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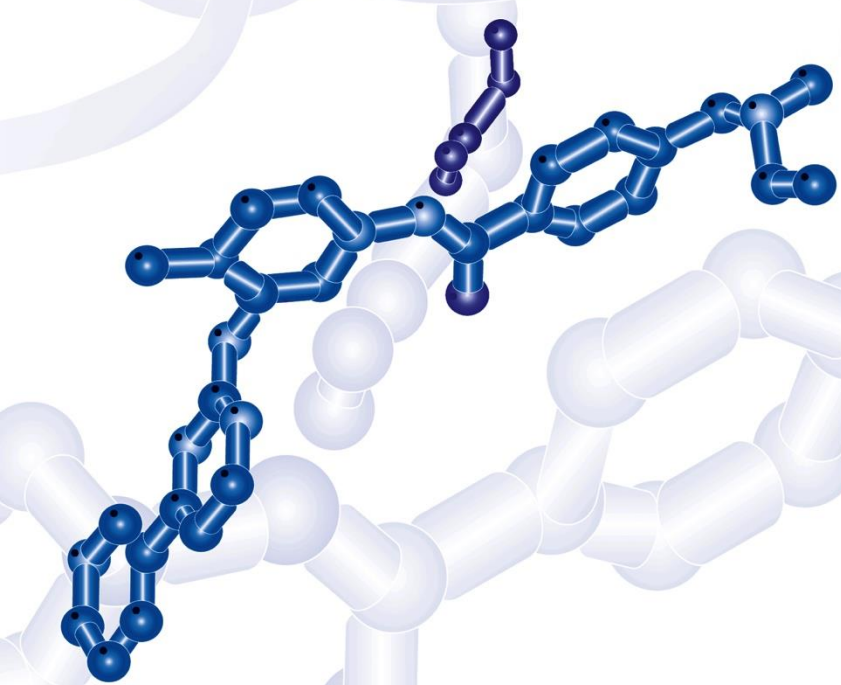

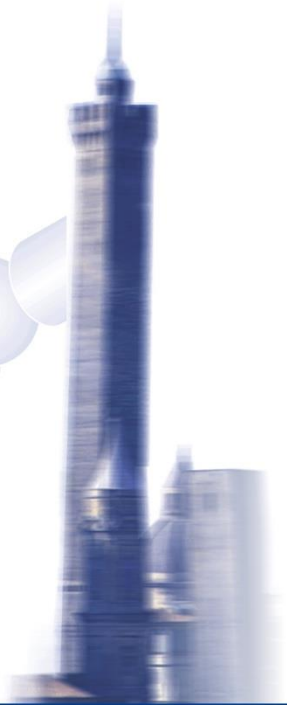

New Drugs in Hematology

President: Pier Luigi Zinzani

Bologna,
Royal Hotel Carlton
May 18-19-20, 2026

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Efficacy And Safety of Birelentinib (DZD8586), a Non-covalent BBB penetrant LYN/BTK Dual Inhibitor, in B-NHL

Disclosures

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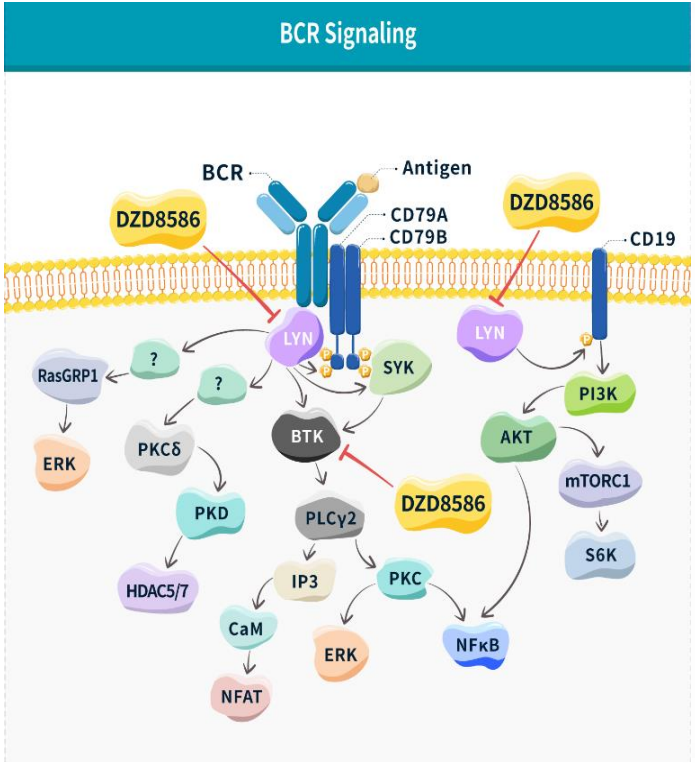
➢ Consultancy/advisory board participation (past 12 months):

- AbbVie, BeOne, AstraZeneca, MSD, Johnson & Johnson, Roche, Hengrui, InnoCare

➢ Research support (managed by institution):

- Janssen, BeOne, MSD, Takeda, Roche

DZD8586 (Birelentinib): A Selective LYN/BTK Dual Inhibitor



- **High selectivity for other TEC family kinases**: may avoid AEs observed with ibrutinib.
- **Binding BTK noncovalently without engaging Cys481:** retaining activity against both wild-type and C481S mutant BTK.
- **Simultaneous inhibition of LYN and BTK**: overcomes both BTK-dependent and BTK-independent activation of pro-tumor survival signaling.
- **Favorable BBB penetration property:** holds promising efficacy in patients with CNS involvement

Trials of Birelentinib in hematological malignant diseases

Trial	Phase	Population	Sample size	Status
TAI-SHAN1	1/2	RR B-NHL	N = 17	Completed
TAI-SHAN5	1	RR B-NHL	N = 17	Completed
TAI-SHAN6	3	RR CLL/SLL	N = 250 (Planned)	Ongoing
TAI-SHAN8	2	CLL/SLL	N = 155 (Planned)	Ongoing
TAI-SHAN9	2	DLBCL	N = 180 (Planned)	Ongoing
TAI-SHAN10	2	CLL/SLL, combo study	N = 66 (Planned)	Ongoing
TAI-SHAN12	2	DLBCL, combo study	N = 150 (Planned)	Ongoing

TAI-SHAN1 and TAI-SHAN5

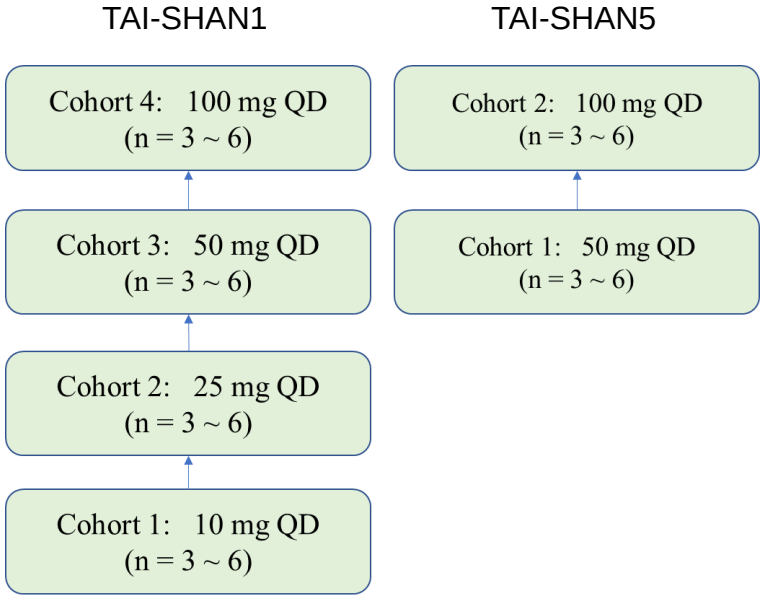
— Phase 1 trials in B-NHL patients

Study Design

Primary objectives
- Safety and tolerability of Birelentinib in patients with B-NHL
- Recommended dose

Secondary objectives
- Preliminary anti-tumor efficacy
- Data of pharmacokinetics

Patient population
- Patients who progressed or intolerant to prior systemic therapies
- Prior BTK inhibitor treatment allowed



- TAI-SHAN1 (NCT05844956; CTR20220558) was phase 1 dose escalation study, TAI-SHAN5 (NCT05824585) was expansion study, both being conducted in China, Australia and US.
- Both studies had similar design for dose escalation. Pooled safety and efficacy analysis was performed.
- Tumor response assessed by investigators per iwCLL 2018 for CLL, IPCG 2005 for CNSL and Lugano 2014 criteria for other B-NHL.

Abbreviations: B-NHL, B-cell Non-Hodgkin lymphoma; BTK, Bruton's tyrosine kinase; ORR, objective response rate; DoR, duration of response; PFS, progression free survival; r/r, relapsed or refractory; QD, once daily

Patient Demographics and Baseline Characteristics

Demographics	Safety set (N = 25)
Median age, y (range)	63 (38 - 77)
Male/Female, n (%)	17 (68.0)/8 (32.0)
Race (White/Asian), n (%)	8 (32.0)/17 (68.0)
ECOG PS (0/≥1), n (%)	11 (44.0)/14 (56.0)

Characteristics	Safety set (N = 25)
Tumor subtypes, n (%)	
Diffuse Large B-Cell Lymphoma (DLBCL)	11 (44.0)
Follicular Lymphoma (FL)	4 (16.0)
Marginal Zone Lymphoma (MZL)	3 (12.0)
Mantle Cell Lymphoma (MCL)	3 (12.0)
*Secondary Central Nervous System Lymphoma (SCNSL)**	*3 (12.0)*
Chronic Lymphocytic Leukemia (CLL)	1 (4.0)
Lines of prior therapies, median (range)	3 (1 - 8)
Types of prior therapies, n (%)	
Chemotherapy	24 (96.0)
Anti-CD20 antibody	24 (96.0)
BTK inhibitor	9 (36.0)
BCL2 inhibitor	2 (8.0)
PI3K inhibitor	2 (8.0)
CAR-T	4 (16.0)

Data cut-off: Oct 10, 2023
ECOG PS, Eastern Cooperative Oncology Group performance status;
N, Number of patients in the analysis set
The percentage was calculated based on N as the denominator.
* All secondary CNSL

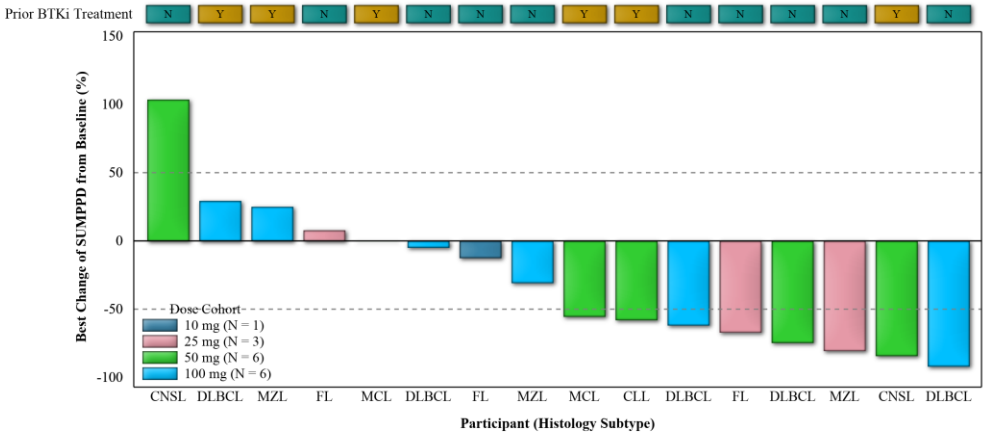
The Most Common TEAEs (≥10%)

TEAEs (n, %)	N = 25	
	All grades	≥ Grade 3
Thrombocytopenia	14 (56.0)	5 (20.0)
Neutropenia	8 (32.0)	4 (16.0)
Pneumonia	5 (20.0)	0 (0.0)
Upper respiratory tract infection	4 (16.0)	1 (4.0)
Anemia	4 (16.0)	0 (0.0)
Alanine aminotransferase increased	4 (16.0)	0 (0.0)
Blood lactate dehydrogenase increased	4 (16.0)	0 (0.0)
Aspartate aminotransferase increased	3 (12.0)	0 (0.0)
Diarrhea	3 (12.0)	0 (0.0)
Fatigue	3 (12.0)	0 (0.0)

- No case of ≥ grade 3 thrombocytopenia was observed at ≤50 mg QD. One DLT case was reported at 100 mg (grade 4 thrombocytopenia).
- No case of bleeding, atrial flutter, atrial fibrillation or arthralgia was reported. The dose level of 100 mg QD were defined as MTD based on SRC review.

Abbreviations: DLT, dose limiting toxicity; MTD, maximum tolerated dose; QD, once daily; SRC, safety review committee; TEAE, treatment emergent adverse event

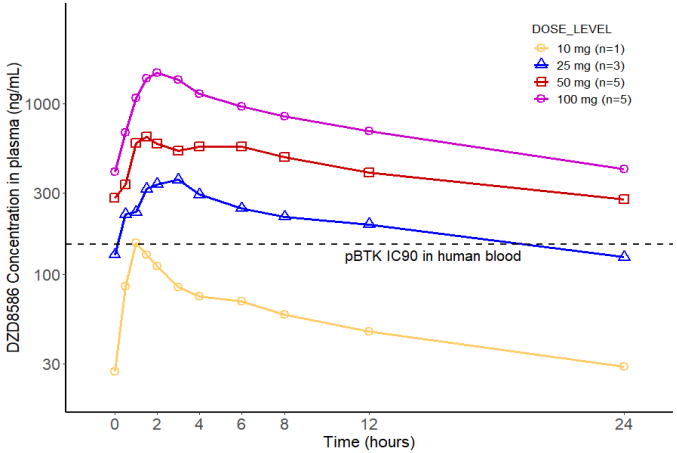
Anti-tumor Activity of Birelentinib in r/r B-NHL

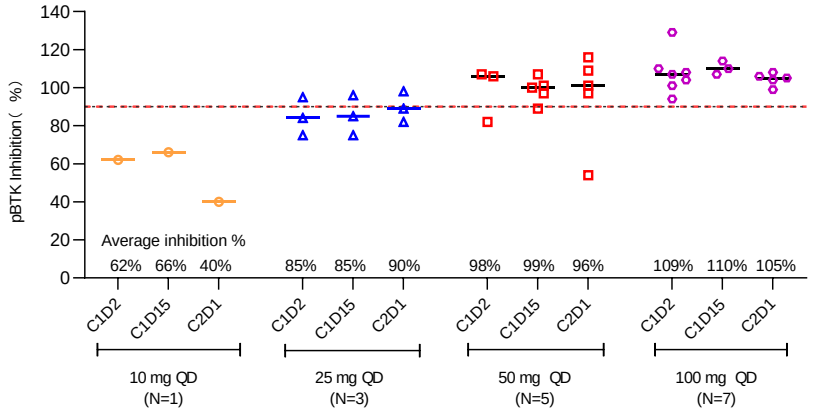


- Across all dose levels, ORR was 64.7% (11/17), including 3 CRs. At 50 mg, ORR was 71.4% (5/7).
- Tumor response observed in different subtypes of B-NHL. In 6 patients with prior BTKi treatment, 3 (50%) achieved tumor response, including one CLL patient with C481S BTK mutation.
- DZD8586 demonstrated manageable safety and favorable PK properties as an oral agent with high CNS penetration.

Abbreviations: CR, complete response; GCB, germinal center B-cell; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease
* A total of 16 patients with measurable disease at the baseline and at least one follow-up tumor assessment were included in this waterfall plot. One patient with DLBCL (metabolic PR) was not included in the waterfall plot due to tumor size measurement of CT scan. The ORR combined PET/CT and CT-based assessment for Lugano criteria.

Pharmacokinetics and Pharmacodynamics





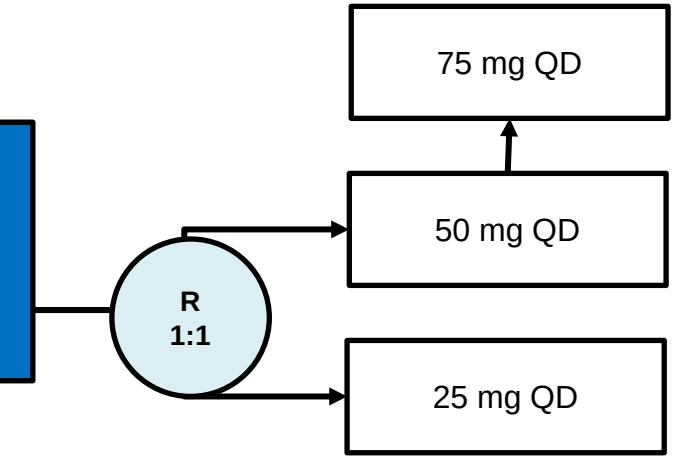
- DZD8586 showed approximately dose-proportional PK profile across 10 mg to 100 mg.
- ***DZD8586 was absorbed rapidly,*** with median T_{max} of ~1.5 hours and eliminated with mean terminal half-life of ~18 hours. As expected from *the* ***long half-life***, accumulation of ~ 2-fold was observed after multiple once daily dosing.
- ***In 2 patients with CNSL, the unbound CSF-to-plasma concentration ratio ($K_{puu,CSF}$) at steady state were 1.21 and 0.98, suggesting high CNS penetration of DZD8586.***
- Sustained pBTK inhibition (> 90%) was observed at steady state following multiple dosing at ≥ 25 mg dose levels.

TAI-SHAN8

— Phase 2 trial in r/r CLL/SLL patients

Study Design

Key Eligibility
- Patients with previously treated CLL/SLL requiring further treatment per iwCLL 2018
- At least one prior line of systemic therapy
- Prior non-covalent BTK inhibitors, BTK degraders, BCL-2 inhibitors allowed.



Primary Endpoint
- ORR assessed by investigator

Secondary Endpoints
- PFS, DoR
- Safety
- Pharmacokinetics

- TAI-SHAN8 is a phase 2 study in patients with r/r CLL/SLL, dose ranged from 25 to 75 mg. (TAI-SHAN5 is a phase 1 study in patients with r/r B-NHL, dose ranged from 50 to 100 mg.)
- Two clinical studies, TAI-SHAN8 (NCT06539182, CTR20240120) and TAI-SHAN5 (NCT05824585) were pooled for the safety and efficacy analysis in patients with CLL/SLL.
- Tumor response was assessed by investigators per iwCLL 2018 or Lugano 2014 criteria as appropriate.

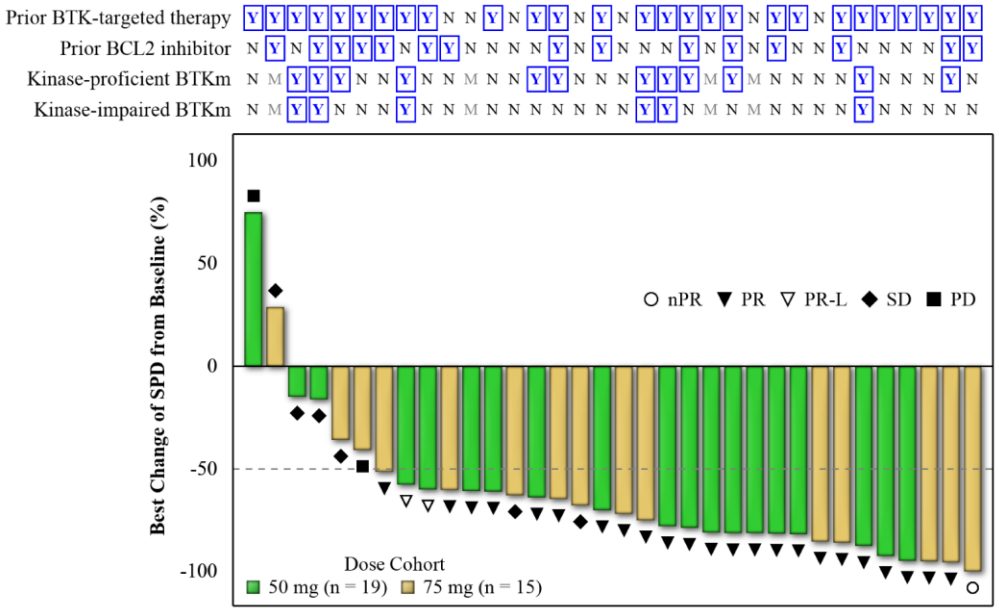
CLL/SLL: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; DoR: Duration of Response; ORR: Objective Response Rate; PFS: Progression Free Survival; QD, once daily; R: randomization; r/r: relapsed or refractory.

Patient Demographics and Baseline Characteristics

Characteristics	Safety Set (N = 63)
Dose 50 mg/ 75 mg, n (%)	42 (67) /17 (27)
Median Age, y (range)	63 (34 - 84)
Male/Female, n (%)	41 (65)/22 (35)
Race (White/Asian), n (%)	4 (6)/59 (94)
ECOG Performance Status (0/≥1), n (%)	26 (41)/37 (59)
Lines of Prior Anti-cancer Therapies, Median (range)	2 (1 - 8)
Types of Prior Anti-cancer Therapies, n (%)	
BTK-targeted therapy	51 (81)
Covalent BTK inhibitor	48 (76)
Non-covalent BTK inhibitor	6 (10)
BTK degrader	5 (8)
Chemoimmunotherapy	35 (56)
BCL2 inhibitor	24 (38)
Risk Characteristics	
Del(17p) and/or TP53 mutation	14/35 (40)
BTK Mutation Status	
Kinase-proficient mutations (C481S/T474I)	18/42 (43)
Kinase-impaired mutations (C481Y/C481R/C481F/L528W)	9/42 (21)

ECOG: Eastern Cooperative Oncology Group. Data cut-off: Oct 10, 2025.

Durable Tumor Response with DZD8586 Treatment



M: Missing; N: No; nPR: Nodular Partial Response; PR: Partial Response; PR-L: Partial Response with Lymphocytosis; SD: Stable Disease; PD: Progressive Disease; SPD: Sum of the Product of the Perpendicular Diameters. Y: Yes.
A total of 35 patients with both baseline and at least one post-treatment tumor assessment were included in the efficacy analysis set, and among them, 34 patients with baseline measurable disease were shown in the figure.
Objective response included nPR, PR and PR-L.
Kinase-proficient mutations included C481S/T474I. Kinase-impaired mutations included C481Y/C481R/C481F/L528W.

At 50 mg QD:

- ✓ **The ORR was 84%.** Tumor response observed in patients with prior BTK-targeted therapy (82%, 14/17), including covalent BTKi (80%, 12/15), non-covalent BTKi (100%, 2/2), and BTK degrader (50%, 1/2).
- ✓ In patients with prior exposure to both BTK-targeted therapy and BCL2 inhibitor, the ORR was 83% (5/6).
- ✓ Tumor response observed in patients with kinase-proficient mutations (75%, 6/8) and kinase-impaired mutations (60%, 3/5).

The recommended phase 3 dose was 50 mg QD.

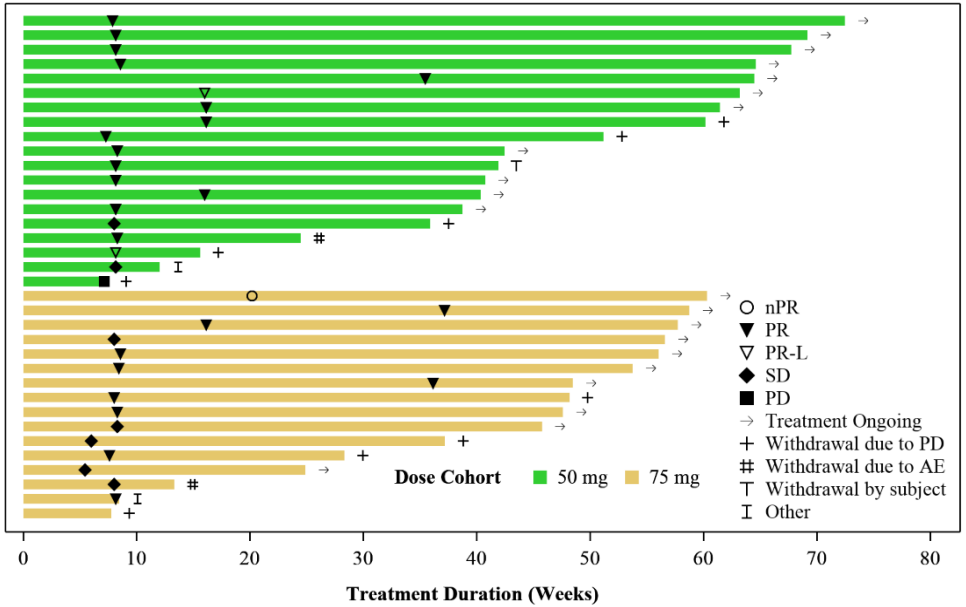
Efficacy of Birelentinib in Different Subgroups

- At 50 mg and 75 mg QD, tumor responses were observed in different subgroups.

Characteristics, n/N with known status (%)	Efficacy Set (N = 35)
Previously received BTK-targeted therapy + BCL-2 inhibitor	10/15 (66.7)
Previously received noncovalent BTK inhibitor	3/4 (75.0)
Previously received BTK degrader	3/5 (60.0)
17p deletion and/or TP53 mutation	8/11 (72.7)
Complex karyotype	10/13 (76.9)
BTK C481X mutation	8/9 (88.9)
Other BTK mutation (including L528W, L528F, T474I)	3/5 (60)

Patients with both baseline and at least one post-treatment tumor assessment were included in the efficacy analysis.

Durable Tumor Response with DZD8586 Treatment



With prolonged follow-up, sustained antitumor efficacy was observed.

At 50 mg cohort:

- ✓Median duration of treatment was longer than 10 months.
- ✓Median PFS was not reached, with 63.2% of the patients still event-free.

Efficacy evaluable set were all enrolled before 13 Jan 2025.

Common TEAE

	25 mg (N = 3)		50 mg (N = 42)		75 mg (N = 17)		100 mg (N = 1)	
Preferred Term	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Participants with any TRAE, n (%)	3 (100)	0 (0)	38 (91)	19 (45)	17 (100)	10 (59)	1 (100)	1 (100)
Thrombocytopenia	1 (33)	0 (0)	20 (48)	2 (5)	11 (65)	4 (24)	1 (100)	1 (100)
Neutropenia	0 (0)	0 (0)	16 (38)	12 (29)	8 (47)	6 (35)	1 (100)	0 (0)
Aspartate aminotransferase increased	0 (0)	0 (0)	7 (17)	1 (2)	9 (53)	0 (0)	0 (0)	0 (0)
Pneumonia	1 (33)	0 (0)	8 (19)	6 (14)	5 (29)	5 (29)	0 (0)	0 (0)
Anemia	2 (67)	0 (0)	7 (17)	0 (0)	4 (24)	0 (0)	0 (0)	0 (0)
White blood cell count decreased	0 (0)	0 (0)	5 (12)	2 (5)	5 (29)	0 (0)	0 (0)	0 (0)
Blood creatinine increased	0 (0)	0 (0)	5 (12)	0 (0)	4 (24)	0 (0)	0 (0)	0 (0)
Rash	1 (33)	0 (0)	5 (12)	0 (0)	2 (12)	0 (0)	0 (0)	0 (0)

TEAE: Treatment-Emergent Adverse Event; TRAE: Treatment-related Adverse Event. TRAE ≥10% in all grades in 50 mg were summarized.

Birelentinib showed favorable safety profile at 50 mg QD (RP3D), no new safety signals were identified:

- ✓The most common TEAEs of all grades included neutropenia and thrombocytopenia.
- ✓No QT prolongation or atrial fibrillation. No drug-related major bleeding.
- ✓TEAE leading to treatment discontinuation in 1 patient (2%). No treatment-related AE leading to death.

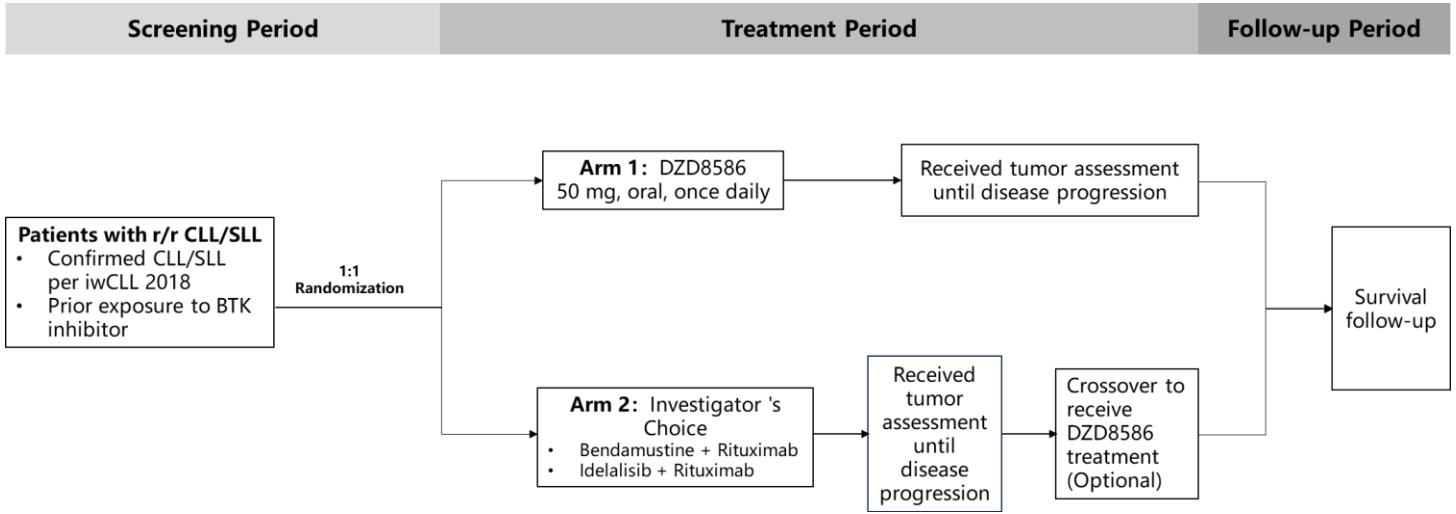
- Birelentinib showed promising efficacy with manageable safety profile in heavily pre-treated CLL/SLL patients.
- At 50 mg QD (RP3D)
  - Efficacy:
    - ✓ **ORR was 84.2%.** Tumor response observed irrespective of **prior BTKi, BTK degrader, or BCL-2 inhibitor treatment,** and in patients with kinase-proficient or kinase-impaired BTK mutation.
    - ✓ Sustained efficacy was also observed.
  - Safety:
    - ✓ No new safety concerns during follow-up.
    - ✓ The most common ≥ grade 3 TEAEs (neutropenia and pneumonia) could be well managed.

TAI-SHAN6

— ongoing global Phase 3 trial in r/r CLL/SLL patients

Study Design

A Phase 3, Open-Label, Randomized, Multicenter Study to Evaluate Anti-tumor Efficacy of Birelentinib vs. Investigator's Choice in Patients with r/r CLL/SLL



Conclusions

- Both pre-clinical and clinical data demonstrated that Birelentinib overcomes resistance to covalent and non-covalent BTK inhibitor via dual inhibition of the LYN and BTK signaling pathways.
- Anti-tumor efficacy has been observed in patients with B-NHL, across distinct pathological subtypes.
- Birelentinib exhibits a manageable safety profile.
- In 3 patients with CNSL, excellent CSF-to-plasma concentration ratio showed high CNS penetration.
- Additional Phase 3 trials in CLL/SLL and other B-NHL subtypes, including CNSL, are currently underway or planned.

Thank you!