

Pharmacotherapy Updates in Lymphoma



FLASCO Fall 2021

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Objectives



Understand the MOA of the newly approved pharmacologic agents in lymphoma

Discuss their place in therapy

Understand and apply the pharmacist role to pharmacotherapy management of these agents

Abbreviations



- ADC: antibody-drug conjugate
- AdjBW: adjusted body weight
- ALT: alanine aminotransferase
- AST: aspartate transaminase
- BTK: Bruton tyrosine kinase
- CK1: casein kinase 1 epsilon
- CMV: cytomegalovirus
- DLBCL: diffuse large B-cell lymphoma
- DOR: duration of response
- FL: follicular lymphoma
- MCL: mantel cell lymphoma
- MOA: Mechanism of action
- MZL: marginal zone lymphoma
- NR: not reached
- ORR: overall response rate
- PBD = pyrrolbenzodiazepine
- PI3K: phosphatidylinositol-3-kinase
- PJP: Pneumocystis jirovecii pneumonia
- R/R: relapsed or refractory
- TSP: tumor suppressor protein
- XPO1: exportin 1

Outline



Loncastuximab tesirine-lpyl

Umbralisib

Tafasitamab-cxix + lenalidomide

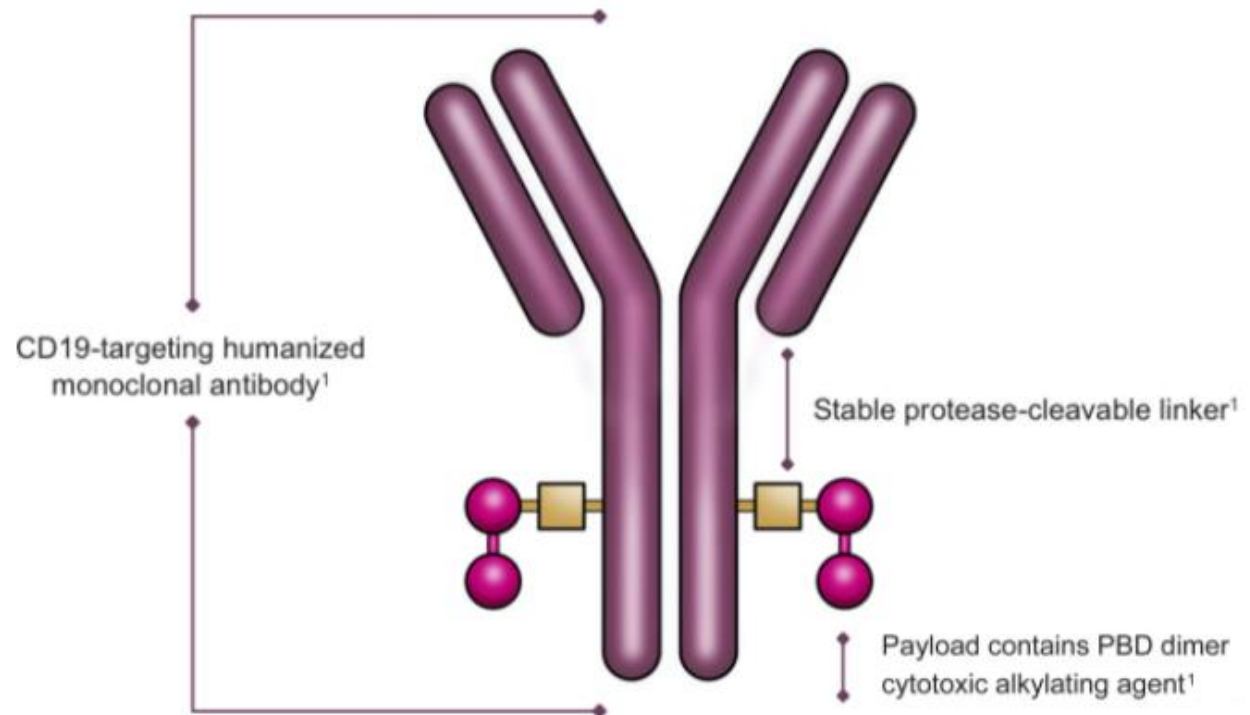
Zanubrutinib

Selinexor

Loncastuximab tesirine-Ipyl



- MOA: CD19-directed antibody and alkylating agent conjugate
 - Bind to CD19 → internalized into cell → release PBD dimer cytotoxin
 - PBD dimer—an alkylating agent—binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks
- induce tumor cell death



Loncastuximab tesirine-Ipyl



- Place in therapy: after ≥ 2 lines of systemic therapy
- FDA approval: adult patients with R/R large B-cell lymphoma
 - DLBCL not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma
- NCCN guidelines category 2A recommendation

Loncastuximab tesirine-Ipyl



- Clinical data and FDA approval
- FDA approval on April 23, 2021
- LOTIS-2 study
 - Open-label, single-arm phase II trial
 - 145 adult patients with R/R DLBCL or high-grade B-cell lymphoma after at least two prior systemic regimens
 - Main efficacy outcome measure was ORR

Loncastuximab tesirine-Ipyl



- Dosing:
 - Cycles 1 & 2: 0.15 mg/kg every 3 weeks
 - Cycle 3 and beyond: 0.075 mg/kg every 3 weeks
 - Continue therapy until progressive disease or unacceptable toxicity
- Administration: IV over 30 minutes
- Premedication: dexamethasone 4 mg PO or IV twice daily for 3 days beginning the day **before** loncastuximab tesirine-Ipyl

Loncastuximab tesirine-Ipyl



- Results:
 - ORR → 48.3% (95% CI: 39.9, 56.7) with a complete response rate of 24.1% (95% CI: 17.4, 31.9)
 - Median follow-up of 7.3 months, median response duration was 10.3 months (95% CI: 6.9, NE)

Loncastuximab tesirine-Ipyl



- Adverse reactions:
 - Thrombocytopenia 58%
 - Neutropenia 52%
 - Anemia 51%
 - Increased gamma-glutamyltransferase 57%
 - Hyperglycemia 48%
 - Transaminase elevation (AST 41%, ALT 34%)
 - Fatigue 38%
 - Hypoalbuminemia 37%
 - Rash 30%
 - Edema 28%
 - Nausea 23%
 - Musculoskeletal pain 14%

Loncastuximab tesirine-Ipyl



- Clinical pearls and pharmacist role in management:
 - For patients with a BMI ≥ 35 kg/m², calculate dose based on adjusted body weight (AdjBW): AdjBW in kg = 35 kg/m² times (height in meters)².
 - Dosing **decreases** starting with cycle 3
 - Premedicate with dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day **before**
 - **Consider giving reminder calls or calendars to patients**

Loncastuximab tesirine-Ipyl

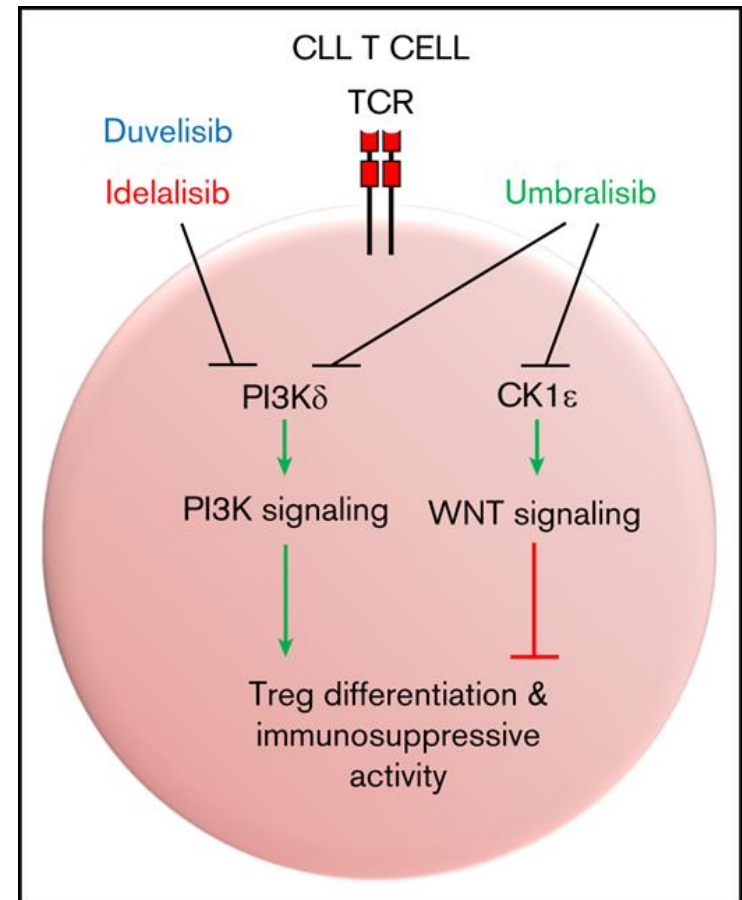


- Clinical pearls and pharmacist role in management:
 - Cutaneous Reactions → advise patients to minimize or avoid exposure to direct natural or artificial sunlight, and to protect skin by wearing sun-protective clothing and/or the use of sunscreen products
 - Due to edema, advise patient to keep a weight log
 - Patients with weight gain of >1 kg from day 1 of cycle one or with edema or pleural effusions received standard doses of spironolactone
 - Refer to package insert regarding dose modifications and delays for adverse reactions

Umbralisib



- MOA: dual inhibitor of PI3K δ and CK1 ϵ with improved selectivity for the PI3K δ isoform
- Activation of the PI3K/AKT/mTOR pathway is a common feature of MZL and FL that results in lymphoma cell growth



Umbralisib



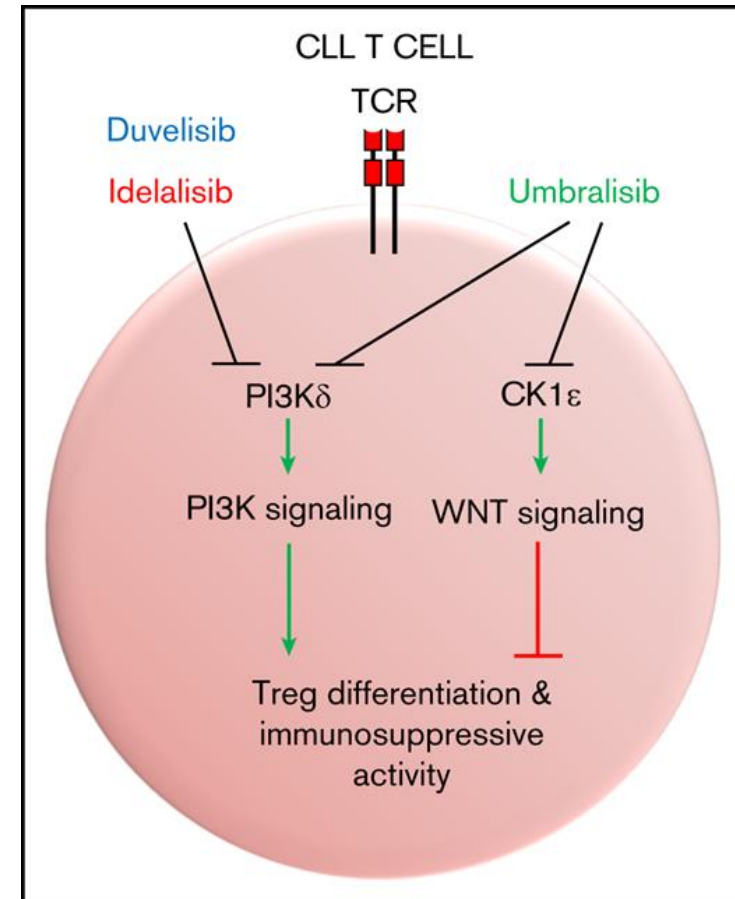
- The delta isoform is highly expressed in normal and malignant B lymphocytes and plays an important role in cell **proliferation, cell survival, and antibody production**

PI3K isoform	Tissue/cell expression	Prominent function
alpha α	Broad distribution ²	<ul style="list-style-type: none">• Plays a role in tumorigenesis^{2,3}• Involved in insulin signaling and glucose metabolism^{2,3}
beta β	Broad distribution ²	<ul style="list-style-type: none">• Involved in platelet activation⁴• Plays a role in the development of thrombotic diseases⁴
gamma γ	T cells, macrophages, neutrophils ⁵⁻⁷	<ul style="list-style-type: none">• Involved in the innate immune response, suppresses inflammation^{5,6}
delta δ	B cells ^{5,8}	<ul style="list-style-type: none">• Involved in the activation, proliferation, and survival of B cells^{5,8,9}

Umbralisib



- Inhibition of CK1-epsilon
 - CK1-epsilon is an important component in the (canonical and noncanonical) Wnt/beta-catenin signaling pathway
 - Inhibition of CK1-epsilon may have effects on:
 - T-cell function and survival
 - Blocks lymphoma cell proliferation by suppressing oncogenes like MYC



Umbralisib



- Clinical data and FDA approval
- FDA approved on February 5, 2021:
 - R/R MZL who have received at least **one** prior anti-CD20-based regimen
 - R/R FL who have received at least **three** prior lines of systemic therapy
- NCCN guidelines category 2A recommendation
- UTX-TGR-205 study:
 - Two single-arm cohorts of an open-label, multi-center trial
 - MZL: 69 patients with MZL who received at least one prior therapy, including an anti-CD20 containing regimen
 - FL: 117 patients with FL after at least 2 prior systemic therapies
 - Efficacy measures were ORR and DOR

Umbralisib



- Dosing and administration:
 - Umbralisib 800 mg orally once daily with food
 - Four 200 mg tablets
 - Continue until disease progression or unacceptable toxicity

Umbralisib



- Results:
 - MZL
 - ORR was 49% (95% CI: 37.0, 61.6) with 16% achieving complete responses
 - Median DOR was not reached (95% CI: 9.3, NE) in these patients
 - FL
 - ORR was 43% (95% CI: 33.6, 52.2) with 3% achieving complete responses
 - Median DOR was 11.1 months (8.3, 16.4)

Umbralisib



- Adverse reactions:
 - Increased creatinine 79 %
 - Diarrhea (diarrhea-colitis) 58%
 - Fatigue 41%
 - Nausea 38%
 - Musculoskeletal pain 27%
 - Thrombocytopenia 26%
 - Vomiting 21%
 - Upper respiratory tract infection 21%
 - Decreased appetite 19%
 - Abdominal pain 19%
 - Rash 18%
 - Neutropenia 33 %
 - Anemia 27%
 - transaminase elevation and hypokalemia >20%

Umbralisib



- Clinical pearls and pharmacist role in management:
 - Allergic Reactions due to inactive ingredient FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma)
 - Provide prophylaxis for PJP during treatment
 - Consider prophylactic antivirals during treatment to prevent CMV infection and reactivation
 - Monitor neutrophil counts at least every 2 weeks for the first 2 months and at least weekly in patients with neutrophil counts $<1 \times 10^9/L$

Umbralisib



- Clinical pearls and pharmacist role in management:
 - Diarrhea-colitis and transaminase elevation were the most common reasons for dose modifications

Dose reduction	Dosage
First	600 mg PO daily
Second	400 mg PO daily
Subsequent	Permanently discontinue UKONIQ in patients unable to tolerate 400 mg orally daily

- No recommended dose modifications due to drug drug interactions
- Pill burden: available in 200 mg tablets

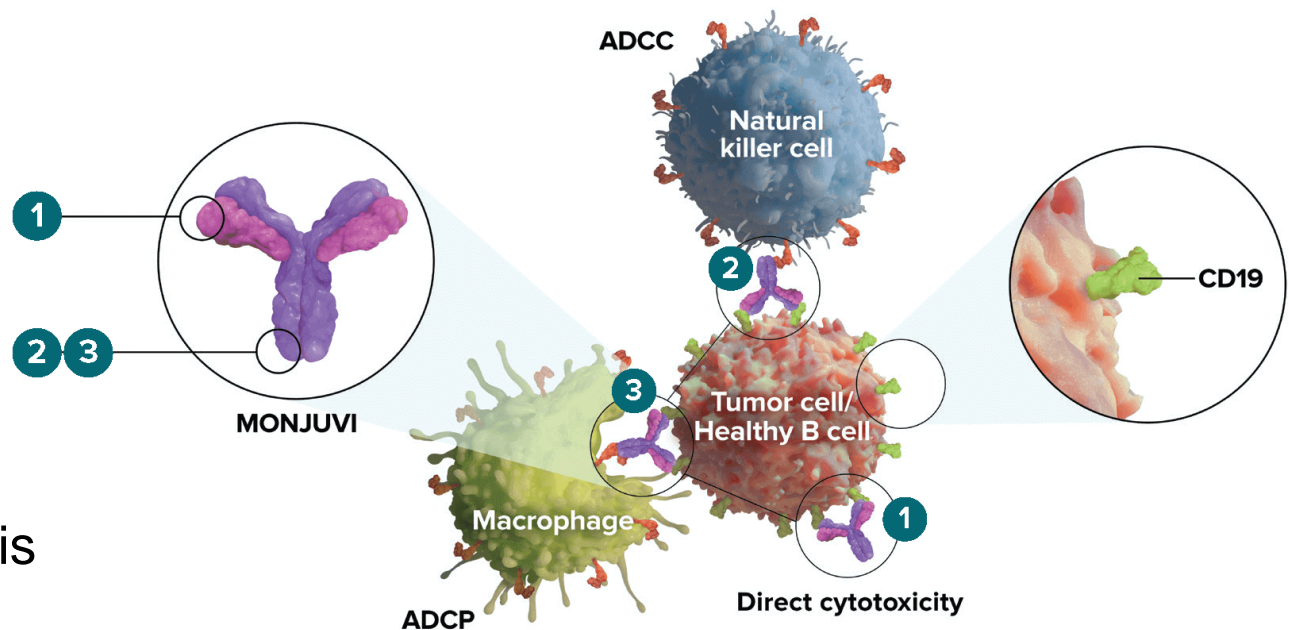
Tafasitamab-cxix + lenalidomide



- MOA

- Fc-modified monoclonal antibody that binds to the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes
- Upon binding to CD19, tafasitamab-cxix mediates B-cell lysis through:

1. Apoptosis
2. Antibody-dependent cellular cytotoxicity
3. Antibody-dependent cellular phagocytosis



Tafasitamab-cxix + lenalidomide



- Place in therapy:
 - In combination with lenalidomide for adult patients with R/R DLBCL with one to three systemic regimens (with at least one anti-CD20 therapy) who are not eligible for autologous stem cell transplant
 - DLBCL not otherwise specified including DLBCL arising from low grade lymphoma
- NCCN guidelines category 2A recommendation

Tafasitamab-cxix + lenalidomide



- Clinical data and FDA approval
- FDA approval on July 31, 2020
- L-MIND study:
 - Open label, multicenter single-arm trial
 - 81 patients with R/R DLBCL and one to three systemic regimens (with at least one anti-CD20 therapy) who are not eligible for autologous stem cell transplant
 - Main efficacy outcome measure was ORR

Tafasitamab-cxix + lenalidomide



- Dosing:
 - Tafasitamab-cxix 12 mg/kg IV with lenalidomide (25 mg PO on days 1 to 21 of each 28-day cycle) for maximum of 12 cycles, followed by tafasitamab-cxix as monotherapy

Cycle (28 days)	Dosing Schedule
Cycle 1	12 mg/kg on days 1, 4, 8, 15, and 22 (in combination with lenalidomide)
Cycle 2 and 3	12 mg/kg on days 1, 8, 15, and 22 (in combination with lenalidomide)
Cycle 4 to 12	12 mg/kg on days 1 and 15 every 28 days (in combination with lenalidomide)
Cycle 13 and beyond	12 mg/kg on days 1 and 15 every 28 days

- IV infusion 70 mL/h for the first 30 minutes, then, increase the rate so that the infusion is administered within 1.5 to 2.5 hours
- Administer all subsequent infusions within 1.5 to 2 hour

Tafasitamab-cxix + lenalidomide



- Results:
 - ORR → 60 % (95% CI: 48.4-70.9) complete responses in 43 % and partial responses in 18% of patients. Median response duration was 21.7 months

Tafasitamab-cxix + lenalidomide



- Adverse reactions:
 - Neutropenia 51%
 - Fatigue 38%
 - Anemia 36%
 - Diarrhea 36%
 - Thrombocytopenia 31%
 - Cough 26%
 - Pyrexia 24%
 - Peripheral edema 24%
 - Respiratory tract infection 24%
 - Decreased appetite 22%

Tafasitamab-cxix + lenalidomide

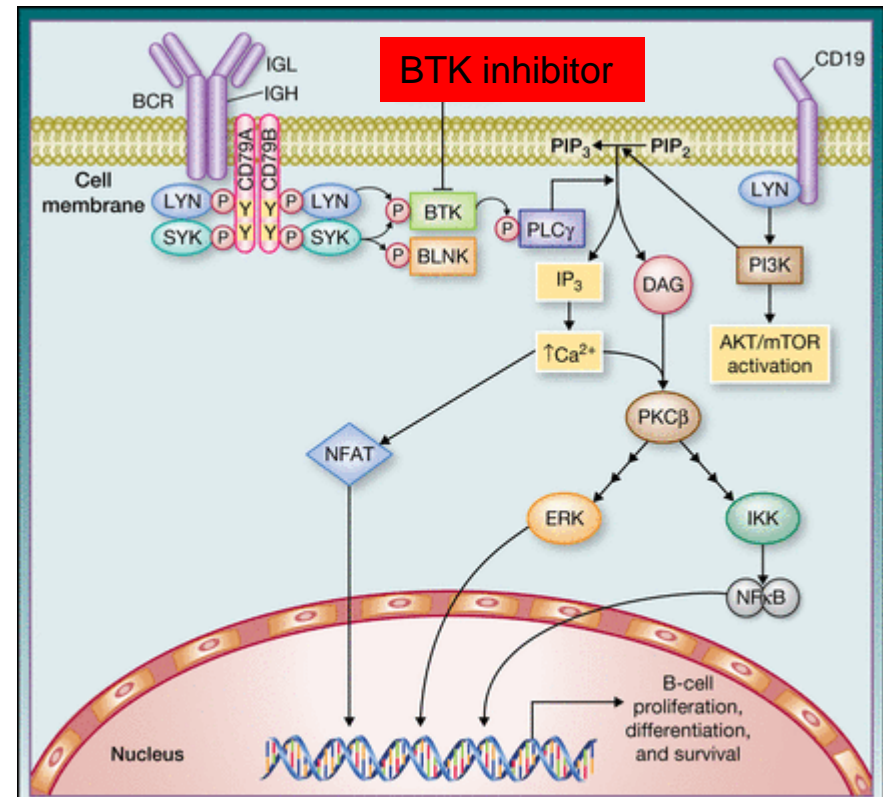


- Clinical pearls and pharmacist role in management:
 - Dosing is based on **actual body weight**
 - Premedication: may include acetaminophen, an H1 receptor antagonist, an H2 receptor antagonist, and/or glucocorticoids 30 minutes to 2 hours prior to infusion to minimize infusion reaction
 - If no infusion reaction during the initial 3 infusions, premedication is optional for subsequent infusions
 - If an infusion reaction occurs, administer premedication(s) prior to each subsequent infusion.
 - Lenalidomide **STOPS** after 12 cycles and tafasitamab-cxix continues until disease progression or unacceptable toxicity
 - Administration days vary per cycle

Zanubrutinib



- MOA
 - Highly selective Bruton tyrosine kinase inhibitor
 - Forms a covalent bond with a cysteine residue in the BTK active site to inhibit BTK activity



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Zanubrutinib



- Place in therapy R/R MZL who have received at least one anti-CD20-based regimen
- FDA approval for adult patients with MCL, MZL, and Waldenström's macroglobulinemia
- NCCN guidelines category 2A recommendation

Zanubrutinib



- Clinical data and FDA approval:
- FDA approval on September 14, 2021
- MAGNOLIA study (BGB-3111-214) and BGB-3111-AU-003 study
 - Open-label, multicenter, single-arm trials
 - Patients with previously treated MZL
 - Efficacy measures were ORR and DOR

Zanubrutinib



- Dosing and administration:
 - Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily with or without food
 - Continue until disease progression or unacceptable toxicity

Zanubrutinib



- Results:
 - BGB-3111-214
 - ORR was 56% (95% CI: 43%, 68%), with 20% achieving complete responses (CR)
 - Median DOR was not estimable; the estimated 1-year rate of DOR was 85% (95% CI: 67, 93)
 - BGB-3111-AU-003
 - ORR was 80% (95% CI: 56%, 94%), with a CR rate of 20%
 - Median DOR was not estimable; the estimated 1-year rate of DOR was 72% (95% CI: 40, 88)

Zanubrutinib



- Adverse reactions:
 - Hyperglycemia 54%
 - Neutropenia 43%
 - Increase in serum creatinine 34%
 - Thrombocytopenia 33%
 - lymphopenia 32%
 - Hypophosphatemia 27%
 - Musculoskeletal pain 27%
 - Respiratory tract infection 26%
 - Anemia 26%
 - Diarrhea 25%
 - **Bruising 24%**
 - **Hemorrhage 23%**
 - Hypocalcemia 23%
 - ALT increase 22%
 - Fatigue 21%
 - **Cardiac arrhythmias 3.2%**

Zanubrutinib



- Clinical pearls and pharmacist role in management:
 - Dose modifications for patients with severe hepatic impairment is 80 mg PO twice daily
 - Drug drug interactions
 - Major substrate of CYP3A4
 - Avoid grapefruit, grapefruit juice, and Seville oranges during therapy
 - Dosage Modifications for Use With CYP3A Inhibitors or Inducers

Co-administered Drug	Recommended Dose
Strong CYP3A inhibitor	80 mg PO once daily
Moderate CYP3A inhibitor	80 mg PO twice daily
Moderate or strong CYP3A inducer	Avoid concomitant use

Zanubrutinib



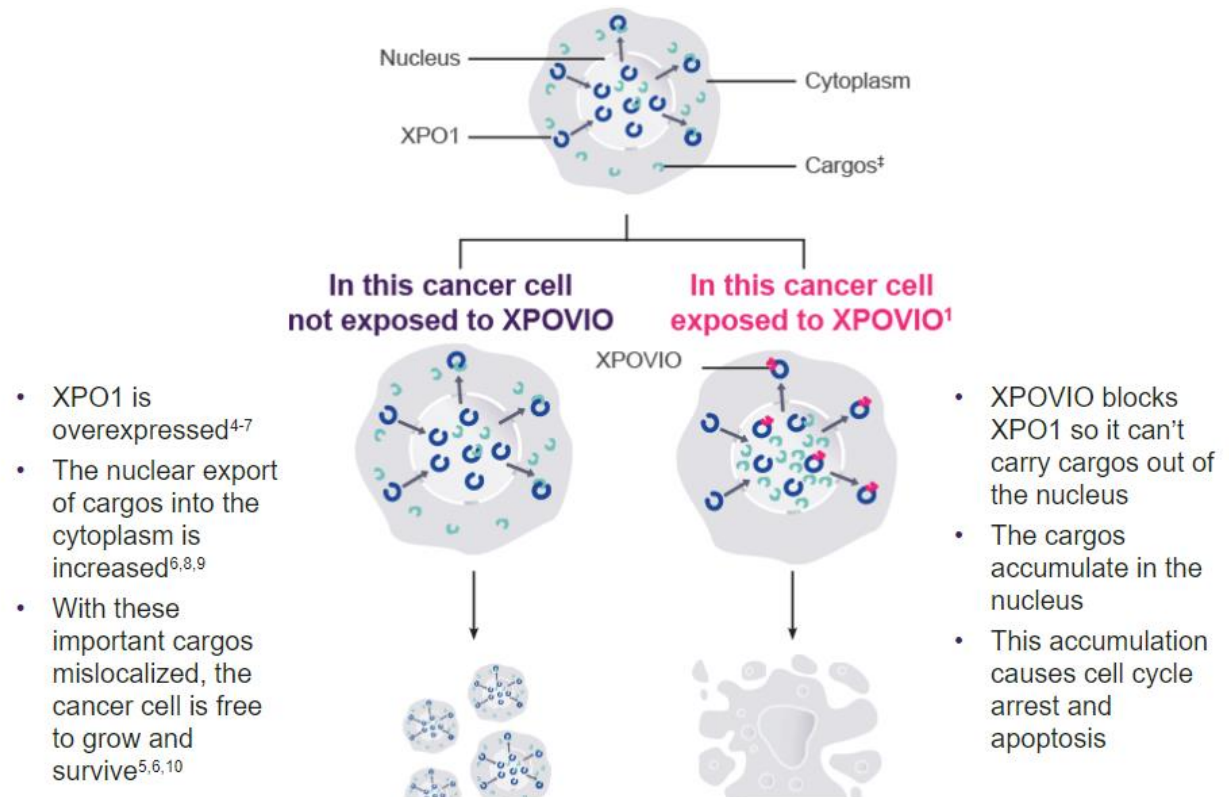
- Clinical pearls and pharmacist role in management:
 - Pill burden: available in 80 mg capsules
 - Bleeding risk: withhold 3-7 days pre- and post-surgery depending on risk of bleeding
 - Consider infection prophylaxis → VZV and PJP

Selinexor



- MOA

- Reversibly inhibits nuclear export of tumor suppressor proteins growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1)
- XPO1 inhibition by selinexor leads to accumulation of TSPs in the nucleus and reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis





- FDA approval on June 22, 2020
 - R/R DLBCL not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy
- NCCN guidelines only after 2 lines of therapy including transplant or CART-cell therapy
 - SADAL trial
 - Multicenter, single-arm, open-label trial in patients with DLBCL after 2 to 5 systemic regimens
 - 134 patients included
 - Efficacy measures were ORR and DOR



- Dosing and administration:
 - Selinexor 60 mg orally on days 1 and 3 of each week
- Results:
 - ORR was 29% (95% CI: 22, 38), with complete response in 13%
 - Of the 39 patients who achieved a partial or complete response, 38% had response durations of at least 6 months and 15% had response durations of at least 12 months

Selinexor



- Adverse reactions:
 - Thrombocytopenia 86%
 - Anemia 82%
 - Fatigue 63%
 - lymphopenia 63%
 - Hyponatremia 62%
 - Neutropenia 58%
 - Hyperglycemia 57%
 - Nausea 57%
 - Increase in serum creatinine 47%
 - Diarrhea 37%
 - Decreased appetite 37%
 - Hypomagnesemia 30%
 - Constipation 29%
 - Hypophosphatemia 34%
 - Hypocalcemia 30%
 - ALT increase 29%
 - AST increase 24%
 - Hypoalbuminemia 25%
 - Pyrexia 22%
 - CK increase 21%



- Clinical pearls and pharmacist role in management:
 - Associated with a moderate or high emetic potential; antiemetics are recommended to prevent nausea and vomiting
 - Maintain adequate hydration and caloric intake throughout treatment; consider IV hydration in patients at risk of dehydration
 - Hyponatremia: median time to onset is 8 days
 - Monitor sodium levels at baseline and during treatment
 - Correct sodium levels for concurrent hyperglycemia
- No recommended dose modifications due to drug drug interactions
- Pill burden: available in 20 mg tablets

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