A Phase 3, Randomized, Double-Blind Study of Tazemetostat or Placebo Plus Lenalidomide and Rituximab in Patients With Relapsed/Refractory Follicular Lymphoma

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Introduction

- Relapsed or refractory (R/R) follicular lymphoma (FL) remains a challenging disease without a universally recognized standard of care, necessitating novel treatment strategies[1,2]
- Lenalidomide in combination with rituximab (R^2) is a preferred chemotherapy-free regimen approved by the US Food and Drug Administration (FDA) for patients with previously treated FL[3,4]
- Tazemetostat (TAZ), an enhancer of zeste homolog 2 (EZH2) inhibitor, is also approved by the FDA for the treatment of patients with R/R FL whose disease has mutant (MT) *EZH2* and who have received ≥2 prior therapies, or for the treatment of patients with R/R FL who have no satisfactory alternative treatment options[5]
- EZH2 is an epigenetic regulator that catalyzes the histone 3 lysine 27 trimethylation gene suppressive mark, essential for B-cell development[6]
- EZH2 has pleiotropic effects on the tumor microenvironment, resulting in decreased tumor immunogenicity,[7,8] thus supporting combination approaches to treatment with TAZ
- SYMPHONY-1 (EZH-302; NCT04224493) is a phase 1b/3 study designed to determine the recommended phase 3 dose (RP3D), efficacy, and safety of TAZ plus R^2 in patients with R/R FL after ≥1 prior therapy
  - In the phase 1b portion of this study,[9] no dose-limiting toxicities were observed, TAZ 800 mg twice daily was selected as the RP3D in combination with R^2, and, after a median follow-up of 11.2 months, the objective response rate (ORR) was 97.6% in the response-evaluable population (n=41)
- Here we present the ongoing phase 3 portion of the SYMPHONY-1 study

Objective

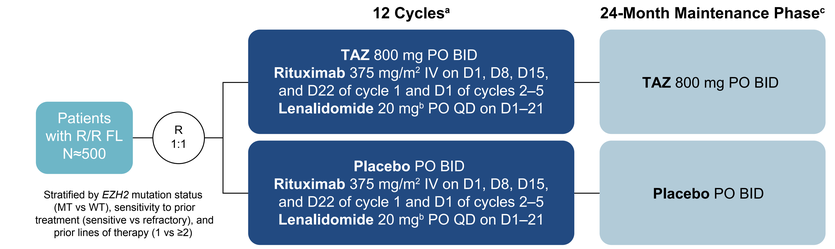
- To evaluate the efficacy and safety of TAZ + R^2 vs placebo + R^2 in patients with R/R FL who received ≥1 prior line of chemotherapy, immunotherapy, or chemoimmunotherapy

Methods

Study Design

- SYMPHONY-1 is an international, double-blind, randomized phase 1b/3 study in patients with R/R FL
- The study design of stage 1 (phase 1b) was previously described, and data have been reported[9]
- In stage 2 (phase 3), approximately 500 patients with R/R FL (*EZH2* all comers) will be enrolled (**Figure 1**)
- Patients will be randomized 1:1 to receive either TAZ + R^2 or placebo + R^2
  - Randomization will be blinded and stratified by *EZH2* mutation status (MT vs wild-type), sensitivity to prior treatment (sensitive vs refractory), and prior lines of therapy (1 vs ≥2)
  - Enrollment of patients with MT *EZH2* will be capped at 150–210 patients to reflect the real-world prevalence (up to 30%) of this patient population
- Stage 2 will include 2 interim futility analyses
  - The first analysis will be based on ORR, to be initiated when 100 patients are evaluable for ORR
  - The second analysis will be based on progression-free survival (PFS), to be initiated 3 years after the first patient is enrolled
- Stage 3 (phase 3) is an optional component of the study that will evaluate the efficacy and safety of TAZ + R^2 in patients with MT *EZH2* R/R FL only
  - Stage 3 will be executed if the efficacy in the overall FL population in stage 2 does not meet the specified threshold, and the efficacy in the MT *EZH2* FL population is sufficiently promising

Figure 1. Study Design



[a]All patients receive treatment in 28-day cycles for 12 cycles or until disease progression, unacceptable toxicity, or withdrawal of consent. [b]Lenalidomide 20 mg (CrCl ≥60 mL/min) or 10 mg (CrCl <60 mL/min). [c]During the maintenance phase, patients will continue to receive treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

BID, twice daily; CrCl, creatinine clearance; D, day; *EZH2*, enhancer of zeste homolog 2; FL, follicular lymphoma; IV, intravenously; MT, mutant; PO, orally; QD, once daily; R, randomized; R/R, relapsed or refractory; TAZ, tazemetostat; WT, wild-type.

Endpoints

- The primary endpoint is investigator-assessed PFS per the 2014 Lugano classification (**Table 1**)
- The key secondary endpoints are independent review committee (IRC)–assessed PFS, ORR, duration of response, and duration of complete response, and changes in patient-reported quality of life as measured by the 5-dimension, 5-level EuroQol (EQ-5D-5L) instrument and Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym)
- Mutations that arise in *EZH2* during the course of treatment compared with baseline circulating tumor DNA (ctDNA) and with tumor biopsy samples, when possible, will be identified in ctDNA isolated from liquid biopsies, using molecular biological approaches, as an exploratory endpoint

Table 1. Primary, Secondary, and Exploratory Endpoints

Primary Endpoint	Secondary Endpoints	Exploratory Endpoint
PFS (investigator assessed)	PFS (IRC assessed)[a]	Identification of *EZH2* mutations during treatment course vs baseline ctDNA and tumor biopsy
	ORR[a]	
	DOR[a]	
	DOCR[a]	
	DCR	
	OS	
	QoL[a]	
	Population PK	
	Safety and tolerability	

[a]Key secondary endpoints.

ctDNA, circulating tumor DNA; DCR, disease control rate; DOCR, duration of complete response; DOR, duration of response; *EZH2*, enhancer of zeste homolog 2; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QoL, quality of life.

Current Status

- The first study patient was enrolled in quarter 1 of 2022
- Enrollment is expected to finish in quarter 4 of 2024
- As of July 2023, 145 sites are currently recruiting patients in Australia, Belgium, Canada, China, France, Germany, Hungary, Italy, South Korea, Poland, Spain, Taiwan, UK, and USA

Patient Population

- Patients with R/R FL who have had ≥1 prior line of chemotherapy, immunotherapy, or chemoimmunotherapy will be enrolled (**Table 2**)

Table 2. Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Aged ≥18 years[a] with a life expectancy of ≥3 months before enrollment	Grade 3b, mixed-histology, or FL that has histologically transformed to DLBCL (patients whose disease transformed from DLBCL to FL may be enrolled)
Histologically confirmed FL, grade 1–3A	Prior exposure to lenalidomide, tazemetostat, or other EZH2 inhibitor(s)
Sufficient tumor tissue for *EZH2* mutation testing	Uncontrolled leptomeningeal or uncontrolled/previously treated brain metastasis
Previously treated with ≥1 prior systemic chemotherapy, immunotherapy, or chemoimmunotherapy • Prior autologous/allogeneic HSCT will be allowed • Prior CAR T-cell therapy will be allowed	Major surgery within 4 weeks before first dose of study treatment
Documented relapsed, refractory, or progressive disease following systemic treatment	Active infection with HBV, HCV, HIV, or HTLV-1
Measurable disease, as defined per the Lugano classification	Prior history of T-LBL or T-ALL
ECOG PS 0–2	Significant cardiovascular impairment
Adequate hematologic, hepatic, and renal function	

[a]Aged ≥20 years in Taiwan.

CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; *EZH2*, enhancer of zeste homolog 2; FL, follicular lymphoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; HTLV-1, human T-cell lymphotropic virus 1; T-ALL, T-cell acute lymphoblastic leukemia; T-LBL, T-cell lymphoblastic lymphoma.

Statistical Analysis

- All demographics and baseline disease characteristics will be summarized descriptively by treatment group for the intent-to-treat (ITT) population
- The primary efficacy analysis will be conducted for the ITT population and analyzed based on the treatment arm in which the patients are assigned initially
- The primary endpoint, investigator-assessed PFS, and a key secondary efficacy endpoint, IRC-assessed PFS, will be compared between the 2 treatment arms using the stratified log-rank test (adjusted for the stratification factors); hazard ratios with corresponding 2-sided 95% confidence intervals will be estimated using a stratified Cox proportional hazards model
  - PFS will also be summarized descriptively using the Kaplan–Meier method
- Another key secondary efficacy endpoint, investigator- and IRC-assessed ORR, will be calculated by treatment group
  - The Cochran-Mantel-Haenszel test will be used to adjust for possible confounding effects of the stratification factors
- The safety analysis will be conducted in the safety population and analyzed based on the treatment received
- Safety analyses will be assessed using adverse events (AEs), clinical laboratory assessments, physical examination findings, vital sign measurements, electrocardiogram results, Eastern Cooperative Oncology Group performance status, study drug exposure, and treatment compliance
  - AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time of the analysis, and the severity of each AE will be graded by the investigator based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

Author Contributions
Substantial contributions to the study conception/design, or acquisition/analysis/interpretation of data: All authors
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Final approval of the publication: All authors

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