20TH INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 21-22, 2023

CAR T-Cells and Targeted Agents in Follicular Lymphoma

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THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

CAR T-Cells and Targeted Agents in Follicular Lymphoma

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Disclosures

- No conflicts to disclose

Abbreviations

CR: complete response

CAR-T: Chimeric antigen receptor T-Cells

CRS: cytokine release syndrome

DOR: duration of response

FL: follicular lymphoma

ICANS: immune effector cell-associated neurotoxicity syndrome

MZL: marginal zone lymphoma

OS: overall survival

ORR: overall response rate

PFS: progression free survival

PR: partial response

POD24: progression of disease within 24 months of first treatment

R/R: relapsed & refractory

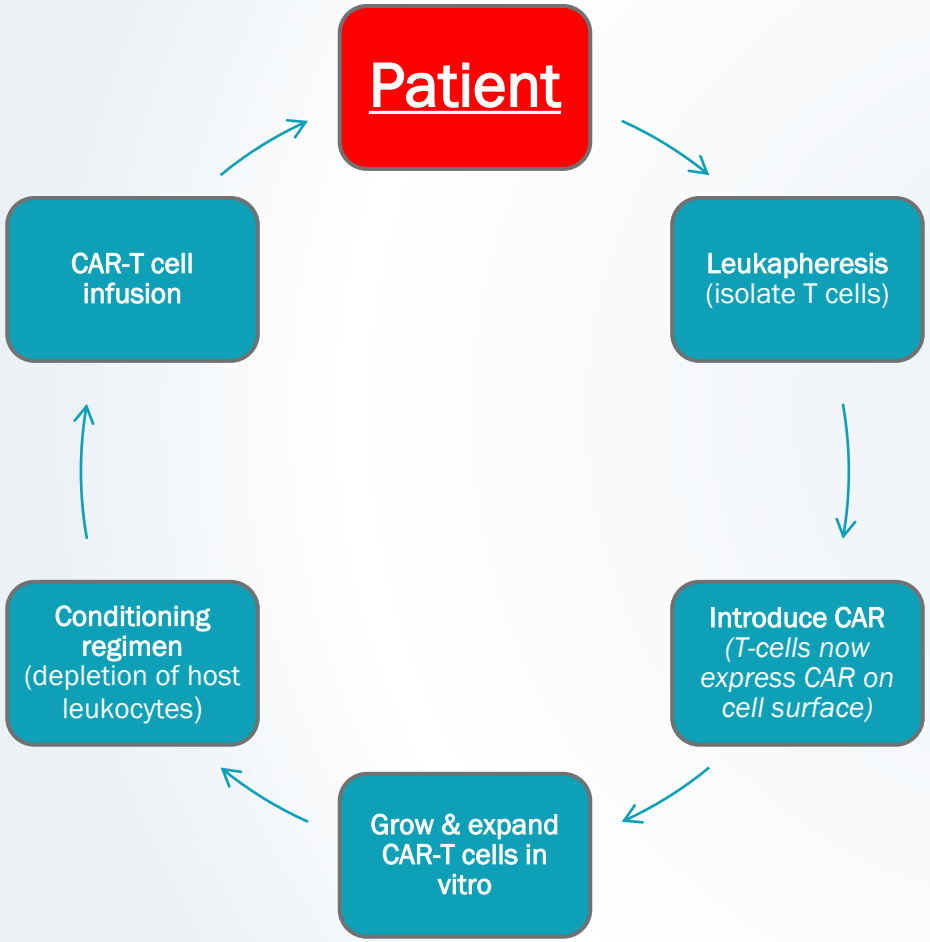
Objectives

- Review different CAR-T products currently approved in follicular lymphoma
- Identify targeted therapies in follicular lymphoma, review mechanism of actions and frequently reported adverse events
- Assess clinical trial data to determine place in therapy of these novel agents

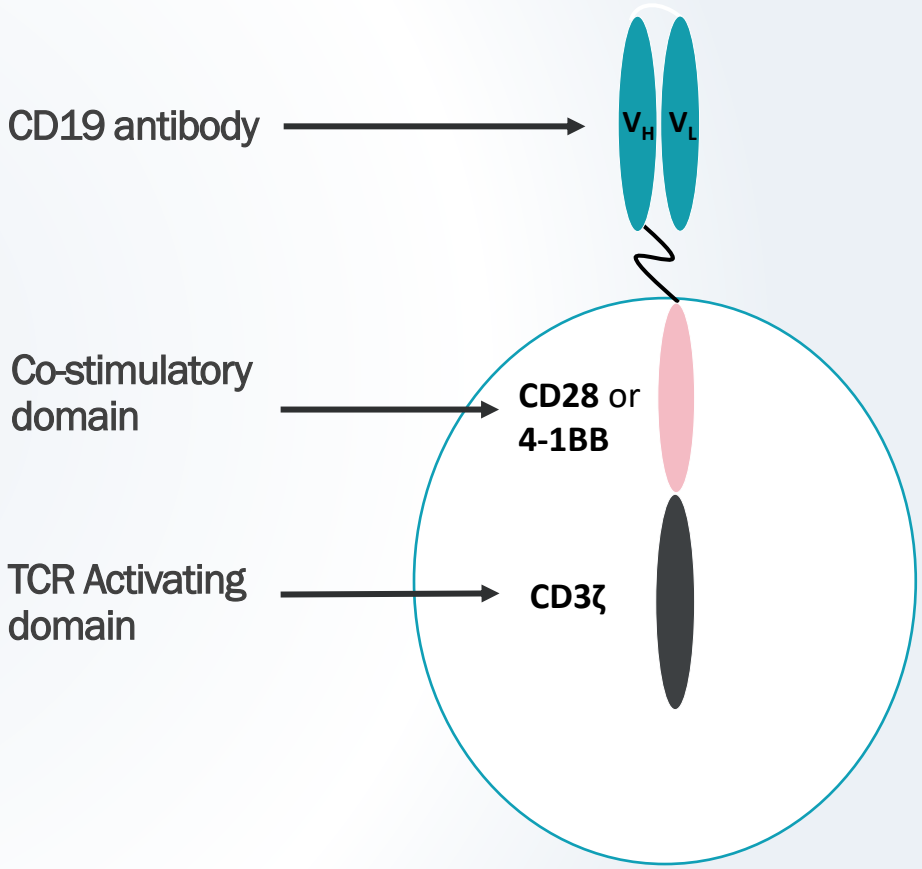
CAR-T

Axicabtagene ciloleucel
Tisagenlecleucel
Lisocabtagene maraleucel

CAR-T Cells



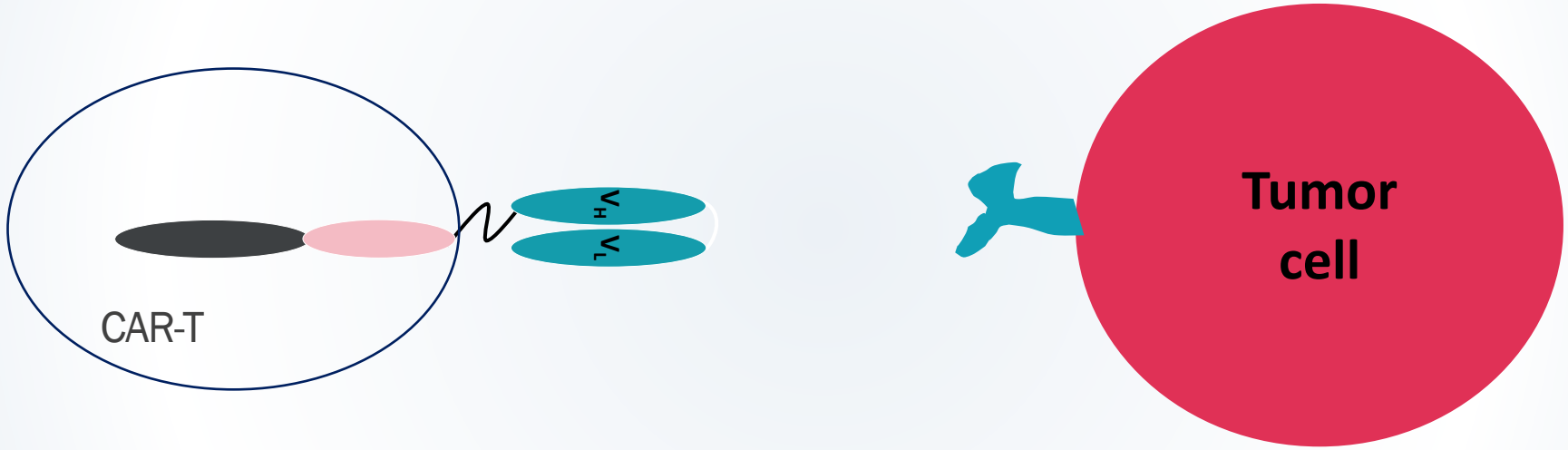
CAR-T Construct



Majzner, R.G. et al. Nat Med 25, 1341–1355 (2019. Chmielewski M, et al. Immunol Rev. 2014;257(1):83-90. Feins S, et al. Am J Hematol. 2019;94(S1):S3-S9. Diagram adapted from: clinicaloptions.com

VH= variable heavy chain
VL= variable light chain

CAR-T Mechanism of Action



FDA Approved CAR-T Therapies

Agents	FDA Approval Date	FDA Approved Indication
Axicabtagene ciloleucel (Axi-cel)	March, 5th 2021	Adults with R/R FL after ≥2 lines of systemic therapy *(accelerated approval)*
Tisagenlecleucel (Tisa-cel)	May, 27th 2022	Adults with R/R FL after ≥2 lines of systemic therapy *(accelerated approval)*
Lisocabtagene maraleucel (Liso-cel)	February, 5th 2021	Follicular lymphoma grade 3B who have: • R/R after ≥2 lines of systemic therapy; or • Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or • Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation due to comorbidities or age

Oncology (Cancer) / Hematologic Malignancies Approval Notifications | FDA. Accessed 04-2023

Axicabtagene Ciloleucel: ZUMA-5

Multicenter, single arm, phase II trial

R/R FL (grade 1-3a) or MZL
-Age ≥ 18 years
-Received ≥ 2 lines of therapies (including anti-CD20 monoclonal antibody + alkylating agent)
-ECOG PS of 0 or 1

Key exclusion:
-CNS involvement
-Stem cell transplant within 6 weeks

→

Lymphodepleting Chemotherapy:
Fludarabine 30 mg/m^2 + Cyclophosphamide 500 mg/m^2 on days -5, -4 and -3

→

Axicabtagene Ciloleucel
Target dose of 2x10^6 anti-CD19 CAR-T/kg
(n = 148)

Median time to delivery was 17 days after leukapheresis

- **Primary endpoint:** ORR (CR + PR)
- **Secondary endpoints:** OS, PFS, DOR, CR, ORR in patients with ≥ 3 L of therapies, best objective response rates, AE

Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91-103.

Axicabtagene Ciloleucel: ZUMA-5

Baseline characteristics:

- 124 patients had FL while 24 patients had MZL
- FL Cohort:
  - Median age 60
- 63% of patients had ≥ 3 lines of therapies
- 55% of patients had POD24
- Median time from diagnosis to leukapheresis was 5.1 years
- Median time to progression from recent therapy was 8.2 months
- Median follow up of 17.5 months

	FL (n=86)	MZL (n=20)
Overall Response Rate	94%	83%
Complete Response	79%	65%
Partial Response	15%	17%
Duration of Response		
Median response duration	Not reached	11.1 months
Survival Outcomes		
Median PFS	Not reached	12 months
Median OS	Not reached	Not reached

- 3 Year follow-up of ZUMA-5 was recently reported
  - Median DOR not reached in patients in CR
  - Median PFS of 40.2 months
  - Median OS not reached with 75% of patients still alive at 3 years

Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91-103.
Neelapu. ASH 2022. Abstr 4660.

Axicabtagene Ciloleucel: ZUMA-5

- Most common grade ≥ 3 toxicities in FL included neutropenia, anemia, and thrombocytopenia
- Grade ≥ 3 cytopenias were present after day 30 in 33% of patients in FL
- No new safety signals
- 1 patient had multiorgan failure and died due to CRS

	Axi-cel (n= 124)	MZL (n= 22)
CRS		
Any grade	78%	100%
Grade ≥ 3	6%	8%
Median time to onset	4 days	6 days
Neurotoxicity*	56%	71%
Grade ≥ 3	15%	38%
Median time to onset	7 days	7 days
Grade ≥ 3 Cytopenias		
Neutropenia	60%	67%
Anemia	23%	29%
Thrombocytopenia	23%	21%

Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91-103.

Tisagenlecleucel: ELARA

Multicenter, single arm, phase II trial

R/R FL (grade 1-3a)
-Age ≥ 18 years
-Received ≥ 2 lines of therapies (including anti-CD20 monoclonal antibody + alkylating agent)
-ECOG PS of 0 or 1

Key exclusion:
-CNS involvement
-Allogeneic transplant
-Prior anti-CD19 therapy

→

Lymphodepleting Chemotherapy:
Fludarabine 25 mg/m^2 +
Cyclophosphamide 250 mg/m^2 for 3 days
Or
Bendamustine 90 mg/m^2 for 2 days

Given 1 week prior to infusion

→

Tisagenlecleucel median dose of
(0.6-6.0 x 10^8 viable T cells)
(n = 97)

Median time to enrollment to infusion was 46 days

- **Primary endpoint:** CR
- **Secondary endpoints:** ORR, DOR, PFS, OS, pharmacokinetics and safety

Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022;28(2):325-332.

Tisagenlecleucel: ELARA

Baseline characteristics:

- Median age 57 years
- Median number of therapies: 4
- 61% of patients had POD24
- Median follow-up of 16.59 months
- Patients with POD24 had lower CR rates versus those without
  - 59% vs 87.9%
- 31 patients who had initially achieved a PR at 3 months, 15 converted to CR
  - 11 converted to CR at 6 month assessment

n=94	Local Assessment	Independent review committee (IRC)
Overall Response Rate	90.4%	86.2%
Complete Response	72.3%	69%
Partial Response	18.1%	17%
Duration of Response		
Median response duration	Not reached	
Survival Outcomes		
Median PFS	Not reached	
PFS at 12 months	67%	
Median OS	Not reached	

- Recently 28.9 month follow-up reported
  - CR rate of 68%
  - ORR of 86.2%
  - mPFS not reached
  - Estimated 24 months OS 87.7%, DOR 64.6%, PFS 57.4%

Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022;28(2):325-332.

Tisagenlecleucel: ELARA

- 7.7% of patients had prolonged grade ≥ 3 lymphopenia at 12 months
- 10.3% had prolonged depletion of normal B cells/agammaglobulinemia
- No new safety signals
- One death due to CRS

	Axi-cel (n= 124)
CRS	
Any grade	48.5%
Grade ≥ 3	0%
Median time to onset	4 days
Neurotoxicity*	37.1%
Grade ≥ 3	3%
Median time to onset	9 days
Grade ≥ 3 Cytopenias	
Neutropenia	32%
Anemia	13%
Thrombocytopenia	9.3%

Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022;28(2):325-332.
Dreyling. ASH 2022. Abstr 608.

Quick Recap for CAR-T Therapy in R/R FL

- Both axi-cel and tisa-cel have high response rates in R/R FL
- Tisa-cel seems to have a safer profile in regard to CRS and neurotoxicity
- Manufacturing time faster with axi-cel versus tisa-cel
- All CAR-T products are only available through REMS

	Axi-cel	Tisa-cel
Overall Response Rate	94%	90%
Complete Response	79%	72%
Partial Response	15%	18%
Cytokine Release Syndrome		
All Grade	78%	49%
Grade ≥ 3	6%	0%
Neurotoxicity		
All Grade	56%	37%
Grade ≥ 3	15%	3%

EZH2 inhibitor

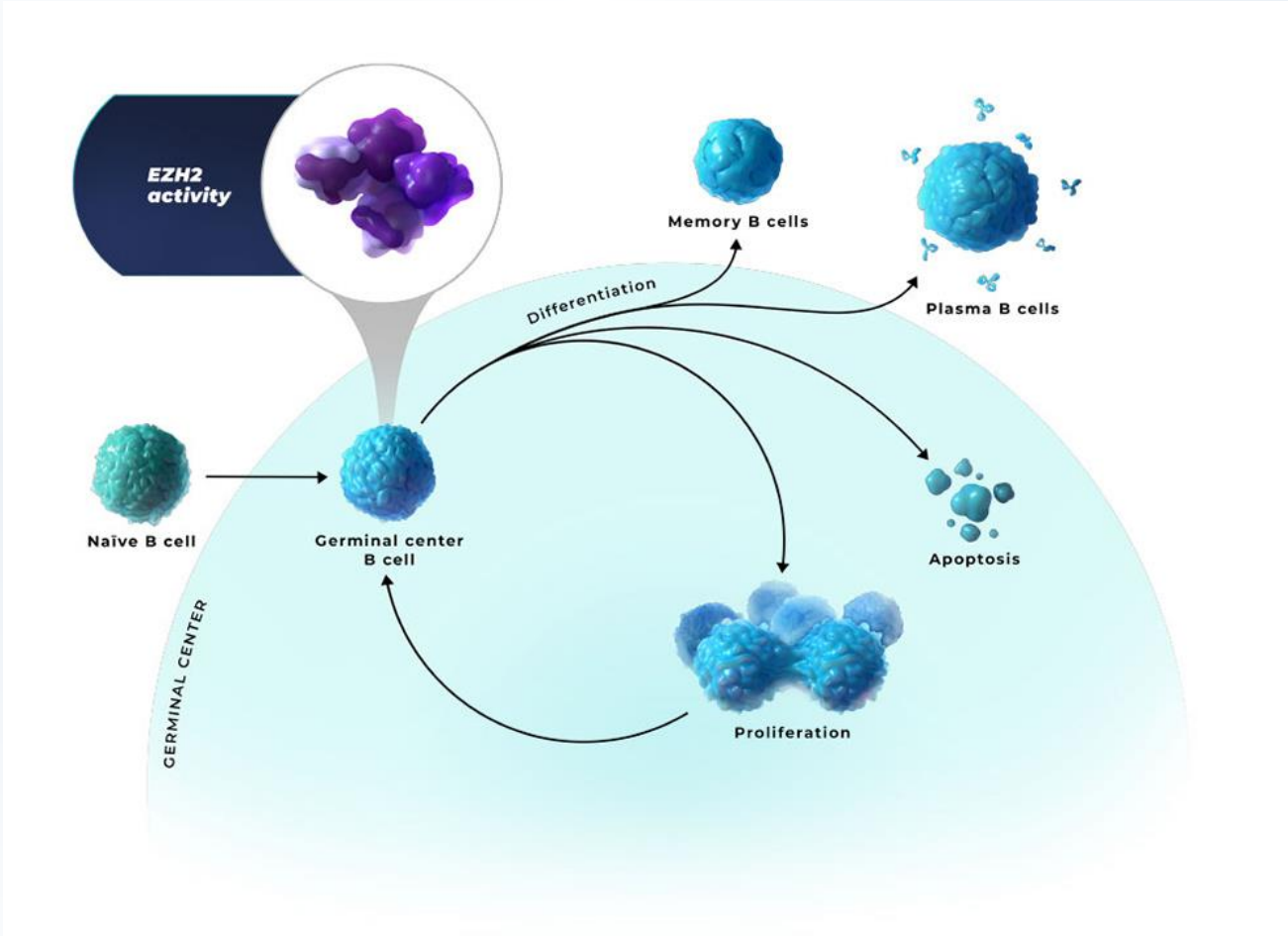
Tazemetostat

Tazemetostat

- Inhibits histone methyltransferase enhancer of zeste homolog-2 (EZH2),
- FDA approval – June, 18th 2020
  - R/R FL whose tumors are positive for EZH2 mutation after ≥ 2 lines of therapy
  - R/R FL who have no satisfactory alternative treatment options
- Dosing:
  - **800 mg by mouth twice daily with or without food**

Tazemetostat: Mechanism of Action

- EZH2 is an epigenetic regulator of B-cell identity in the germinal center (GC)
  - Mutations reprogram the GC microenvironment and initiate lymphomagenesis
  - EZH2 inhibition by tazemetostat suppresses proliferation of B-Cell lymphoma cells with or without EZH2 gain-of-function mutation.



Béguelin W, Teater M, Meydan C, et al. Mutant ezh2 induces a pre-malignant lymphoma niche by reprogramming the immune response. Cancer Cell. 2020;37(5):655-673.e11.
https://www.tazverik.com/hcp/follicular-lymphoma/mechanism-of-action

Tazemetostat

International, open-label, multi-cohort, single-arm, phase II trial

R/R FL (grade 1-3a)
-Age ≥ 18 years
-Received ≥ 2 lines of therapy (including anti-CD20 monoclonal antibody)
-ECOG PS of 0-2

Key exclusion:
-Leptomeningeal or brain metastases
- Grade ≥ 3 Thrombocytopenia, neutropenia, or anemia

→

Mutant EZH2
n=45

WT EZH2
n=54

→

Tazemetostat 800 mg BID
until progression, toxicity or withdrawal

- **Primary endpoint:** Objective response rate (CR + PR)
- **Secondary endpoints:** DOR, PFS, Safety

Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020;21(11):1433-1442.

Tazemetostat

Baseline characteristics:

- Baseline characteristics differed between two cohorts, with more clinically challenging patients in the EZH2^{wt}
- Median follow-up was 22 months EZH2^{mut} and 35.9 months in EZH2^{wt}
- Most patients had ECOG PS of 1 or 2
- Median age 62 in EZH2^{mut} and 61 in EZH2^{wt}
- POD24 was 42% EZH2^{mut} and 59% EZH2^{wt}
- Median number of prior therapies was 2 in EZH2^{mut} and 3 in EZH2^{wt}
- Median time from diagnosis was 4.7 years in EZH2^{mut} and 6.3 years in EZH2^{wt}

	EZH2^{mut} n=45		EZH2^{WT} n=54	
	IRC* assessed	Investigator assessed	IRC* assessed	Investigator assessed
Objective Response Rate	69%	78%	35%	33%
Complete Response	13%	9%	4%	6%
Partial Response	56%	69%	31%	28%
Stable Disease	29%	22%	33%	30%
Duration of Response				
Median duration	10.9 months		13 months	
Survival Outcomes				
Median PFS	13.8 months		11.1 months	
Median OS	Not reached		Not reached	

*IRC= independent radiology committee

Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020;21(11):1433-1442.

Tazemetostat

- Overall well tolerated
  - Low rates of grade ≥ 3 treatment-related adverse events (TRAEs)
- No treatment-related deaths
- Most common treatment TRAEs included nausea, diarrhea, alopecia, asthenia and fatigue
- 8% of patients discontinued due to treatment emergent adverse events (TEAEs)
- 28% required dosing interruptions due to TEAEs
  - 9% required dose adjustments
- Two patients developed secondary malignancies (AML and MDS)

Treatment-related adverse events Grade ≥ 3	Both Cohorts n=99
Grade ≥ 3	
Thrombocytopenia	3%
Neutropenia	3%
Anemia	2%

Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020;21(11):1433-1442.

PI3K Inhibitors

Copanlisib

~~Idelalisib~~

~~Duvelisib~~

Copanlisib

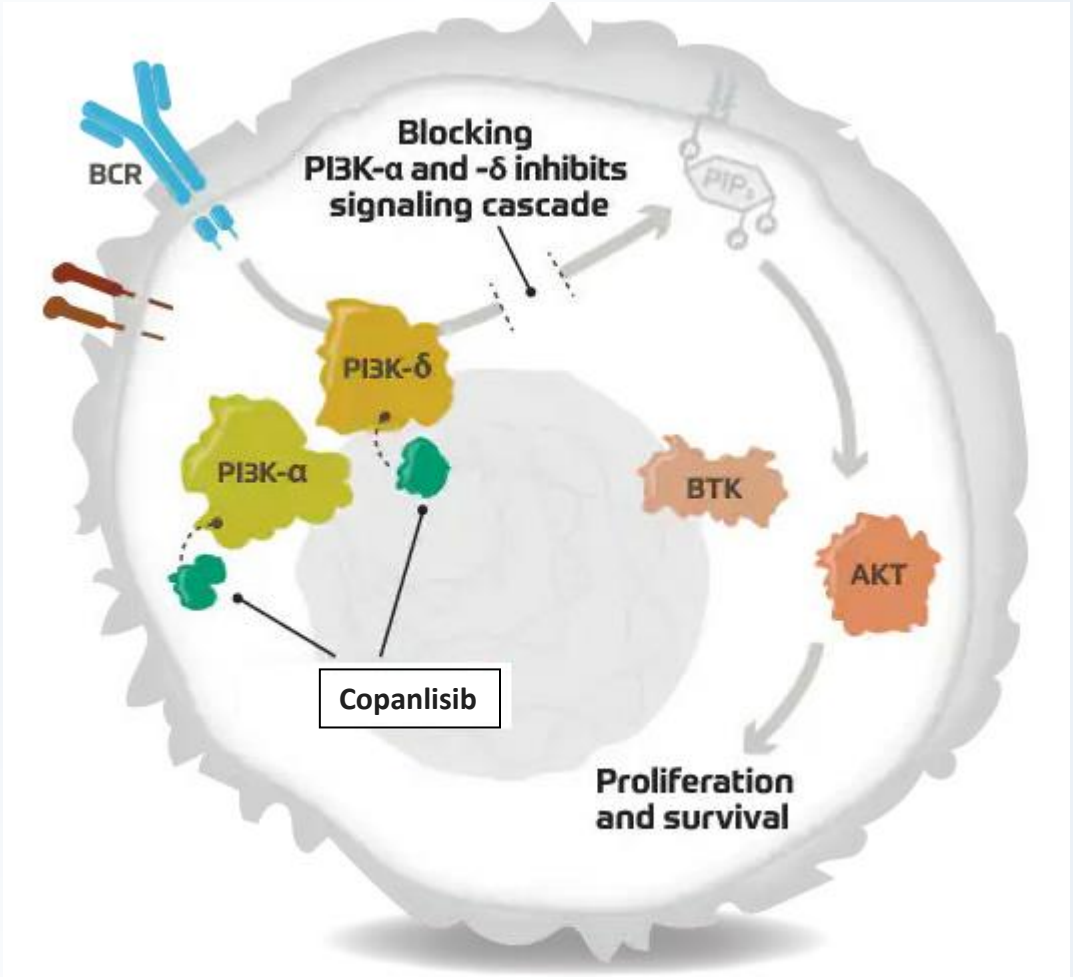
- Phosphatidylinositol 3-Kinase (PI3K) inhibitor
- FDA approval – September 14th 2017
  - R/R FL after ≥ 2 lines of therapy
- Dosing:
  - **60 mg IV on days 1, 8, and 15 of a 28 day treatment cycle**

august 2023

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SAT/SUN
31 July	1 August Cycle 1 Day 1 Copanlisib 60 mg IV	2	3	4	5/6
7	8 Cycle 1 Day 15 Copanlisib 60 mg IV	9	10	11	12/13
14	15 Cycle 1 Day 15 Copanlisib 60 mg IV	16	17	18	19/20
21	22	23	24	25	26/27
28	29 Cycle 2 Day 1 Copanlisib 60 mg IV	30	31	1 September	2/3

Copanlisib: Mechanism of Action

- PI3K plays a significant role in B-cell receptor signaling (BCR)
- Copanlisib inhibits PI3K alpha and delta isoforms which are expressed in malignant B-cells
  - Inhibition induces tumor cell death through apoptosis and inhibition of proliferation



Copanlisib [package insert]. Bayer HealthCare Pharmaceuticals Inc., March 2023. https://www.hcp.aliqopa-us.com/mechanism-of-action

Copanlisib: CHRONOS-1

International, open-label, multi-cohort, single-arm, phase II trial

Indolent B-cell lymphoma (FL grade 1-3a, MZL, SLL, WM/LPL)
-Age ≥ 18 years
-Received ≥ 2 lines of therapy (including anti-CD20 monoclonal antibody)
-ECOG PS of 0-2

Key exclusion:
-Prior PI3K inhibitors
-Allogeneic transplant

*SLL=small lymphocytic lymphoma; WM/LPL=waldenstrom macroglobulinemia/lymphoplasmacytoid lymphoma

→ Copanlisib 60 mg IV on Days 1, 8, and 15 every 28 days

- **Primary endpoint:** Objective response rate (CR + PR)
- **Secondary endpoints**: DOR, PFS, OS and safety

Dreyling M, Santoro A, Mollica L, et al. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. Am J Hematol. 2020;95(4):362-371.

Copanlisib: CHRONOS-1

Baseline characteristics:

- Total 142 patients enrolled
  - 104 patients had FL
- Median age 63
- 73% of patients with FL (grade 1-3a)
- Majority had ECOG PS 0-1
- Median number of prior therapies was 3
- Median time from most recent progression was 8.3 weeks

	FL n=104
Overall Response Rate	58.7%
Complete Response	20.2%
Partial Response	38.5%
Duration of Response	
Median DOR	12.2 months
Survival Outcomes	
Median PFS	11.2 months
Median OS	38.4 months

Leppä S, Santoro A, Demeter J, et al. Long-term follow-up of patients (Pts) with relapsed or refractory (R/r) follicular lymphoma (Fl) treated with copanlisib. JCO. 2019;37(15_suppl):7553-7553.

Copanlisib: CHRONOS-1

- Most common TEAEs were hyperglycemia, diarrhea, transient hypertension, neutropenia, pyrexia and fatigue
- Median duration of safety follow-up 6.7 months
- Grade 3 TEAEs were experienced by 54.2% of patients and grade 4 TEAEs by 28.9%
- 26.8% discontinued due to adverse events
- 28.9% required dose reductions
- 81.7% had dose interruptions or delays

Treatment-related adverse events Grade ≥ 3	All Cohorts N=142
Grade ≥ 3	
Hyperglycemia	**40.1%**
Diarrhea	8.5%
Transient Hypertension	**23.9%**
Pneumonitis	1.4%
Colitis	0.7%
Infection (URTI & PNA)	**12%**
Neutropenia	**24%**
Anemia	4.9%
Thrombocytopenia	4.9%

Dreyling M, Santoro A, Mollica L, et al. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. Am J Hematol. 2020;95(4):362-371.

Quick Recap of Targeted Agents

- As monotherapy both agents have low response rates
  - Niche likely with combination therapies which are under investigation
- Tazemetostat is well tolerated but low response rates seen in $EZH2^{WT}$
- Copanlisib requires frequent visits due to IV administrations and several high grade ADRs
  - Consider opportunistic infection prophylaxis

	Tazemetostat		Copanlisib
	$EZH2^{mut}$	$EZH2^{WT}$	FF Cohort
Overall Response Rate	69%	35%	59%
Complete Response	13%	4%	20%
Partial Response	56%	31%	39%
Survival Outcomes			
Median PFS	13.8 months	11.1 months	11.2 months
Median OS	Not reached	Not reached	38.4 months
Grade ≥ 3 ADRs			
Thrombocytopenia	3%		5%
Neutropenia	3%		24%
Anemia	2%		5%
Infections	2%		12%
Diarrhea	0%		9%
Hyperglycemia	1%		40%
Hypertension	1%		24%

Future Directions

- Multicenter Phase 1/2, single arm, study of **Tazemetostat + Rituximab and Abbreviated Bendamustine** in the Frontline setting in FL with High Tumor Burden
- MAHOGANY: Multicenter, open-label, phase 3 trial comparing **Zanubrutinib + Obinutuzumab vs Lenalidomide + Rituximab (R^2)** in R/R FL with ≥ prior 1 line of therapy
- ROSEWOOD: International, randomized, phase 2 trial comparing **Zanubrutinib + Obinutuzumab vs Obinutuzumab** in R/R FL with ≥ 2 prior lines of therapy
- InMIND: International, double-blind, placebo-controlled, randomized phase 3 trial comparing **Tafasitamab + R^2 vs R^2** alone in patients with R/R FL or MZL with ≥ 1 prior line of therapy
- ZUMA-22: Multicenter, open label, phase 3 trial evaluating **Axi-cel vs investigator's choice of SoC** therapy after 1 line of therapy in high risk with POD24 or in patients with ≥ 2 prior lines of systemic therapies
- SYMPHONY-1: International, double-blind, active-controlled, randomized, phase 1b/3 comparing **Tazemetostat + R^2 vs Placebo + R^2** in patients with R/R FL ≥ 1 prior line of therapy
- CHRONOS-3: Multicenter, double-blind, placebo-controlled, randomized, phase 3 trial comparing **Copanlisib + rituximab versus placebo + rituximab** in R/R indolent B-Cell lymphomas (FL, MZL, SLL, LPL/WM)

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