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FOLLICULAR LYMPHOMA: RECENT AND EMERGING THERAPIES, TREATMENT STRATEGIES, AND REMAINING UNMET NEEDS

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SUMMARY

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- A **personalized approach** to management of follicular lymphoma (FL) continues to emerge, based on disease biology, patient characteristics, and other factors
- Current management of previously untreated and relapsed/refractory (R/R) FL requires an understanding of **available 1st-line treatment options** and new therapies under development
- While the number of available therapies to treat FL has increased, the best approach to select the most appropriate treatment strategy for an individual patient at a particular time, continues to be elucidated

HETEROGENEITY OF FL PRESENTS CHALLENGES

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- FL is a **heterogeneous** disease with varying prognosis
  - **Spontaneous regressions** occur in 5-10% of patients[1]
  - Whilst many patients can be initially observed, most require therapy 3-4 years post diagnosis[2]
  - ~20% will have **early relapse** ⩽2 (POD 24) years[3]
- Accordingly, the course of the disease is typically protracted with **multiple remissions** and **relapses**
- Continued elucidation of the biologic and **molecular basis** of FL is leading to identification of new potential therapeutic avenues
- Despite these advances, the **heterogeneity of FL** presents **challenges**, including selection of appropriate management for individual patients

FL, follicular lymphoma; POD24, progression of disease within 24 months.

1. Ardeshna KM, et al. Lancet Oncol 2014;15:424-4235; 2. Soumerai JD, et al. Blood 2016;128:1777-1777;
3. Casulo C, et al. J Clin Oncol 2015;33:2516-2522.

CURRENT PROGNOSTIC MODELS HAVE LIMITATIONS

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- Current **risk stratification models** do not have sufficient sensitivity/specificity to guide decision making and remain primarily research tools:

Model	Criteria	Risk stratification	Prognosis
FLIPI[1,2]	1. Age: >60 y 2. Ann Arbor Stage: III–IV 3. Hb concentration: <12 g/dL 4. Number of nodal sites: >4 5. Serum LDH concentration: > normal	Low: 0–1 risk factors	2-y OS: 98%; 2-y PFS: 84%
		Intermediate: 2 risk factors	2-y OS: 94%; 2-y PFS: 72%
		High: 3–5 risk factors	2-y OS: 87%; 2-y PFS: 65%
FLIPI-2[3]	1. Age: >60 y 2. Bone marrow involvement: yes 3. Hb concentration: <12 g/dL 4. Greatest diameter of largest involved node: >6 cm 5. Serum β2 microglobulin concentration: >ULN	Low: 0–1 risk factors	3-y PFS: 91%
		Intermediate: 2 risk factors	3-y PFS: 69%
		High: 3–5 risk factors	3-y PFS: 51%
GELF[4]	1. Tumor size: any site >7 cm or ⩾3 sites >3 cm 2. B symptoms: yes 3. Spleen: below umbilical line 4. Compressive symptoms: yes 5. Pleural or peritoneal effusion: yes 6. Leukemic phase >5 × 10^9/L 7. Neutropenia (<1 × 10^9/L) or thrombocytopenia (<100 × 1^{09}/L) due to disease	High tumor burden: ⩾1 risk factors	

FLIPI, Follicular Lymphoma International Prognostic Index; Groupe d'Etude des Lymphomes Folliculaires; Hb, haemoglobin; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal; y, year

1. Solal-Celigny P, et al. Blood 2004;104:1258-1265, 2. Nooka AK, et al. Ann Oncol 2013;24:441-448, 3. Federico M, et al. J Clin Oncol 2009;27:4555-4562, 4. Brice P, et al. J Clin Oncol 1997;15:1110-1117.

TREATMENT OPTIONS IN NEWLY-DIAGNOSED FL

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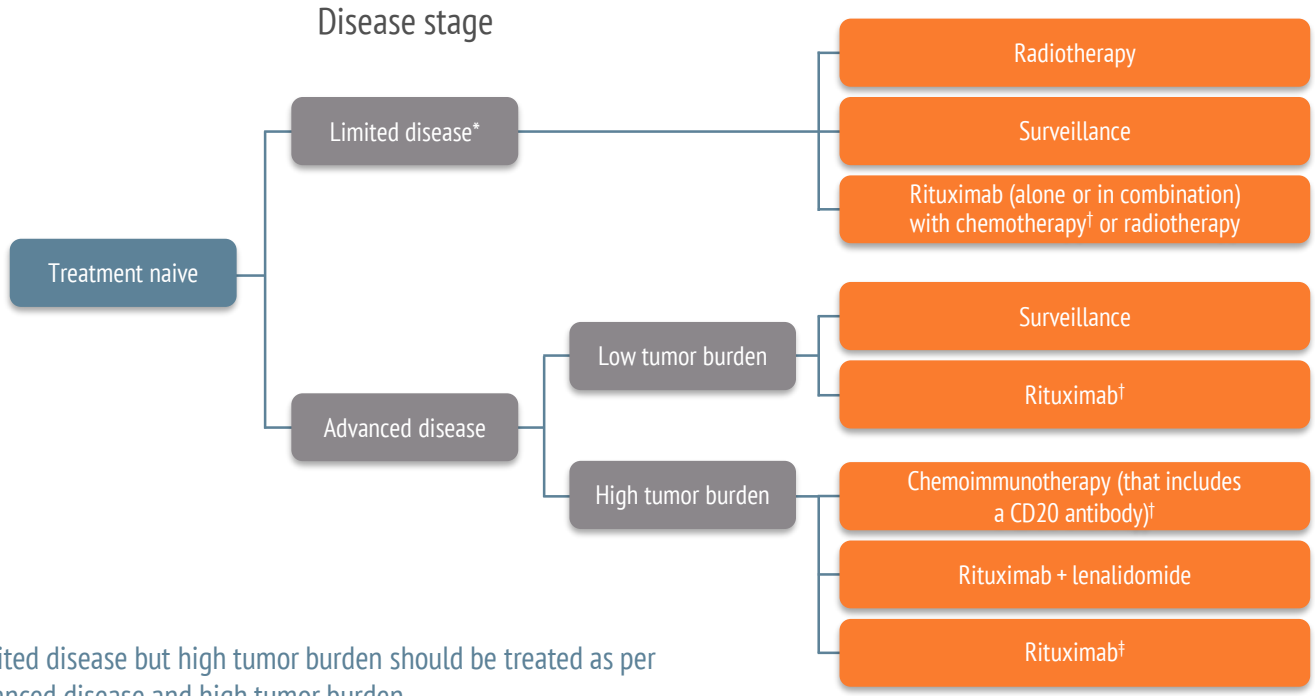
- **Newly-diagnosed FL** can be broadly classified as limited- or advanced-stage disease, which can further be classified based on the **degree of tumor burden**, with the choice of management varying accordingly



*Patients with limited disease but high tumor burden should be treated as per patients with advanced disease and high tumor burden.

†With or without anti-CD20 maintenance therapy.
‡For frail patients; FL, follicular lymphoma.

TREATMENT OPTIONS IN R/R FL

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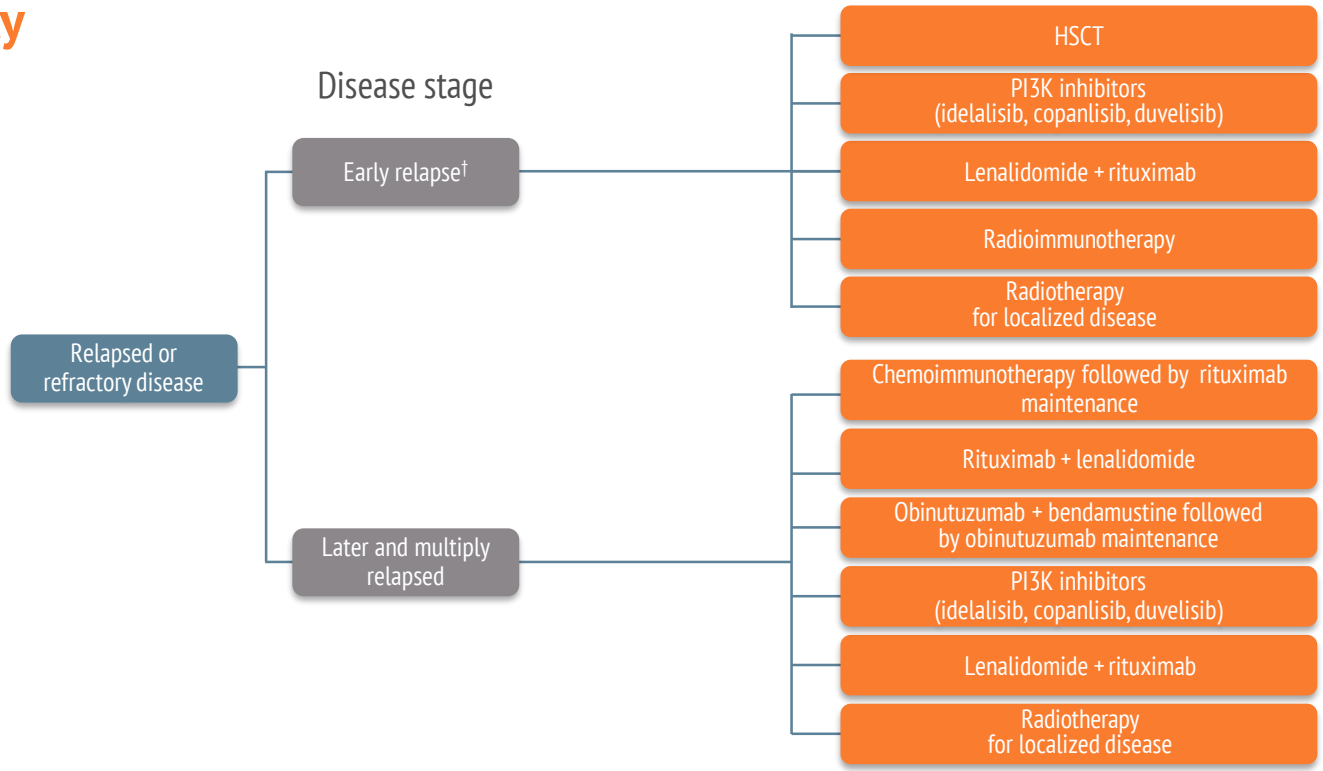
- In patients with R/R FL, **successive lines of therapy** will often be required in the disease course, and the choice of each treatment should **aim to achieve disease control, promote QoL**, and minimize **treatment-related toxicity**



†Relapse within 2 years of initial therapy (POD 24, progression of disease within 24 months).
FL, follicular lymphoma; HSCT, haemopoietic stem cell transplantation; R/R, relapsed/ refractory; QoL, quality of life.

TREATMENT OPTIONS ARE CONTINUALLY EXPANDING IN FL

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- The **number of therapies** available to treat FL has increased together with an improved understanding of the underlying **biologic basis** of disease
- However, the **best approach** to select the most appropriate treatment strategy for an individual patient at a particular time continues to be **elucidated**
- Enrollment in clinical trials evaluating emerging therapies remains a high priority for patients with R/R FL, especially those-who are refractory to both rituximab and alkylating agents (**double refractory**)

FL, follicular lymphoma; R/R, relapsed/refractory.

INVESTIGATIONAL THERAPIES

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- Investigational therapies discussed this review include:

Agent	Type
BCL-2 inhibitors	
Venetoclax	BCL-2 inhibitor
Histone-modifying enzyme inhibitors	
Tazemetostat	EZH2 inhibitor
CPI-1205	EZH2 inhibitor
Abexinostat	HDAC inhibitor
Mocetinostat	HDAC inhibitor
Panobinostat	HDAC inhibitor
Vorinostat	HDAC inhibitor
Immune checkpoint inhibitors	
Atezolizumab	PD-L1 inhibitor
Nivolumab	PD-1 inhibitor
Pembrolizumab	PD-1 inhibitor

Agent	Type
B-cell receptor pathway inhibitors	
Umbralisib	PI3K inhibitor
ME-401	PI3K inhibitor
Cerdulatinib	Syk/Jak inhibitor
Ibrutinib	BTK inhibitor
Antibody-drug conjugates	
Polatuzumab vedotin	Anti-CD79 mAb conjugated to a microtubule toxin
Bispecific antibodies	
Mosunetuzumab	Bispecific CD3 and CD20 inhibitor
Anti-CD47 therapies	
Hu5F9-G4	CD47 antigen inhibitor
CAR-T	
Tisagenlecleucel	
Axicabtagene ciloleucel	
JCAR017	

BCL-2, B-cell leukemia/lymphoma-2; BTK, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; HDAC, histone deacetylasetransferase; mAb, monoclonal antibody; PD-L1, programmed death–ligand 1; R/R, relapsed/ refractory.

REMAINING UNMET NEEDS IN FL (1)

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- While the armamentarium of FL therapies has expanded, the optimal approach to **selecting and sequencing treatments** for an individual patient continues to be elucidated:

Unmet need	Current practice[a]	Areas of research and potential solutions[a]
Selecting the most appropriate treatment for an individual patient at a particular time	• **Identifying patients** with limited disease who are candidates for RT vs R monotherapy or CIT as front-line management is not always clear[b] • **Identifying therapies** to manage disease refractory to anti-CD20 regimens is difficult, as the activity and safety of investigational agents in this setting has been limited	• **Consensus** is needed regarding how to manage patients with high risk disease • Development of novel therapies in FL should consider how to tailor and **optimize** the **benefit–risk ratio** • Determining **predictive biomarkers** of progression, response and resistance to improve patient selection for observation and intervention • **Therapeutic strategies** should be developed to reduce the risk for **histologic transformation**

[a]For brevity, some text has been re-worded; full recommendations can be found in the manuscript; [b]it is not known whether surveillance should be a management option for these patients in the context of the availability of active and minimally-toxic therapies.
CIT, chemoimmunotherapy; FL, follicular lymphoma; R, rituximab; RT, radiotherapy.

REMAINING UNMET NEEDS IN FL (2)

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Unmet need	Current practice[a]	Areas of research and potential solutions[a]
Availability of a clinically useful tool to identify patients with high-risk disease	• Most **prognostic tools** do not guide therapy, are measured at diagnoses and never measured again during the disease course as they have not been validated in these later settings	• Prospective validation, head-to-head comparisons, and international consensus for **clinically useful tools** to identify patients with high-risk disease • Potential integration of molecular, clinical and imaging parameters may be required to define with improved prognostic accuracy
Specific genetic and epigenetic aberrations in an individual patient are not currently accounted for in their management	• Therapies **targeting molecular alterations** do not feature in the current standard-of-care	• A better understanding of **disease biology** may reveal new therapeutic avenues • **Targeted therapies** need to be **matched** to individual disease biology

[a]For brevity, some text has been re-worded; full recommendations can be found in the manuscript.
CIT, chemoimmunotherapy; FL, follicular lymphoma; R, rituximab; RT, radiotherapy.

CONCLUSIONS (1)

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- Significant strides have been made in outcomes for FL patients
- The **next priorities** must tackle the subsets of patients that are early progressors or multiply relapsed by defining optimum strategies to improve survival
- Successfully achieving this will require:
  1. Improved prognostication
  2. Understanding and integration of the disease
  3. Delineating molecular determinants of response and resistance to existing and emergent therapies
- Most notably, **POD24** has been shown to be a powerful **predictor of poor outcome**, although it is not clear if it can become a standard surrogate endpoint to evaluate efficacy of investigational treatments

FL, follicular lymphoma; POD24, progression of disease within 24 months of completing induction chemoimmunotherapy.

CONCLUSIONS (2)

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- Current FL treatment strategies are based on a "**one size fits all**" approach; specific **genetic** and **epigenetic aberrations** in an individual patient are **not currently accounted for in their management**
- **No genomic studies** can be currently recommended with sufficient validation, although this is an area of ongoing investigation
- In the future, a **personalized approach** could help determine the most appropriate treatment for an individual patient
  - Based on specific patient, clinical, genetic, and epigenetic factors - improving the ability to marry disease biology to therapy

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