%) with initial signs of response durability (DOR: 8.02 months) with Lonca plus rituximab in patients with R/R DLBCL[3]

CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; ORR, overall response rate; R/R, relapsed or refractory.

1. Hamadani M, et al. *Blood*. 2021; 137(19):2634-2645.
2. Ryan MC, et al. *Blood*. 2017; 130(18):2018-2026.
3. Kwiatek, et al. Poster presented at: Eleventh Annual Meeting of the Society of Hematologic Oncology (SOHO 2023); September 6-9, 2023; Houston, TX.

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Trial Design: Phase 2 Investigator Initiated Trial of Lonca with Rituximab in R/R FL

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Induction (12 weeks; 21-day cycles)

Cycle 1:
Lonca 150 µg/kg (D1)
Rituximab 375 mg/m² (D1, 8, 15)

Cycle 2:
Lonca 150 µg/kg (D1)
Rituximab 375 mg/m² (D1)

Cycles 3-4:
Lonca 75 µg/kg (D1)

PET/CT evaluation – week 12

Maintenance I (9 weeks)

- CR/PR: Lonca 75 µg/kg (Q3W), Rituximab 375 mg/m² (Q8W)
- SD/PD: Off treatment

PET/CT evaluation – week 21

Maintenance II (18 weeks)

- CR: Rituximab 375 mg/m² (Q8W)
- PR: Lonca 75 µg/kg (Q3W), Rituximab 375 mg/m² (Q8W)
- SD/PD: Off treatment

PET/CT evaluation – EOT

Select inclusion criteria

- R/R FL grade 1, 2, or 3A
- ≥1 line of systemic therapy
- GELF, POD24, or 2nd relapse
- ECOG PS 0-2
- Measurable disease by Lugano classification
- Adequate organ function

Study endpoints

- Primary endpoint: CR at week 12 (Lugano response criteria)
- Secondary endpoints: ORR, safety/tolerability, and 2-year PFS/OS
- Exploratory endpoints: metabolic tumor volume/radiomics analyses, circulatory biomarkers, and HRQoL

CMR, complete metabolic response; CMR, complete metabolic response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; HRQoL, health-related quality of life; Lonca, loncastuximab tesirine; ORR, overall response rate; OS, overall survival; PD, progressive disease; PET/CT, positron emission tomography/computer tomography; PFS, progression-free survival; POD24, disease progression within 24 months; PR, partial response; Q3W, every 3 weeks; Q8W, every 8 weeks; R/R, relapsed or refractory; SD, stable disease.

Alderuccio, et al. Oral presented at: 66th American Society of Hematology (ASH) Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA.

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Patient Demographic and Characteristics: Phase 2 Investigator Initiated Trial of Lonca with Rituximab in R/R FL

Patient demographics (N = 39)	
Age, median (range), years	68 (47-89)
Male, n (%)	21 (53.8)
Hispanic, n (%)	22 (56.4)
Prior transformed FL, n (%)	11 (28.2)
FL grade 3A, n (%)	11 (28.2)
Bone marrow involvement, n (%)	13 (33.3)
ECOG PS, n (%)	
0	29 (74.3)
1	10 (25.6)
Elevated β_2-microglobulin, n (%)	27 (69.2)
Ann Arbor stage, n (%)	
II	7 (17.9)
III-IV	32 (79.1)
FLIPI risk score, n (%)	
0-1	9 (23.1)
2	6 (15.4)
3-5	24 (61.6)
POD24, n (%)	20 (51.3)
High-tumor burden by GELF criteria, n (%)	36 (92.3)
Bulky disease (>7 cm)	9 (23.1)

Prior treatment characteristics (N = 39)	
Refractory to last therapy, n (%)	20 (51.3)
Relapsed FL, n (%)	19 (48.7)
Prior lines of therapy, median (range)	1 (1-6)
≥3 lines of prior therapy, n (%)	11 (28.2)
Prior frontline regimens, n (%)	
R-CHOP	22 (56.4)
Bendamustine with rituximab	10 (25.6)
Rituximab	6 (15.4)
Fludarabine, mitoxantrone, dexamethasone with rituximab	1 (2.6)

Data cutoff: September 13, 2024

Median follow-up: 18 months (95% CI, 12-19.3 months)

ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, follicular lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; Lonca, loncastuximab tesirine; POD24, disease progression within 24 months; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed or refractory.

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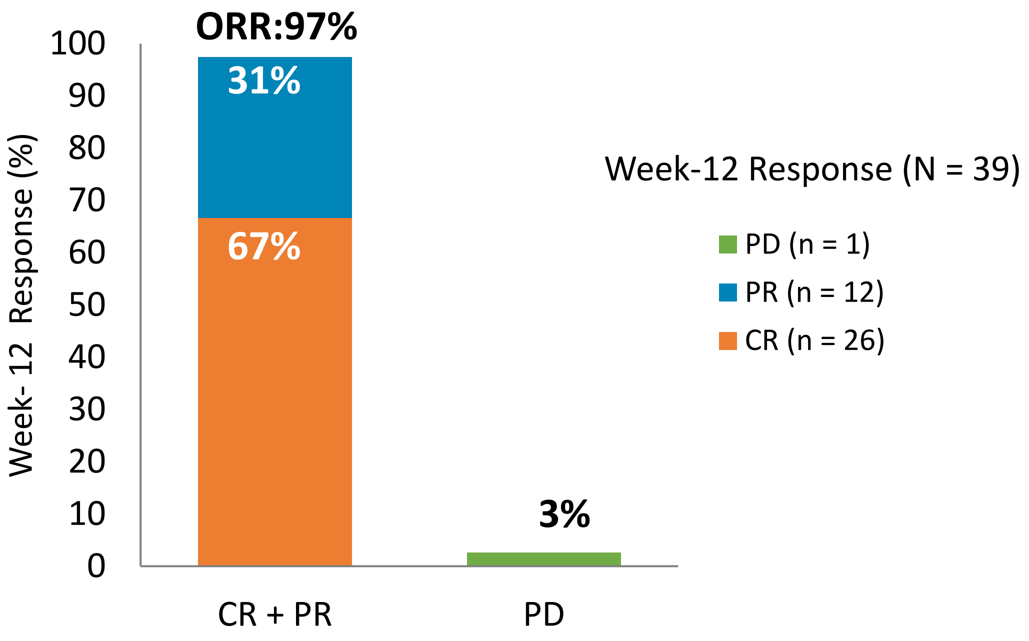
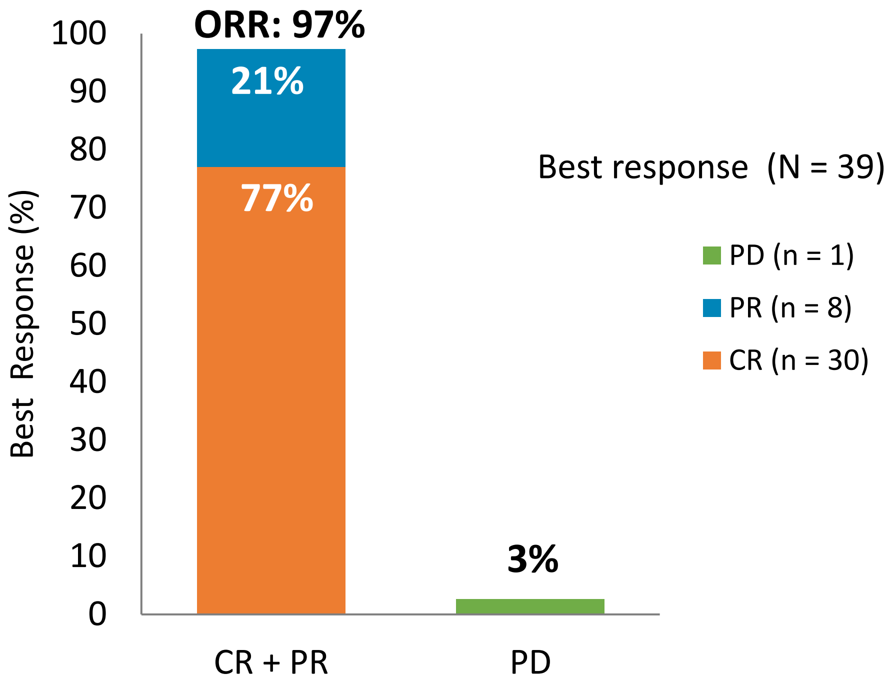
Efficacy: Phase 2 Investigator Initiated Trial of Lonca with Rituximab in R/R FL [1/2]





At 21 weeks, 4 patients converted from PR to CR

C, cycle; CR, complete metabolic response; D, day; FL, follicular lymphoma; FLIPI, follicular lymphoma International Prognostic Index; Lonca, loncastuximab tesirine; ORR, overall response rate; PD, progressive disease; PR, partial response; POD24, disease progression within 24 months; R/R, relapsed or refractory.

Alderuccio JP, et al. Lancet Haematol. 2025;12(1):e23-e34.

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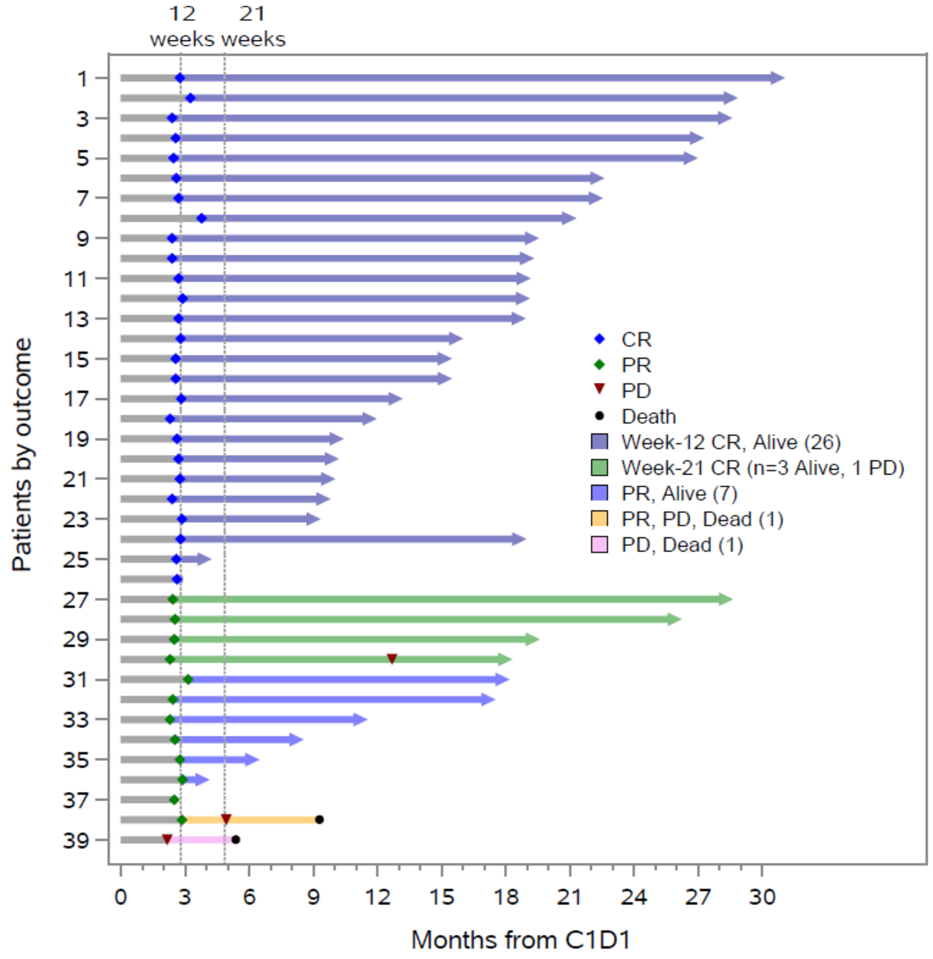
Efficacy: Phase 2 Investigator Initiated Trial of Lonca with Rituximab in R/R FL 2/2



Post-hoc efficacy analyses	n	Best ORR, %	Best CR, %
POD24	20	100	85
High risk FLIPI score	24	96	67
Prior transformed FL	11	100	73
Rituximab with an alkylating agent	32	100	75

C, cycle; CR, complete metabolic response; D, day; FL, follicular lymphoma; FLIPI, follicular lymphoma International Prognostic Index; Lonca, loncastuximab tesirine; ORR, overall response rate; PD, progressive disease; PR, partial response; POD24, disease progression within 24 months; R/R, relapsed or refractory.

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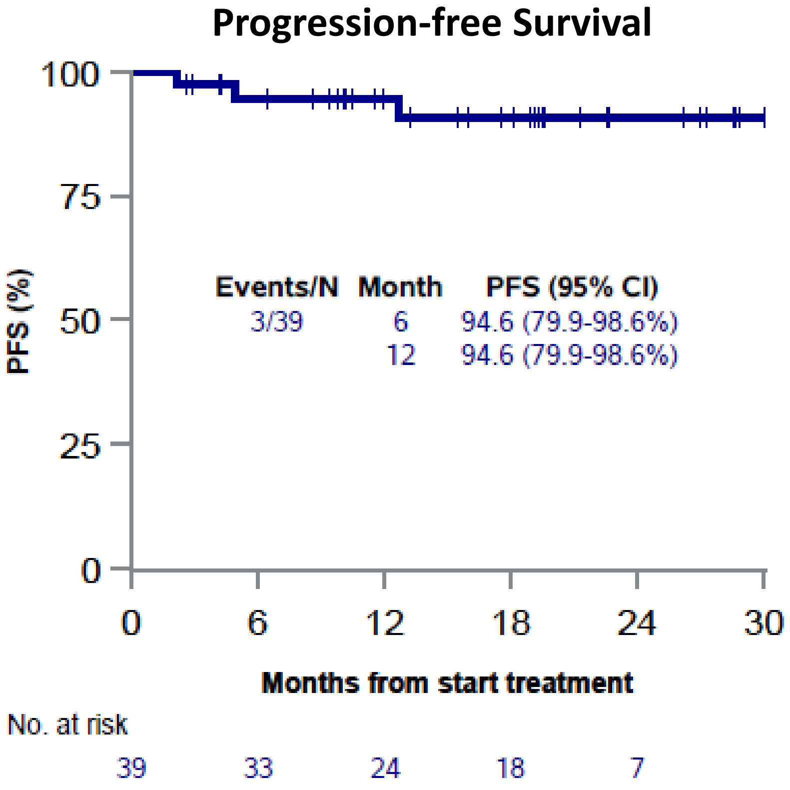

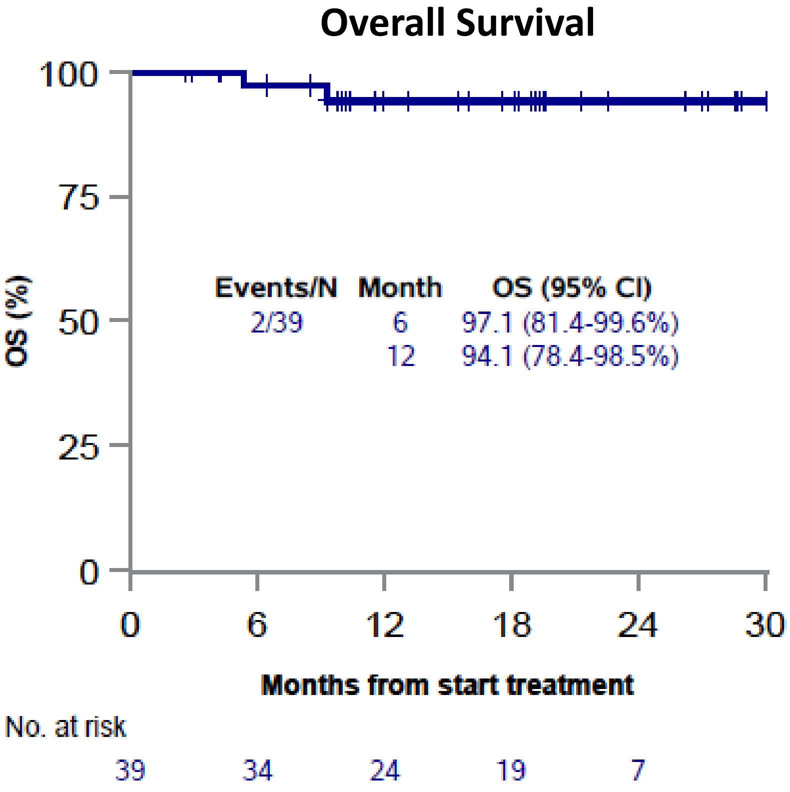

Survival	
12-month PFS, % (95% CI)	94.6 (79.9-98.6)
12-month OS, % (95% CI)	94.1 (78.4-98.5)

FL, follicular lymphoma; Lonca, loncastuximab tesirine; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory.
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Safety: Phase 2 Investigator Initiated Trial of Lonca with Rituximab in R/R FL

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Most Common TEAEs (≥10% for All Grades in 39 Evaluable Patients)				
AEs, n (%)	Any grade	Grade 1-2	Grade 3	Grade 4
Hematological AEs				
Neutropenia	15 (38.5)	10 (25.6)	4 (10.3)	1 (2.6)
Anemia	14 (35.9)	14 (35.9)	0 (0)	0 (0)
Lymphopenia	13 (33.3)	5 (12.8)	5 (12.8)	3 (7.7)
Thrombocytopenia	9 (23.1)	9 (23.1)	0 (0)	0 (0)
Non-hematological AEs				
Hyperglycemia	17 (43.6)	16 (41.0)	1 (2.6)	0 (0)
Increased ALP	16 (41.0)	16 (41.0)	0 (0)	0 (0)
Increased ALT	15 (38.5)	14 (35.9)	1 (2.6)	0 (0)
Fatigue	15 (38.5)	15 (38.5)	1 (2.6)	0 (0)
Increased AST	15 (38.5)	15 (38.5)	0 (0)	0 (0)
Rash maculo-papular	14 (35.9)	14 (35.9)	0 (0)	0 (0)
Localized edema	6 (15.4)	5 (12.8)	1 (2.6)	0 (0)
Photosensitivity	6 (15.4)	6 (15.4)	0 (0)	0 (0)
Generalized edema	6 (15.4)	5 (12.8)	1 (2.6)	0 (0)
Diarrhea	6 (15.4)	6 (15.4)	0 (0)	0 (0)
Pleural effusion	5 (12.8)	5 (12.8)	0 (0)	0 (0)
Dyspnea	5 (12.8)	4 (10.3)	1 (2.6)	0 (0)

Infectious AEs (All Grades in 39 Evaluable Patients)				
Infectious AEs, n (%)	Any grade	Grade 1-2	Grade 3	Grade 4
Upper respiratory infection	5 (12.8)	4 (10.3)	1 (2.6)	0 (0)
Infections, other[a]	5 (12.8)	5 (12.8)	0 (0)	0 (0)
UTI	4 (10.3)	4 (10.3)	0 (0)	0 (0)
Skin infection	3 (7.7)	2 (5.1)	1 (2.6)	0 (0)

[a]Includes 3 cases of COVID-19 infection.

- **Serious AEs occurred in 4 patients (10.3%)**
  - Cellulitis after Lonca extravasation
  - Febrile neutropenia
  - Dyspnea secondary to pleural effusion
  - Generalized edema
- **Disease progression (n = 2) was the most common cause of treatment discontinuation**
- **No treatment-related deaths occurred during the study**

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete response; FL, follicular lymphoma; Lonca, loncastuximab tesirine; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event; URI, upper respiratory tract infection; UTI, urinary tract infection.
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Author Conclusions: Phase 2 Investigator Initiated Trial of Lonca with Rituximab in R/R FL

- Limited duration Lonca + rituximab drove significant CR rates in patients with second-line and later R/R FL with high-tumor burden or POD24
- This study met its primary endpoint with a week 12 CR rate of more than 50%
- The CR rates appeared prolonged with a 12-month PFS of 94.6% and a median PFS that was not reached at the current follow-up
- The safety profile in R/R FL was deemed by the investigator consistent with prior studies in large B-cell lymphoma with no new safety signals
  - Most AEs were grade 1-2, including hyperglycemia, increases in liver enzymes, fatigue, and rash
- This study suggests that a fixed-duration program of Lonca plus rituximab is a promising combination in second-line and later FL

AE, adverse event; CR, complete metabolic response; FL, follicular lymphoma; Lonca, loncastuximab tesirine; PFS, progression-free survival; POD24, progression of diseases within 24 months; R/R, relapsed or refractory.

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Summary

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Summary

- FL is the second most common lymphoma
- While survival rates are high, some patients continue to have poor prognosis
  - Patients with FL with POD24, multiple relapses, and histologic transformation continue to represent unmet needs
- Diagnosis of FL is made on the basis of histology; almost all cases are positive for cell surface CD19, CD20, CD10, and monoclonal immunoglobulin
- Currently, the choice of therapy for FL is highly dependent on patient and disease characteristics, including the stage of diagnosis
  - Approved therapies for FL include bispecific antibodies, BTK inhibitors, CAR-T therapies, EZH2 inhibitors, immunomodulators, and monoclonal antibodies
  - In addition, investigational therapies for FL include antibody–drug conjugates, bispecific antibodies, BCL-2 inhibitors, BTK inhibitors, CAR-T therapies, checkpoint inhibitors, EZH2 inhibitors, HDAC inhibitors, immunomodulators, monoclonal antibodies, and PI3K inhibitors
- In an IIT, Lonca + rituximab has demonstrated a best ORR of 97.4% and a CR of 76.9% in patients with R/R FL with high tumor burden and POD24
  - The safety profile was deemed by the investigator to be consistent with previous studies in large B-cell lymphoma

BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR-T, chimeric antigen receptor T cell; CMR, complete metabolic response; FL, follicular lymphoma; IIT, investigator-initiated trial; ORR, overall response rate; POD24, progression of disease within 24 months; R/R, relapsed/refractory.

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