PERSPECTIVES FOR PHARMACY PRACTICE

Implementing Epigenetic-targeting Therapies in Follicular Lymphoma

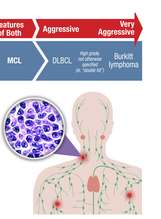
DISEASE BACKGROUND

14,000 estimated new cases of FL diagnosed in the United States annually

63 years Median age at diagnosis

Indolent	Features of Both	Aggressive	Very Aggressive
Follicular lymphoma (FL), CLL, MZL, WM	MCL	DLBCL (High grade, not otherwise specified; aka "double hit")	Burkitt lymphoma

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinemia (lymphoplasmacytic lymphoma)



Follicular lymphoma (FL) is the most common subtype of indolent NHL

FL makes up about 22% of all NHL cases. FL has generally favorable outcomes but a variable clinical course. Recent studies have elucidated that early disease progression in FL occurs in 20% of patients.

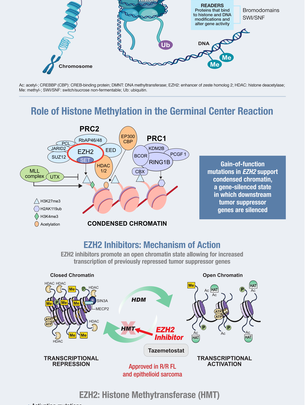
40% of all NHL cases are indolent subtypes

22% of all NHL cases are FL

Relapse of FL within 24 months of chemoimmunotherapy is now established as a robust marker of poor survival, leading to increased risk of death.

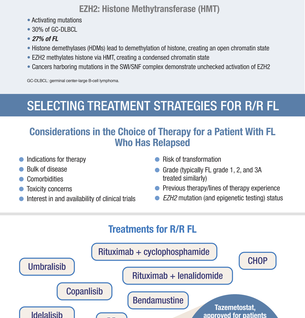
20% of all FL cases are relapsed/refractory (R/R)

EPIGENETICS IN THE PATHOLOGY AND TREATMENT OF FL



Ac: acetyl; CREBBP (CBP): CREB-binding protein; DNMT: DNA methyltransferase; EZH2: enhancer of zeste homolog 2; HDAC: histone deacetylase; Me: methyl-; SWI/SNF: switch/sucrose non-fermentable; Ub: ubiquitin.

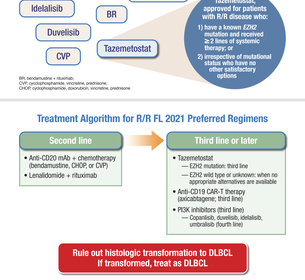
Role of Histone Methylation in the Germinal Center Reaction



Gain-of-function mutations in *EZH2* support condensed chromatin, a gene-silenced state in which downstream tumor suppressor genes are silenced

EZH2 Inhibitors: Mechanism of Action

EZH2 inhibitors promote an open chromatin state allowing for increased transcription of previously repressed tumor suppressor genes



Approved in R/R FL and epithelioid sarcoma

EZH2: Histone Methyltransferase (HMT)

- Activating mutations
- 30% of GC-DLBCL
- ***27% of FL***
- Histone demethylases (HDMs) lead to demethylation of histone, creating an open chromatin state
- EZH2 methylates histone via HMT, creating a condensed chromatin state
- Cancers harboring mutations in the SWI/SNF complex demonstrate unchecked activation of EZH2

GC-DLBCL, germinal center-large B-cell lymphoma.

SELECTING TREATMENT STRATEGIES FOR R/R FL

Considerations in the Choice of Therapy for a Patient With FL Who Has Relapsed

- Indications for therapy
- Bulk of disease
- Comorbidities
- Toxicity concerns
- Interest in and availability of clinical trials
- Risk of transformation
- Grade (typically FL grade 1, 2, and 3A treated similarly)
- Previous therapy/lines of therapy experience
- *EZH2* mutation (and epigenetic testing) status

Treatments for R/R FL

- Rituximab + cyclophosphamide
- CHOP
- Umbralisib
- Rituximab + lenalidomide
- Copanlisib
- Bendamustine
- Idelalisib
- BR
- Duvelisib
- Tazemetostat
- CVP

Tazemetostat, approved for patients with R/R disease who:

1) have a known *EZH2* mutation and received ≥ 2 lines of systemic therapy; or

2) irrespective of mutational status who have no other satisfactory options

BR, bendamustine + rituximab; CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone

Treatment Algorithm for R/R FL 2021 Preferred Regimens

Second line

- Anti-CD20 mAb + chemotherapy (bendamustine, CHOP, or CVP)
- Lenalidomide + rituximab

Third line or later

- Tazemetostat
  - EZH2 mutation: third line
  - EZH2 wild type or unknown: when no appropriate alternatives are available
- Anti-CD19 CAR-T therapy (axicabtagene; third line)
- PI3K inhibitors (third line)
  - Copanlisib, duvelisib, idelalisib, umbralisib (fourth line)

Rule out histologic transformation to DLBCL if transformed, treat as DLBCL

DRUG INTERACTIONS: DETAILS MATTER

Tazemetostat Oral medication

Mild adverse events (Mostly grade 1-2): gastrointestinal disturbances, cytopenia

CYP3A4 substrate (major)

Azole antifungals
Diltiazem
Verapamil
Protease inhibitors
Clarithromycin
Grapefruit juice

Tazemetostat

P-gp ABCB1 substrate (minor)

Amiodarone
Atorvastatin
Simvastatin
Propranolol
Carvedilol
Cyclosporine
Digoxin
Diltiazem

CYP3A4 inducer (weak)

Dose Modifications for Drug Interactions

Concurrent use with strong or moderate CYP3A4 inhibitors is discouraged
If a moderate CYP3A4 inhibitor must be used, follow these dosing recommendations:

Currently Administered Dose	Dose Adjustments for Moderate CYP3A4 Inhibitors
800 mg twice daily	400 mg twice daily
600 mg twice daily	400 mg in the morning and 200 mg in the evening
400 mg twice daily	200 mg twice daily

- No data are currently available to recommend dose adjustments for concomitant CYP3A4 inducers
- Don't forget to resume normal tazemetostat dosing if the offending agent is discontinued!

MULTIDISCIPLINARY AND MULTIFACETED CARE

KEY TAKE-AWAY MESSAGES

- FL makes up about 22% of all NHL cases; early disease progression in FL occurs in ~20% of patients
- IB-cell lymphomas originating from the germinal center (FL, DLBCL) may be the most sensitive to epigenetic therapies
- **EZH2 inhibitors** have enhanced efficacy in *EZH2*-mutated lymphomas and perhaps copy number gain-of-function conditions such as FL
  - Inhibition of EZH2 may restore normal LZ-DZ recycling, interactions with T cells, and immune surveillance
- Tazemetostat is the first EZH2 inhibitor approved for patients with R/R disease who have a known *EZH2* mutation and have received ≥ 2 lines of systemic therapy or for patients with R/R disease irrespective of mutational status who have no other satisfactory options

IB: immunoblastic; LZ-DZ: light zone-dark zone.

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