

Advancing BTKi Therapy for MZL & FL Patients: From Clinical Trials to Real-world Impact

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01

Pathogenesis of FL making the exploration of BTKi in FL (early evidences from ibrutinib had demonstrated its possibility in MZL)

02

Evidence-based indications of BTKi approved in R/R FL and MZL in China

03

BTKi combination regimens moving to 1L treatment for FL and MZL

BTK inhibitors for FL by blocking BCR signaling pathway

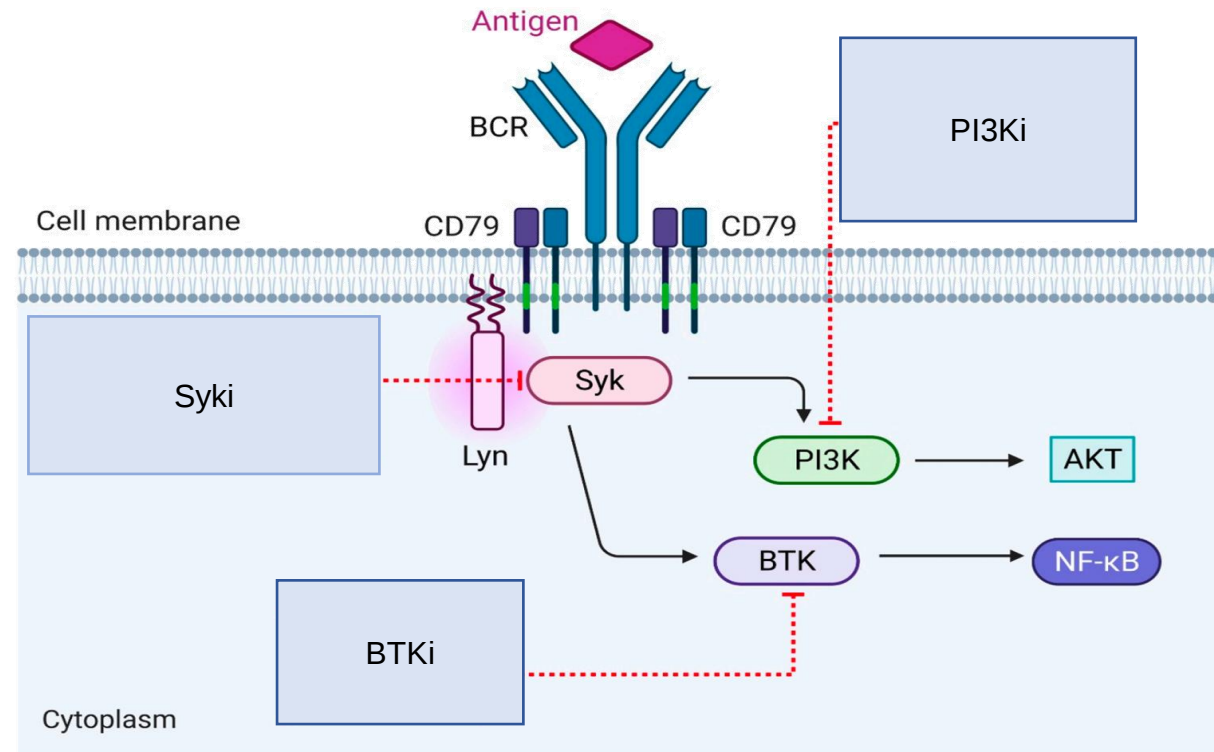
MOA of BTKi¹⁻³

In FL, BCR signaling is slowly upregulated, activating many proliferation and survival pathways, including NF- κ B, JAK/STAT, PI3K/AKT/mTOR, to promote B cell survival

BTK is an important kinase in the BCR signaling pathway, playing a crucial role in the survival and proliferation of B cells

BTK inhibitors regulate downstream pathways by blocking the BCR signaling pathway, thereby reducing B cell proliferation and survival

Drugs targeting BCR in FL

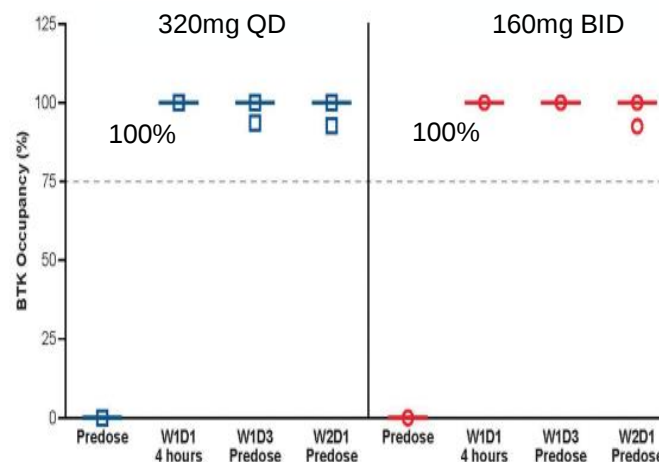


1. Nath K, Gandhi MK. Targeted Treatment of Follicular Lymphoma. J Pers Med. 2021;11(2):152.
2. 陈惠敏, 陈伟, 徐开林. 滤泡淋巴瘤分子靶向治疗的研究现状[J]. 国际输血及血液学杂志, 2023(2).
3. 于慧, 邓丽娟, 朱军. 布鲁顿酪氨酸激酶抑制剂在淋巴瘤中的研究进展[J]. 肿瘤综合治疗电子杂志, 2020, 6(02): 29-35.

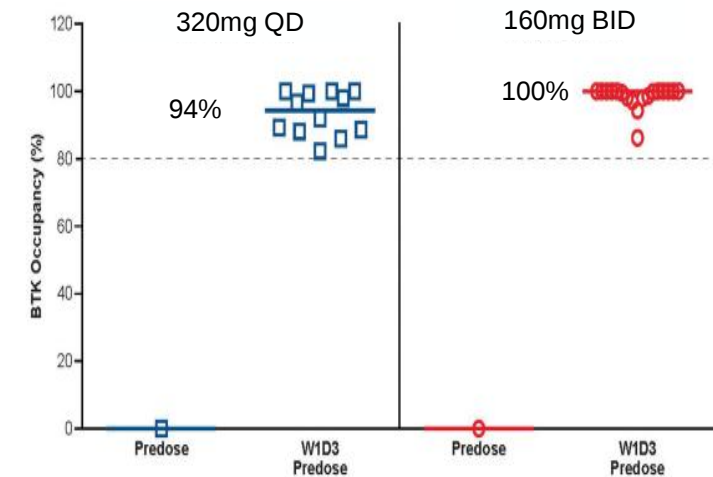
New generation of BTKi zanubrutinib had a higher BTK occupancy, penetrating into LN, BM

- With doses of 320 mg QD and 160 mg BID, the BTK occupancy in PBMCs was up to **100%**, and the occupancy in lymph nodes was **higher than 94%**.²
- High plasma levels of **Zanubrutinib** can allow it to **penetrate lymph nodes and other parts (bone marrow)**.¹

BTK occupancy in Zanubrutinib (PBMC)



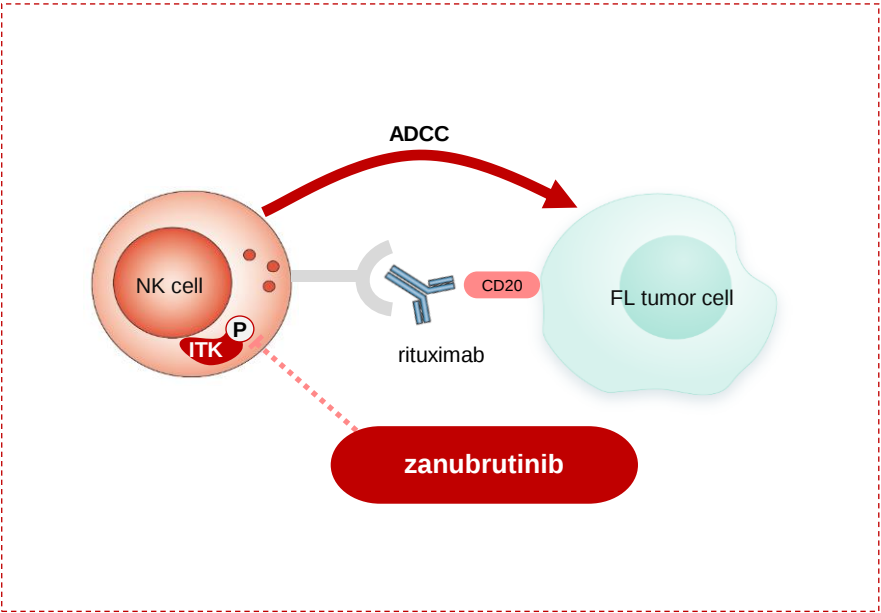
BTK occupancy in Zanubrutinib (lymph nodes)



1. Tam CS, Muñoz JL, Seymour JF, Opat S. Zanubrutinib: past, present, and future [published correction appears in Blood Cancer J. 2023 Oct 2;13(1):154]. Blood Cancer J. 2023;13(1):141. Published 2023 Sep 11.
2. Tam CS, Ou YC, Trotman J, Opat S. Clinical pharmacology and PK/PD translation of the second-generation Bruton's tyrosine kinase inhibitor, zanubrutinib. Expert Rev Clin Pharmacol. 2021;14(11):1329-1344.

Zanubrutinib less off-target inhibition of ITK, making it possible to combine CD20 mAbs for FL

- The anti-tumor effect of CD20 mAbs dependeds on the ADCC by NK cells.
- ITK played a key role in the ADCC and direct cytotoxicity of NK cells.
- **New generation of BTKi zanubrutinib showed less off-target of ITK inhibition and less inhibition of ADCC by NK cells, without affecting the efficacy of CD20 mAbs**



	zanubrutinib
IC ₅₀ (ITK)	56
ADCC in NK cells	less inhibition
Direct cytotoxicity of NK cells	less inhibition
Effect of combination on the efficacy of CD20 mAbs	less inhibition

1. Kaptein A, et al. Blood 2018; 132(suppl 1):1871.
2. Tam CS, et al. Expert Rev Clin Pharmacol 2021; 14(11):1329-1344.
3. Thijs W H Flinsenberg, et al. Haematologica. 2020 Jan 31;105(2):e76-e79
4. Zinzani PL,et al.J Clin Oncol. 2023;JCO2300775
5. Yu H, et al. Mol Ther Oncolytics. 2021;21:158-170

01

Pathogenesis of FL making the exploration of BTKi in FL and MZL

02

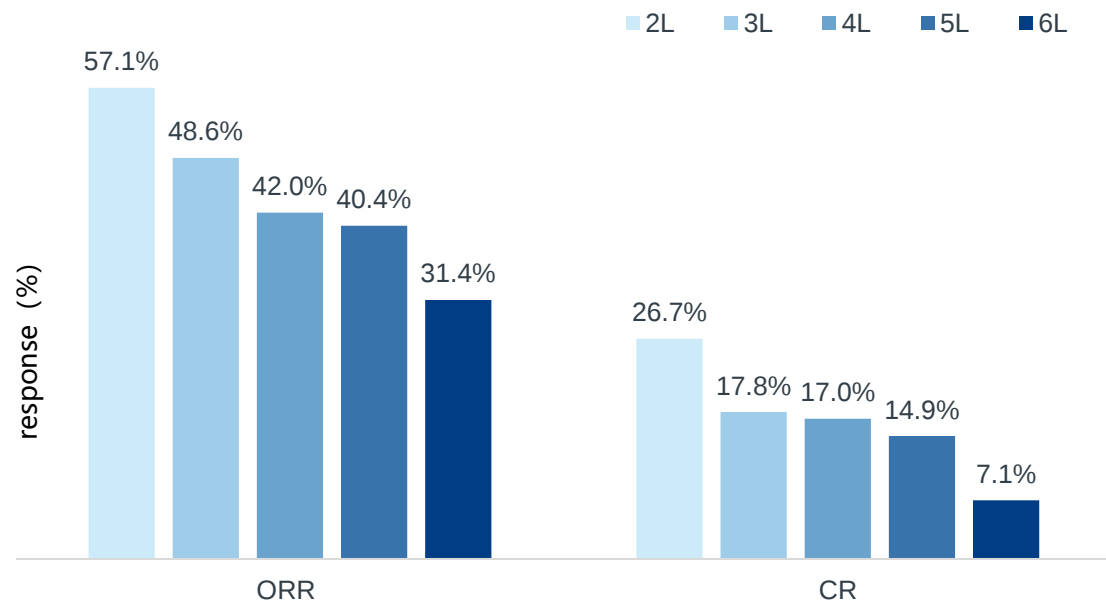
Evidence-based indications of BTKi approved in R/R FL and MZL in China

03

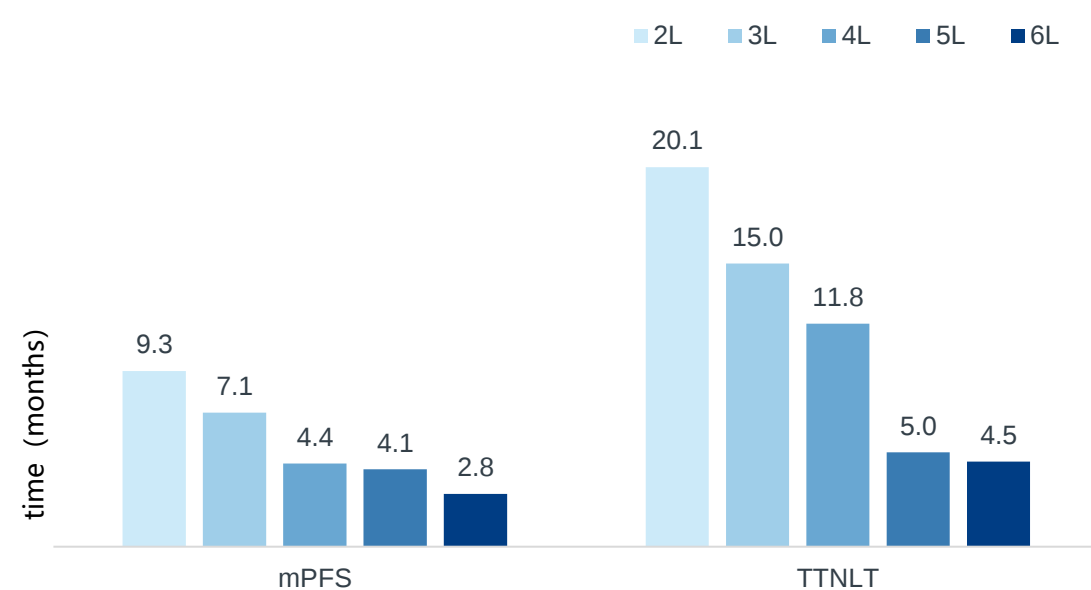
BTKi combination regimens moving to IL treatment for FL and MZL

FL is incurable disease, survival gradually shortened after multiple relapses

**ORR of 2L, 3L, 4L, 5L, 6L
treatment gradually decreased**



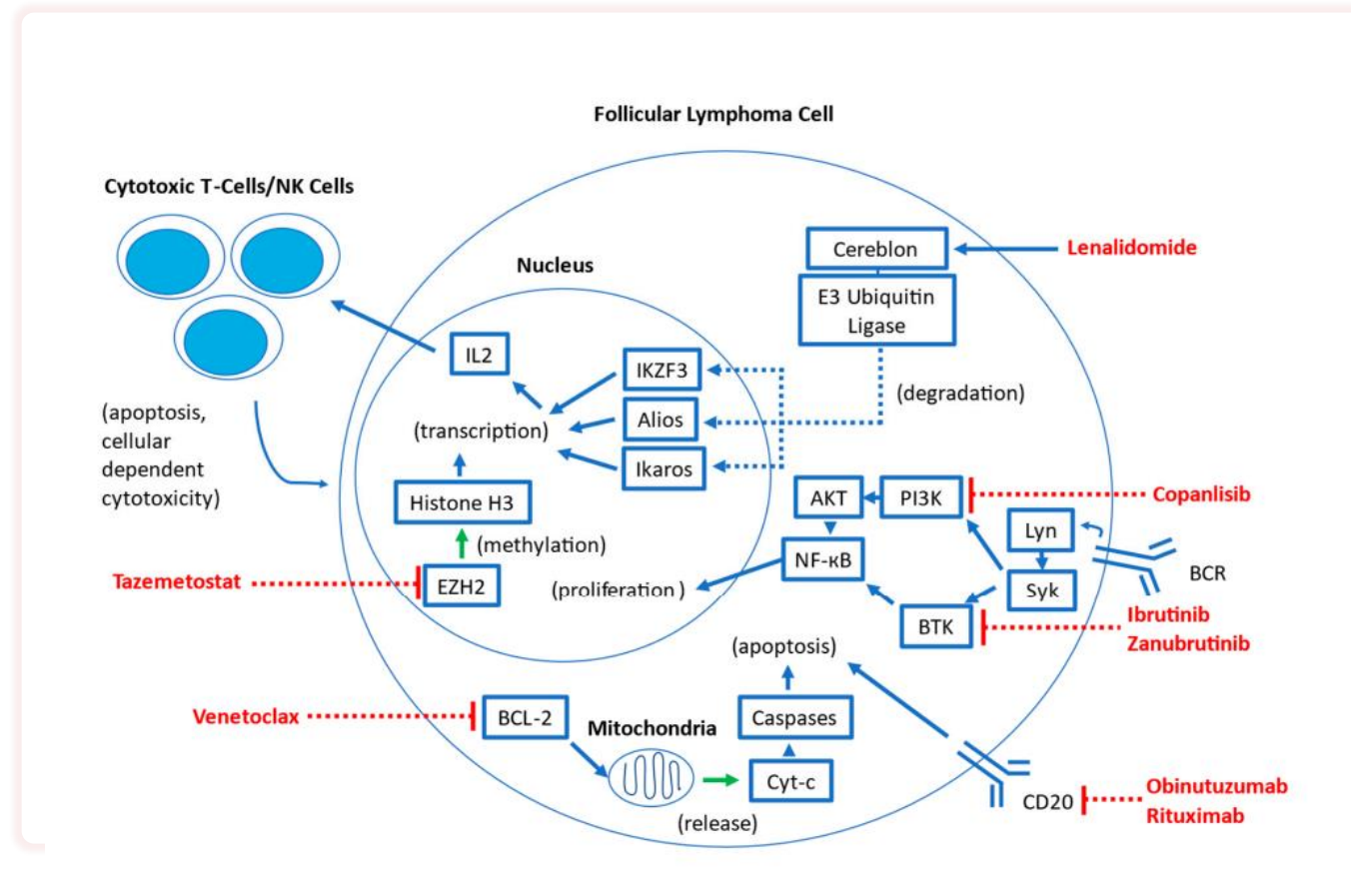
**PFS of 2L, 3L, 4L, 5L, 6L
treatment gradually shortened**



A retrospective study of 566 patients diagnosed with grade 1-3a FL in Peking University Cancer Hospital from January 2002 to December 2019.

21 patients were under observation until cut-off data; 544 patients received first-line treatment; 240, 146, 88, 47, and 28 patients received 2nd line, 3rd line, 4th line, 5th line, and 6th line treatment, respectively.

Unmet medical needs in FL promoting novel agents development



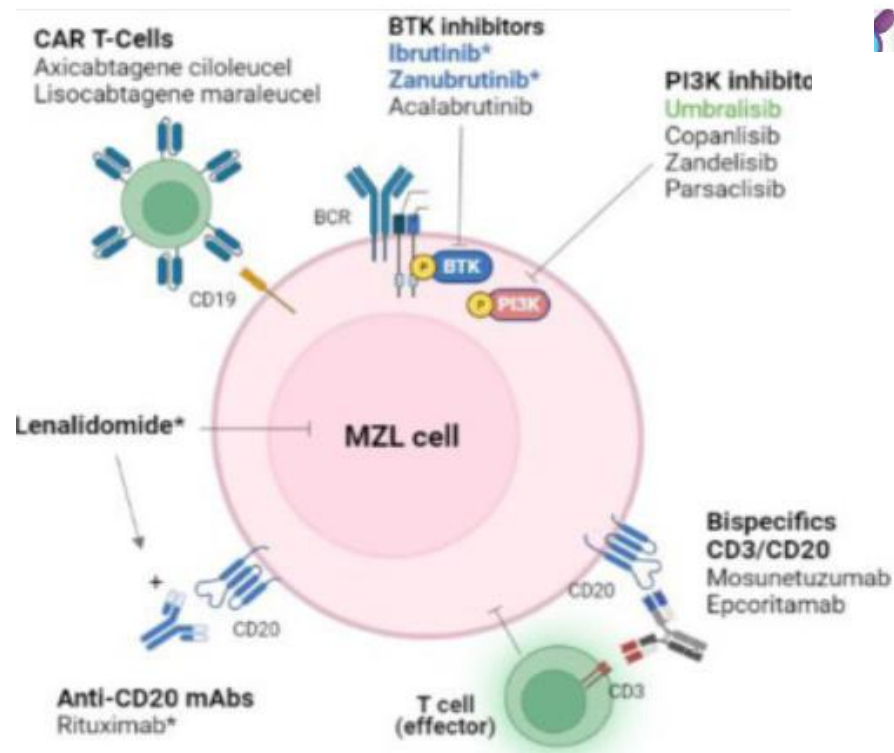
More and more new therapies are emerging in the treatment of FL

BTKi+BR
BTKi+R/G $\pm$ L
EZH2i $\pm$ R-CHOP
BsAbs $\pm$ L
Novel antibodies
CART
ADC

...

A large variety of novel agents being tested in MZL

- MZL facing the same situation, incurable, higher incidence than FL in China.
- The first BTKi ibrutinib had demonstrated promising efficacy and safety profiles.



More and more new therapies are also emerging in MZL

BTKi
Bispecific antibodies
Novel antibodies
CART
PI3Ki+R
...

Zanubrutinib combined with obinutuzumab became a new choice for R/R FL



Pier Luigi Zinzani

- ROSEWOOD is a phase 2 randomized study to evaluate the efficacy and safety of zanubrutinib with obinutuzumab (ZG) R/R FL patients.
- The updated data was reported with a median follow-up time of 20.2 months.



study design

R/R FL pts

Inclusion criteria

- ≥ 18 years old, grade 1-3a
- R/R disease, previously treated with ≥ 2L systemic therapy, including CD20 mAbs and appropriate alkylating agent combination therapy
- Measurable lesions
- ECOG PS 0-2
- Adequate organ function
- Untreated with BTKi

R
2:1

Arm A

Z+G

Until PD or unacceptable toxicity
N=145

Arm B

G

If PD confirmed or NR after 12 months of treatment, switch to Group A was allowed
N=72

Primary endpoint

- ORR assessed by IRC

Secondary endpoint

- ORR assessed by INV
- DOR, PFS, CR and CMR, OS assessed by INV and IRC

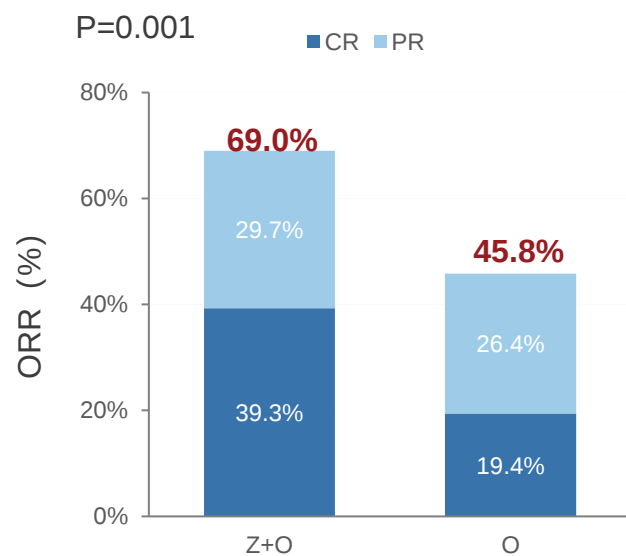
baseline characteristics	all (N=217)
median age	64 years
FLIPI-high	114 (52.5%)
GELF-high tumor burden	123 (56.7%)
median prior LOT (range)	3 (2-11)
refractory to rituximab	114 (52.5%)
prior therapy:	
immunochemotherapy	213 (98.6%)
anthracycline agents	172 (80.6%)
cyclophosphamide	204 (94.0%)
bendamustine	119 (54.8%)

dosing: zanu (160mg bid); obi IV 1000mg, C1, D1,8,15; C2-6, D1; q8w, up to 20 doses

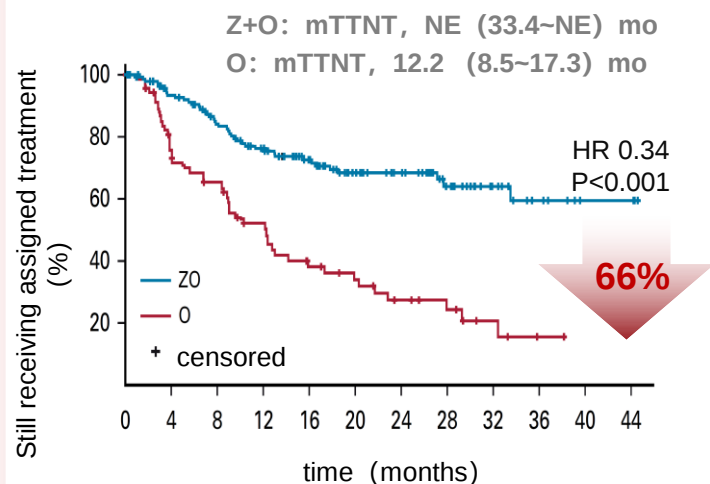
ROSEWOOD: ORR 69%, CR 39.3%, mPFS 28.0 months

- ORR in ZG and G group were **69.0% vs 45.8%**; **CR 39.3% vs 19.4%**;
- DOR rates at 18m were 69.3% vs 41.9%;
- Median PFS were **28.0ms vs 10.4ms**;
- Estimated 24m OS rate were 77.3% vs 71.4%.

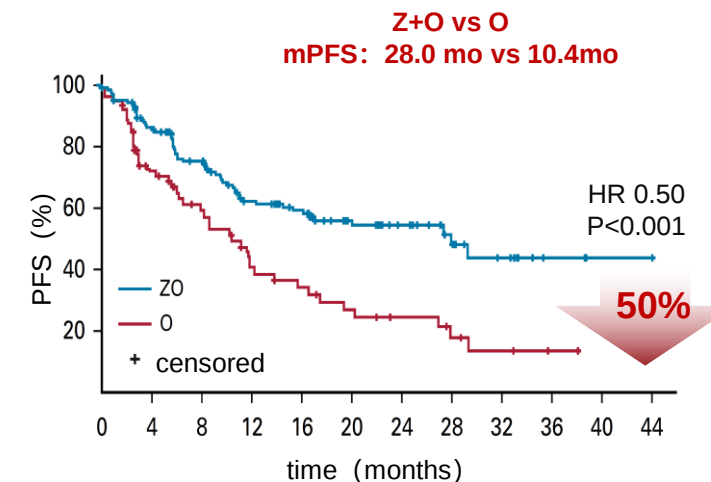
ORR



TTNT



IRC-PFS



Z+O regimen was relative safe and well tolerated

AE	ZO (n=143)		O (n=71)	
	any grade, N (%)	≥G3, N (%)	any grade, N (%)	≥G3, N (%)
≥1 TEAE	135(94)	90(63)	64(90)	34(48)
Thrombocytopenia ^a	51(36)	22(15)	17(24)	5(7)
Neutropenia ^b	42(29)	35(24)	20(28)	16(23)
Diarrhea	26(18)	4(3)	12(17)	1(1)
Fatigue	22(15)	0(0)	10(14)	1(1)
Constipation	19(13)	0(0)	6(8)	0(0)
Pyrexia	19(13)	0(0)	14(20)	0(0)
Cough	18(13)	0(0)	9(13)	0(0)
Pneumonia	17(12)	14(10)	5(7)	3(4)
Asthenia	17(12)	1(1)	6(8)	0(0)
Dyspnea	16(11)	3(2)	7(10)	0(0)
Back pain	15(10)	1(1)	4(6)	1(1)
Anemia	16(11)	7(5)	7(10)	4(6)
COVID - 19	14(10)	8(6)	7(10)	2(3)

^aIncludes thrombocytopenia and platelet count decreased; ^bIncludes neutropenia and neutrophil count decrease.

- Grade ≥3 thrombocytopenia, pneumonia ,diarrhea, and dyspnea were more frequent with ZO
- Grade≥3 neutropenia and anemia were similar between 2 groups
- **Incidence of bleeding, atrial fibrillation and hypertension were low** with ZO and similar to O.

Recommendation of zanubrutinib + obinutuzumab for R/R FL

NCCN 2025 V2 Z+O for R/R FL

NCCN National Comprehensive Cancer Network®
NCCN Guidelines Version 2.2025
Classic Follicular Lymphoma
[NCCN Guidelines Index](#)
[Table of Contents](#)
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SUGGESTED TREATMENT REGIMENS^{a,b,c}

THIRD-LINE AND SUBSEQUENT THERAPY	
Subsequent systemic therapy options include second-line therapy regimens (FOLL-B 2 of 6) that were not previously given.	
Preferred regimens (in alphabetical order) • T-cell engager therapy ◊ Bispecific antibody therapy^{l,m} ◊ Epcoritamab-bysp ◊ Mosunetuzumab-axgb ◊ Chimeric antigen receptor (CAR) T-cell therapyⁿ ◊ Axicabtagene ciloleucel (CD19-directed) ◊ Lisocabtagene maraleucel (CD19-directed) ◊ Tisagenlecleucel (CD19-directed)	Other recommended regimens • EZH2 inhibitor ◊ Tazemetostat^o (irrespective of EZH2 mutation status) • BTK inhibitor (BTKi) ◊ Zanubrutinib^l + obinutuzumab • Loncastuximab tesirine-tpyl + rituximab (category 2B)^k

THIRD-LINE CONSOLIDATION THERAPY

Useful in Certain Circumstances

- Allogeneic hematopoietic cell transplantation (HCT) in selected cases^o

CSCO 2025 in China

Z+O for R/R FL (category 1 recommendation)

4.3 复发 / 难治 FL (FL1~3a 级) 的治疗

	I 级推荐	II 级推荐	III 级推荐
二线、三线或后续治疗	利妥昔单抗 / 奥妥珠单抗 -CHOP [2A 类] 利妥昔单抗 / 奥妥珠单抗 -CVP [2A 类] 利妥昔单抗 / 奥妥珠单抗 + 苯达莫司汀 (既往使用过苯达莫司汀患者不推荐再使用) [2A 类] 利妥昔单抗 + 来那度胺 [2A 类] 莫妥珠单抗 ^c [2A 类] 奥妥珠单抗 + 泽布替尼^b [2A 类] 参照弥漫大 B 细胞淋巴瘤的二线治疗方案 [2A 类] 临床试验 [2A 类]	可泮利塞 ^a [2A 类] 利妥昔单抗 [2A 类] 来那度胺 [2A 类] 奥妥珠单抗 + 来那度胺 [2A 类] 奥妥珠单抗 [2A 类] 林普利塞 ^e [2A 类] 瑞基奥仑赛 ^d [2A 类] 他泽司他 ^f [3 类]	
老年或体弱患者的二线治疗	利妥昔单抗 (优选) [2A 类]	烷化剂单药 ± 利妥昔单抗 [2A 类]	
二线巩固和维持治疗	利妥昔单抗 ^g [1 类] 奥妥珠单抗 ^h [2A 类]	自体造血干细胞移植 ⁱ [2A 类]	

注: *. 该药在国外已批准上市, 国内尚未批准上市。

a~f 一般为三线或后续用药。

Zanubrutinib approved for R/R MZL indication globally (without China) by MAGNOLIA

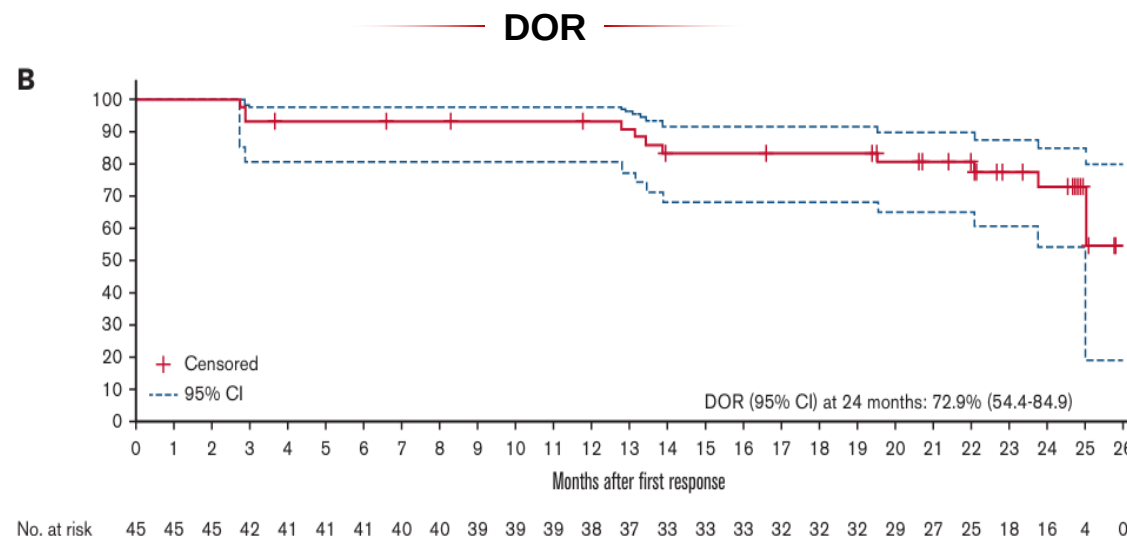
≥ 18 years old
≥1 CD20 mAbs regimen
R/R MZL
(N=68)

zanubrutinib
(160mg bid, till PD or unacceptable toxicity or
patient withdrawal)

- Primary endpoint: IRC-ORR
- Secondary endpoint: Safety, DOR, PFS and OS

	Extranodal (n=25)	Nodal (n=25)	Splenic (n=12)	Unknown (n=4)	Total (n=66)
ORR %	64.0	76.0	66.7	50.0	68.2
CR, n(%)	10(40.0)	5(20.0)	1(8.3)	1(25.0)	17(25.8)
PR, n(%)	6(24.0)	14(56.0)	7(58.3)	1(25.0)	28(42.4)
SD, n(%)	4(16.0)	5(20.0)	3(25.0)	1(25.0)	13(19.7)
PD, n(%)	3(12.0)	1(4.0)	1(8.3)	1(25.0)	6(9.1)
Median time to response, mo (IQR)	2.8 (2.7-2.9)	2.8 (2.7-3.8)	3.6 (2.7-6.0)	2.7 (2.6-2.8)	2.8 (2.7-3.7)

- With a median follow-up of 27.4ms, 24ms DOR rate was **72.9%**, PFS and OS at 24ms were **70.9%** and **85.9%**, respectively.



Ongoing MAHOGANY: ZG vs R2 for R/R FL or MZL

Study design: Randomized, open label, phase 3 clinical trial

R/R FL or R/R MZL pts

Inclusion criteria

- FL(1-3A) or MZL confirmed by histology
- Previously received ≥ 1 CD20 mAbs regimen
- Relapse or refractory after recent systemic treatment
- Require treatment
- No prior BTK inhibitors
- No resistance to lenalidomide

FL cohort

Stratification

- age (≥ 60 vs < 60 years old)
- LOT (1-2L vs $> 2L$)
- refractory to Rituximab (yes or no)

R
1:1

ZG (N=300)

R2 (N=300)

Primary endpoint

- PFS by IRC

Secondary endpoint

- ORR and OS by IRC

MZL cohort

Stratification

- age (≥ 60 vs < 60 years old)
- LOT (1-2L vs $> 2L$)

R
1:1

ZR (N=75)

R2 (N=75)

Primary endpoint

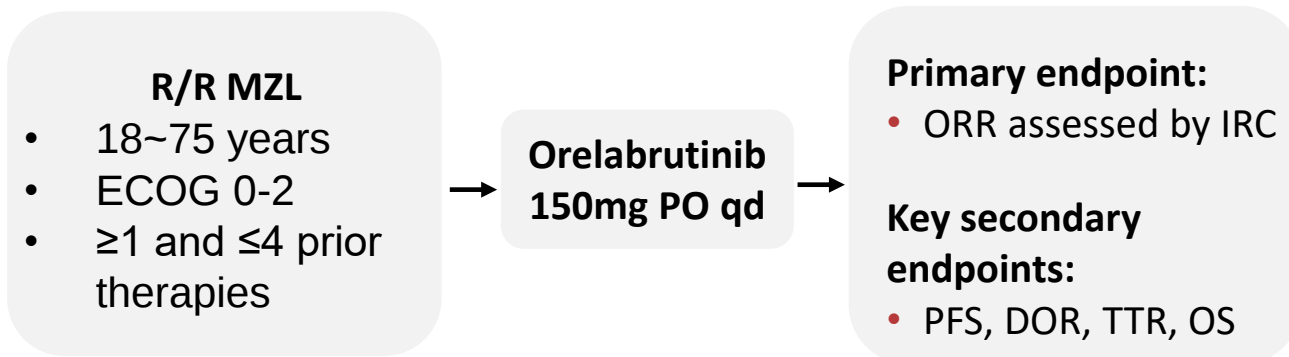
- PFS by IRC

Secondary endpoint

- ORR by IRC

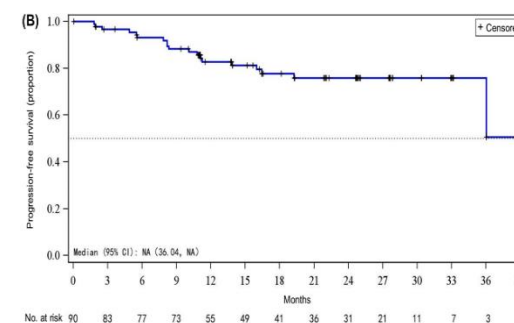
dosing: zanu (160mg bid or 320mg qd) till PD or unacceptable toxicity; obinutuzumab or rituximab up to 8 doses, len up to 1 cycles

Orelabrutinib in R/R MZL: registered study

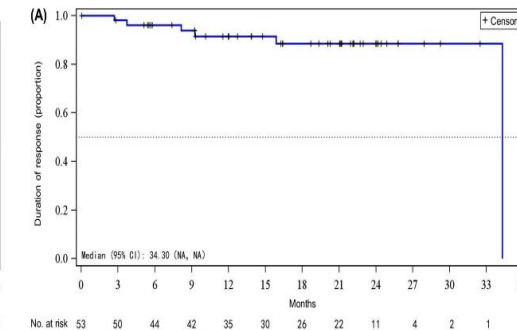


- 111 patients enrolled
- **90 patients had MZL confirmed by central pathology review**
- Efficacy assessment based on the 2014 Lugano Classification
- All patients underwent CT or MRI at baseline, every 8 weeks in C1–6, and every 12 weeks C7 and onwards
- The median follow up was 24.3 months

PFS by IRC



DOR by IRC



- ORR 58.9%, CR 11.1%
- mDOR 34.3m, mPFS not reached
- 12-m PFS 82.8%, 12-m OS 91.0%
- Approved for R/R MZL in China

01

Pathogenesis of FL make the exploration of BTKi in FL and MZL

02

Evidence-based Indications approved in China therapy BTKi in R/R FL and MZL

03

BTKi combination regimens moving to IL treatment for FL and MZL

Ibrutinib + rituximab for untreated FL

untreated FL (N=445)

- ≥70y or 60-69y with ≥1 comorbidity
- untreated CD20+FL
- met GELF criterion

R
3:1

Ibr+R: N=334

Ibr (560mg QD PO), until PD
R 375mg/m² qw for 4 wk then every 8 wk for up to 12 cycles

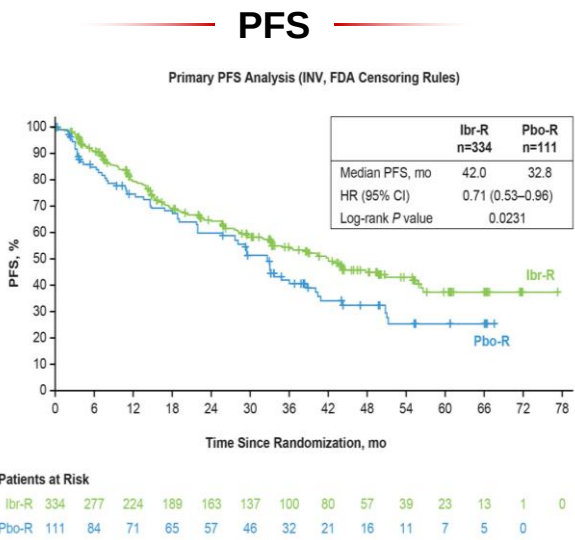
Pbo+R: N=111

Pbo (560mg QD PO), until PD
R 375mg/m² qw for 4 wk then every 8 wk for up to 12 cycles

- **Primary endpoint: PFS**
- **Secondary endpoint: ORR, OS, IRR, safety**

• Randomization was stratified by age (60–69 years vs. ≥ 70 years), FLIPI-1 score (low vs. intermediate/high), and ECOG PS (0–1 vs. 2).

Efficacy



- **PFS was significantly improved with Ibr-R vs Pbo-R** (HR, 0.71 [95% CI 0.53–0.96]; p = 0.02; median **42.0** vs. 32.8 mo)
- **ORR was 81% vs 68% with Ibr-R vs Pbo-R** (rate ratio 1.19 [95% CI 1.04–1.36]; p = 0.004)
- **4-y OS rates were 67% vs 71%** (HR 1.12 [95% CI 0.77 – 1.63]; p = 0.55).
- IRRs occurred in 21% vs 27% of pts with Ibr-R vs Pbo-R.

Safety

- **Grade ≥ 3 AEs occurred in 78% vs 57% of pts**
- Most frequent grade ≥ 3 AEs were neutropenia (16% vs 7%), pneumonia (9% vs. 5%), hypertension (8% vs. 5%), COVID-19 (6% vs. 2%), COVID-19 pneumonia (6% vs. 3%), and diarrhea (6% vs. 2%)
- **Atrial fibrillation occurred in 5% versus 2%.**
- Primary causes of death included AEs (**14%** vs. 7%) and FL (7% vs. 9%).
- COVID-19-related death occurred in 9% of pts in the Ibr-R arm and 7% in the Pbo-R arm.

Addition of Ibr led to significant improved PFS and consistent increased ORR, but AE rates were increased.

ibrutinib + obinutuzumab + BCL-2i for untreated FL

Age $\geq$ 18 y
untreated FL pts
(N=40)

OBINUTUZUMAB
(C1D1, 8, 15, C2-6 D1, followed by every other month)
+Venetoclax (D4-28, 400mg QD)
+Ibrutinib (D1-28, 560mg QD)

- **Primary:** CR rate at 12 months
- **Secondary:** safety, CR at 30 months, ORR, DOR, PFS and OS
- **Exploratory:** MRD in all responding pts

Therapy was continued for 24 cycles or until disease progression, unacceptable toxicity or voluntary withdrawal

Efficacy

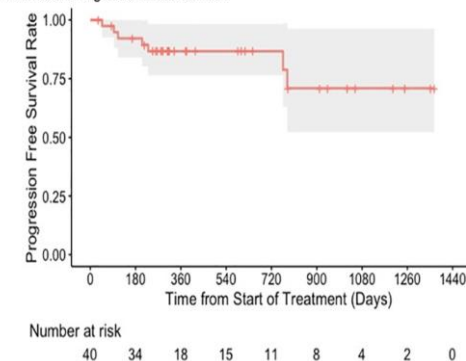
- CR rate at 12-ms was 92% for the 12 patients who completed at least 12 cycles.
- ORR for the entire cohort was 90% [73% CR + 17% PR].
- At 12-ms, PFS & OS were 86.8% & 97%.

Safety

- Most frequent hematologic toxicities were anemia in 25%, grade $\geq$ 3 in 5%, neutropenia 25% and grade $\geq$ 3 20%, thrombocytopenia 23% and grade $\geq$ 3 10%

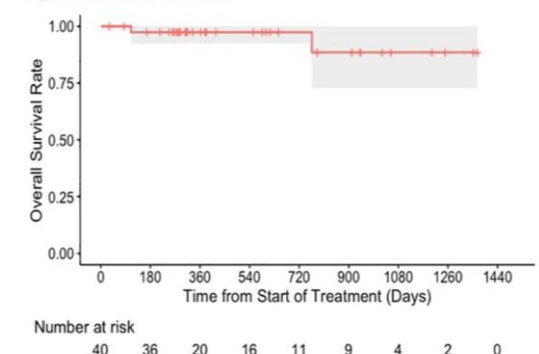
PFS

Figure 1A: median Progression Free Survival



OS

Figure 1B: median Overall Survival



Ibrutinib with obinutuzumab and BCL-2i was active as frontline therapy for untreated FL without any unexpected toxicities

Zanubrutinib + BR for untreated advanced FL

18-75 years old,
untreated advanced
(grade 1-3a, stage III/IV)
FL pts
(N=29)

Induction (every 4 weeks 1 cycle)
zanu (160 mg BID, C1-C6, D1-D21)
+ bendamustine (90 mg/m², C1 D2-3, C2-6 D1-2)
+ rituximab (375 mg/m², C1-6 D1)

CR/PR

**Maintenance
(every 12 weeks 1 cycle)**
R (375 mg/m², up to 2 years
or to PD/unacceptable
toxicity)

- **Primary : CRR**
- **Secondary : ORR, PFS, OS, safety**

Among 29 pts included in the analysis, 27 underwent tumor assessment after completing ≥ 1 treatment

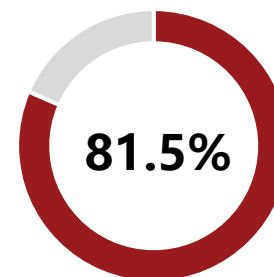
Efficacy

- CRR **81.5%**, ORR **100%**
- During a median follow-up of 6.2 months, **no deaths** were observed. The median PFS and OS **have not yet been reached** (6-month PFS rate: **88.29%**; 95%CI: 73.79-100%)

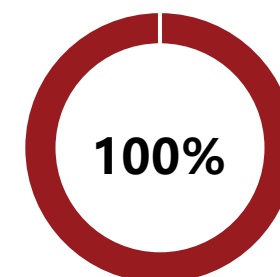
Safety

- Common AEs including neutropenia (43.3%), and rash (20%)
- Combination therapy did not show any new safety signals, overall safety was tolerable

CRR



ORR



Zanubrutinib combined BR showed excellent efficacy in 1L FL treatment, with CR rate of 81.5%, ORR 100%, and safety was manageable, which was significantly better than traditional immunotherapy



Mechanism of zanubrutinib makes it possible to combine with CD20 mAbs and explore its therapeutic potential in FL and MZL.



Exploring high efficacy and low toxicity combination regimens of BTKi in R/R FL and MZL or even newly diagnosed patients is ongoing.

I would like to thank all patients and their family, investigators and team members!

Thanks

