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Phase I Study of TAK-659, an Investigational, Dual SYK/FLT3 Inhibitor, in Patients with B-Cell Lymphoma

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ABSTRACT

Purpose: TAK-659 is an investigational, dual SYK/FLT3 inhibitor with preclinical activity in B-cell malignancy models. This first-in-human, dose-escalation/expansion study aimed to determine the safety, tolerability, MTD/recommended phase II dose (RP2D), and preliminary efficacy of TAK-659 in relapsed/refractory solid tumors and B-cell lymphomas.

Patients and Methods: Patients received continuous, once-daily oral TAK-659, 60–120 mg in 28-day cycles, until disease progression or unacceptable toxicity. The study applied an accelerated dose-escalation design to determine the MTD and RP2D. In the expansion phase, patients with lymphoma were enrolled in five disease cohorts at the MTD.

Results: Overall, 105 patients were enrolled [dose escalation, $n = 36$ (solid tumors, $n = 19$; lymphoma, $n = 17$); expansion, $n = 69$]. The MTD was 100 mg once daily. TAK-659 absorption was fast (T_{max} ~2 hours) with a long terminal half-life (~37 hours). Exposure generally increased with dose (60–120 mg), with moderate variability. The most common treatment-related adverse events were generally asymptomatic and reversible elevations in clinical laboratory values. Among 43 response-evaluable patients with diffuse large B-cell lymphoma, 8 (19%) achieved a complete response (CR) with an overall response rate (ORR) of 28% [23% intent-to-treat (ITT)]. Responses were seen in both *de novo* and transformed disease and appeared independent of cell-of-origin classification. Among 9 response-evaluable patients with follicular lymphoma, 2 (22%) achieved CR with an ORR of 89% (57% ITT).

Conclusions: TAK-659 has single-agent activity in patients with B-cell lymphoma. Further studies of the drug in combination, including an evaluation of the biologically optimal and safest long-term dose and schedule, are warranted.

Introduction

Spleen tyrosine kinase (SYK) is a nonreceptor cytoplasmic kinase expressed primarily in hematopoietic cells. It is an essential component of the signaling machinery involved in B-cell receptor (BCR)–mediated signaling (1–3). Once activated, SYK propagates the BCR signal by associating with adaptor proteins and phosphorylating signaling intermediates, such as B-cell linker protein, Bruton tyrosine kinase (BTK), and phospholipase Cγ2 (PLC-γ2), leading to cell proliferation, differentiation, and survival (4, 5). SYK also appears to play a role in nonimmune functions, including cellular adhesion, bone metabolism, and platelet function (6).

Aberrant SYK-mediated signaling from the BCR has been implicated in the pathogenesis of several B-cell malignancies (7, 8), including upregulated SYK mRNA and protein levels (4), and constitutive SYK activation (9). Consequently, SYK is an attractive target in the treatment of B-cell malignancies mediated by BCR signaling (8–10). Recent data also suggest that SYK is a component of the cellular signaling cascade associated with Epstein–Barr virus (EBV) latency and transformation, and is involved with cell–cell and cell–matrix interactions (11), which may be relevant in EBV-positive posttransplant lymphoproliferative disorder (PTLD). In addition, evidence suggests that the SYK pathway may also be implicated in select solid tumors (12–15).

TAK-659 is an investigational, oral, reversible, and potent dual inhibitor of SYK and FMS-like tyrosine kinase 3 (FLT3; ref. 16). TAK-659 has demonstrated inhibitory activity in preclinical models of diffuse large B-cell lymphoma (DLBCL), in a RL follicular lymphoma (FL) cell line (17), and in chronic lymphocytic leukemia (CLL) cells (18). Preclinical studies in multiple syngeneic or xenograft models have also shown that TAK-659 administration can result in reductions

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Translational Relevance

In this phase I study, the MTD of TAK-659 was 100 mg once daily. The safety and activity of TAK-659 at the MTD was evaluated in an additional 69 patients with lymphoma (expansion phase). Common treatment-emergent adverse events were generally asymptomatic and reversible elevations in clinical laboratory values. TAK-659 showed single-agent activity across different histologic subtypes. Responses occurred in both *de novo* and transformed disease and appeared independent of cell-of-origin classification.

These data suggest that targeting spleen tyrosine kinase (the role of FLT3 is unclear) with TAK-659 has clinical activity in B-cell malignancies. Further studies are needed to elucidate the exact mechanism of this effect and to further evaluate TAK-659 monotherapy or combination therapy in patients with relapsed/refractory B-cell malignancies.

in immunosuppressive cell populations, such as myeloid-derived suppressor cells (MDSC) and regulatory T cells, which are mediated by both SYK and FLT3 signaling (19), suggesting an immune-modulating effect (20, 21). It is not clear whether antagonizing FLT3 signaling in parallel will contribute further to the clinical activity of TAK-659 in B-cell malignancies. To date, FLT3 inhibitors have no reported activity in B-cell lymphomas.

On the basis of these preclinical data, we conducted a first-in-human study of TAK-659 to determine the safety, tolerability, and MTD/recommended phase II dose (RP2D) of TAK-659 in patients with solid tumors and B-cell lymphomas. Four dose levels of TAK-659 were explored in patients with relapsed/refractory solid tumors or lymphomas (60, 80, 100, and 120 mg). Additional patients with lymphoma were treated with TAK-659 at the MTD in expansion cohorts. This manuscript primarily focuses on the results for patients with lymphoma.

Patients and Methods

Study design

This was a phase I, multicenter, open-label, dose-escalation, and expansion study of single-agent TAK-659. The primary objective was to determine the MTD/RP2D of TAK-659 administered orally once daily. Secondary objectives were to characterize the pharmacokinetics of TAK-659 and to assess the preliminary antitumor activity of TAK-659 in patients with relapsed/refractory B-cell lymphoma treated at the MTD/RP2D.

Patients received oral TAK-659 (tablets) continuously once daily in 28-day cycles. Patients were treated until disease progression or unacceptable toxicity.

The safe starting dose of TAK-659 based on nonclinical Good Laboratory Practice-compliant toxicology data for this first-in-human study was estimated to be 80 mg once daily (see Supplementary Information). However, 60 mg once daily was selected as the starting dose based on available tablet strengths at study start.

The phase I portion of the study applied an accelerated dose-escalation design to determine the MTD/RP2D. One patient was planned to be enrolled at the 60 mg starting dose and the two subsequent dose levels of 120 and 200 mg. In the initial single-patient cohorts, if either a dose-limiting toxicity (DLT; defined in Supplementary Table S1) or a related grade ≥2 adverse event (AE) occurred in cycle 1, the current and subsequent dose levels were to be tested in ≥3 patient cohorts. Dose escalation was then to follow a standard 3+3 design.

In expansion, patients with lymphoma were enrolled to five disease cohorts to receive TAK-659 at the MTD/RP2D, including CLL ($n = 12$ planned), DLBCL ($n = 12$–25 planned based on Simon's two-stage design; ≥3 responses in 12 patients required to proceed to the second stage), indolent non-Hodgkin lymphoma (iNHL; $n = 10$–23 planned based on Simon's two-stage design; ≥5 responses in 10 patients required to proceed to the second stage), mantle cell lymphoma (MCL; $n = 16$ planned), and PTLD ($n = 16$ planned). Prior to cycle 1, approximately 12 patients with iNHL were planned to complete a single-dose, 7-day, pharmacokinetic run-in to obtain at least 8 half-life–evaluable patients.

Patients

The dose-escalation phase enrolled adults with confirmed metastatic and/or advanced solid tumors or lymphoma. Patients had measurable or evaluable disease. The expansion phase enrolled patients with CLL, DLBCL, iNHL, MCL, or PTLD who had received ≥1 prior line(s) of therapy. Measurable disease was determined by the RECIST version 1.1 for solid tumors, or by the modified International Working Group criteria for malignant lymphoma (IWG 2007), or International Workshop on CLL criteria (22–24; Supplementary Information). Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, adequate organ function, and recovery from prior therapy. Patients with lymphoma in the expansion cohorts could have been previously treated with BCR pathway inhibitors not directly targeting SYK. Details on inclusion/exclusion criteria are reported in the Supplementary Information.

The study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice standards, and applicable regulatory requirements. Relevant institutional review boards or ethics committees approved all aspects of the study, and all authors had access to primary clinical trial data. All patients provided written informed consent. The trial is registered at ClinicalTrials.gov (NCT02000934).

Assessments

AEs were assessed throughout the study and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03. Plasma and urine samples were collected (Supplementary Information) for TAK-659 concentration measurements by high-performance liquid chromatography with tandem mass spectrometry detection. During dose escalation, responses were assessed at cycles 2, 4, 6, and every three cycles thereafter in patients with lymphoma. In expansion, responses were assessed at every even-numbered cycle through cycle 12, every four cycles through cycle 24, and every 6 months thereafter.

DLBCL cell of origin was determined by IHC when available (local laboratory) and was classified as germinal center B-cell (GCB) or non-GCB (Supplementary Information; ref. 25).

Statistical analysis

Statistical analyses were primarily descriptive without formal hypothesis testing. Median time to response, duration of response, and progression-free survival (PFS) were estimated using Kaplan–Meier methodology. Plasma and urine TAK-659 pharmacokinetic parameters in dose-escalation patients were derived using noncompartmental analysis with Phoenix WinNonlin 7.0 (Certara).

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Dose escalation was conducted according to a modified dose escalation rule, with 1 patient only for the first three cohorts, then 3–6 patients evaluated at each subsequent dose level, up to six planned ascending dose cohorts. Approximately 21–30 evaluable patients were planned to be enrolled according to the modified 3+3 dose-escalation scheme. The MTD/RP2D cohort was planned to have at least 6 patients, including a minimum of 3 patients with lymphoma or CLL.

The estimated sample size of 12 for the CLL expansion cohort was based on the following considerations: 12 patients would provide 61% power to detect a statistically significant difference between the uninteresting (20%) and interesting (50%) overall response rates (ORR) based on the exact one-sample binomial test.

A Simon two-stage design was built into the largest expansion cohorts, DLBCL and iNHL, for futility stopping because these two indications were considered the priority for development based on the preclinical experience. The estimated sample sizes for the DLBCL and iNHL expansion cohorts were based on a Simon two-stage design using the following parameters: a one-sided test at the significance level of $\alpha = 0.1$, a power of 80%, a null hypothesis of an ORR of ≤20% for DLBCL and ≤35% for iNHL, and an alternative hypothesis of an ORR of ≥40% for DLBCL and ≥60% for iNHL. A total of 12–25 patients with DLBCL (14–29 patients projected on the basis of a 15% dropout rate) and 10–23 patients with iNHL (14–27 patients projected on the basis of a 15% dropout rate) would be needed for the expansion cohorts.

The estimated sample size of 16 for the MCL and EBV-positive PTLD expansion cohorts was based on the following considerations: 16 patients in each cohort would provide 77% power to detect a statistically significant difference between the uninteresting (20%) and interesting (50%) ORRs based on the exact one-sample binomial test.

Data Sharing Statement

Takeda makes patient-level, deidentified datasets and associated documents available after applicable marketing approvals and commercial availability have been received, an opportunity for the primary publication of the research has been allowed, and other criteria have been met as set forth in Takeda's Data Sharing Policy (see https://www.takedaclinicaltrials.com/ for details). To obtain access, researchers must submit a legitimate academic research proposal for adjudication by an independent review panel, who will review the scientific merit of the research and the requestor's qualifications and conflict of interest that can result in potential bias. Once approved, qualified researchers who sign a data sharing agreement are provided access to these data in a secure research environment.

Results

Patients and treatment

A total of 105 patients (36 dose escalation, 69 expansion) were enrolled by the data cutoff of April 9, 2018. In dose escalation, 36 patients (solid tumors, $n = 19$; lymphoma, $n = 17$) received TAK-659 at the following doses: 60 mg ($n = 10$), 80 mg ($n = 4$), 100 mg ($n = 15$), and 120 mg ($n = 7$). In both dose escalation ($n = 17$) and expansion ($n = 69$), a total of 86 relapsed/refractory patients with lymphoma [DLBCL, $n = 53$; iNHL, $n = 21$ (FL, $n = 14$); CLL, $n = 6$; MCL, $n = 5$; PTLD, $n = 1$] received TAK-659 60–120 mg once daily. A total of 84 patients (80%; 46 with DLBCL) received TAK-659 at the MTD/RP2D of 100 mg once daily. In this manuscript, when DLBCL and iNHL/FL are discussed, we are referring to patients who were enrolled into both dose-escalation and dose-expansion cohorts.

Baseline characteristics and demographics of enrolled patients are shown in **Table 1** and disease subtypes are shown in Supplementary Table S2. Patients with DLBCL had a median time from initial diagnosis of 15 months, 57% of patients with DLBCL were Ann Arbor stage III–IV at study entry, 60% had evidence of extranodal involvement, and 19% received prior autologous transplant (prior allogeneic transplantation was excluded). Patients with FL had a median time from initial diagnosis of 53 months, 78% of patients with FL were Ann Arbor stage III–IV at initial diagnosis, 86% had three or more prior lines of therapy, and 50% received a prior autologous transplant (prior allogeneic transplantation was excluded).

Table 1. Baseline demographics and disease characteristics by tumor type.

		Lymphoma			
	Solid tumors[a] $n = 19$	DLBCL $n = 53$	FL $n = 14$	All lymphomas[a] $n = 86$	All patients $N = 105$
Age, median (range) years	59 (38–80)	60 (23–84)	57 (33–82)	65 (23–85)	63 (23–85)
Gender, male, *n* (%)	9 (47)	35 (66)	8 (57)	54 (63)	63 (60)
ECOG performance status, 0, *n* (%)	8 (42)	17 (32)	7 (50)	29 (34)	37 (35)
Disease characteristics					
TNM or Ann Arbor stage III–IV, *n* (%)	15 (79)	30 (57)	8 (57)	49 (57)	64 (61)
Months since diagnosis, median (range)	27 (2–144)	15 (0–257)	53 (15–99)	21 (0–257)	23 (0–257)
Nodal sites ≥ 5, *n* (%)	-	18 (34)	7 (50)	30 (35)	30 (29)
Bulky disease at entry, *n* (%)	-	4 (8)	1 (7)	7 (8)	7 (7)
Bone marrow involvement at entry, *n* (%)	-	7 (13)	5 (36)	24 (28)	24 (23)
Genetic classification (DLBCL only)					
Double/triple hit	-	7 (13)	-	-	-
GCB/non-GCB[b]	-	29 (55)/8 (15)	-	-	-
Prior treatment					
Lines of prior therapy, median (range)	3 (1–11)	3 (1–9)	3 (2–9)	3 (1–9)	3 (1–11)
Prior autologous transplant, *n* (%)	-	10 (19)	7 (50)	18 (21)	18 (17)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; GCB, germinal center B-cell; TNM, tumor node metastasis.

[a]See Supplementary Table S2 for details of specific diseases.

[b]Unknown in 16 patients.

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At data cutoff, 79 of 86 patients with lymphoma (92%) had discontinued treatment; mostly due to disease progression ($n = 35$; Supplementary Table S3). Twenty-eight patients (33%) discontinued treatment due to a treatment-emergent AE (TEAE). Of patients with lymphoma receiving TAK-659 100 mg, 23 of 78 patients (29%) proceeded through cycle 1 without dose modification (all causes included, regardless of whether they were disease related or treatment related) and 19 of 54 (35%) proceeded through cycle 2 without dose modification. There were 25 on-study deaths (defined as death that occurs between the first dose and 28 days after the last dose of study drug) in patients with lymphoma (29%), of which 4 were considered by investigators to be related or possibly related to study drug [respiratory failure, multiorgan failure, disseminated varicella, and pneumocystis jirovecii pneumonia (PJP) infection, all in patients receiving TAK-659 100 mg once daily]; all 4 patients (DLBCL, $n = 2$; B-cell lymphoplasmacytic lymphoma/immunocytoma, $n = 1$; mucosa-associated lymphoid tissue, $n = 1$) had confounders and alternative etiologies, and 1 had concurrent progressive disease. The four related deaths occurred within 3.6 months of the initial dose of TAK-659, with two occurring within the first 2 months. Two of the 3 patients without concurrent disease progression initially presented with infection and were later positive for viral reactivation; 1 had PJP and cytomegalovirus (CMV) reactivation, and 1 had nonspecific pneumonitis followed by varicella. These infectious processes, among other factors, led to death. Prophylaxis measures (not mandatory for every patient) against PJP and viral infection were later introduced to the protocol. The third patient without concurrent disease progression who came onto the study with an existing dry cough, did not benefit from the recommended prophylactic measures because they were not started on antibiotics until after documentation of the PJP.

Dose-escalation phase

In dose escalation, the safety of four TAK-659 dose levels was assessed sequentially in 36 patients (19 solid tumor, 17 lymphoma; Supplementary Table S4). The observed safety in the single-patient cohorts at the initial three dose levels allowed for escalation based on standard 3+3 escalation criterion. The tested dose levels included the initial starting dose of 60 mg ($n = 10$), 80 mg ($n = 4$), 100 mg ($n = 15$), and 120 mg ($n = 7$). One DLT [increased aspartate aminotransferase (AST), grade 3] occurred in 1 of 10 patients at the 60-mg dose level, and no DLTs occurred at either the 80-mg dose level or in the initial cohort enrolled at the 100-mg dose level. At the 120-mg dose level, DLTs occurred in 4 of 7 patients, including stomatitis (grade 3), generalized edema (grade 3), and increased lipase in 2 patients (grades 3 and 4). The 120-mg dose was thus confirmed to have exceeded the MTD, and the MTD was determined to be 100 mg. Expanded testing of the 100-mg dose was undertaken with 12 additional patients where a single DLT of grade 3 hypophosphatemia was identified; thus the 100-mg dose was determined to be the MTD per the standard 3+3 dose-escalation criteria (see Supplementary Table S4). Among the 15 patients who were treated at the 100-mg dose, 10 (67%) received ≥2 cycles, 4 (27%) received ≥4 cycles, 4 (27%) received ≥6 cycles, 2 (13%) received ≥12 cycles, and 1 (7%) received ≥24 cycles.

Herein, we report the results for the 86 patients with lymphoma who received TAK-659 during dose escalation or expansion.

Treatment exposure and safety in patients with lymphoma

All 86 patients with lymphoma received ≥1 dose of TAK-659 (60 mg, $n = 4$; 80 mg, $n = 3$; 100 mg, $n = 78$; 120 mg, $n = 1$) and were evaluable for safety analysis. The median number of cycles of TAK-659 received was 2.0 (range, 1−46); 37% of patients received ≥4 cycles of treatment. All patients experienced at least one TEAE, and 80 (93%) experienced at least one grade ≥3 TEAE (**Fig. 1**). The most common TEAEs (occurring in ≥35% of patients; **Fig. 1**) were elevations in transaminase (increased AST 64%), pyrexia (60%), increased amylase (44%), diarrhea (44%), hypophosphatemia (40%), anemia (36%), increased blood creatine phosphokinase (CPK; 36%), and increased lipase (35%). The changes in laboratory parameters, including AST, amylase, blood CPK, lipase, and hypophosphatemia, resulted in no symptoms and were reversible upon withholding study drug or with phosphate repletion for hypophosphatemia. The total incidence of increased blood CPK is likely underreported, because collection of this laboratory parameter was only implemented in a later protocol amendment. The majority of the pyrexia, anemia, and diarrhea events were grade 1 or 2. The most common grade ≥3 TEAEs (occurring in >15% of patients) were increased amylase and hypophosphatemia (both 26%), neutropenia (24%), anemia, increased blood CPK, and increased lipase (16% each), and thrombocytopenia (15%). Serious AEs (SAEs) were reported in 67 patients (78%); the most common were pyrexia (23%) and pneumonia (12%).

Lactate dehydrogenase (LDH) levels increased from baseline in nearly all patients, but no clinical correlates (e.g., histology, disease burden, response to therapy) were found to be associated with the level of increase. Laboratory-parameter changes in the three most frequent treatment-related AEs (AST, amylase, and lipase elevations) and LDH over the first three cycles of treatment showed that the increases generally occurred early (approximately 1 week into treatment) and remained relatively stable over time (**Fig. 2**). There were no known episodes of tumor lysis syndrome and therefore no actions were taken clinically for increases in LDH. TAK-659 was only interrupted per protocol for grade 4 increases in amylase or lipase, or grade 3 increases in both amylase and lipase. Transaminase increases were mostly mild and often involved a single enzyme [either AST or alanine aminotransferase (ALT)]. TAK-659 was only interrupted per protocol for grade 4 elevations in AST or ALT with significant bilirubin elevation (grade ≥3), or grade 3 elevations in both enzymes with significant bilirubin elevation (grade ≥3); dose interruption for these reasons was infrequent.

Overall, 81 patients (94%) had at least one treatment-related AE and 65 (76%) had at least one grade ≥3 treatment-related AE (Supplementary Table S5). Diarrhea (23%), pyrexia (22%), and periorbital edema (21%) were the most common (occurring in ≥20% of patients) nonlaboratory-parameter and nonhematologic treatment-related AEs, most of which were grade 1 or 2. The most common hematologic treatment-related grade ≥3 AEs were neutropenia (17%) and thrombocytopenia (6%); anemia was only reported in 1 patient (1%). Treatment-related SAEs were experienced by 29 patients (34%); each treatment-related SAE occurred in 1 patient only, except for pyrexia ($n = 8$), pneumonia ($n = 6$), pneumonitis ($n = 4$), and febrile neutropenia, PJP, and sepsis (all $n = 2$).

Pharmacokinetics

TAK-659 plasma concentration–time profiles on day 1 of cycle 1 and at steady state (day 15 of cycle 1) after oral once-daily administration in patients with lymphoma are presented in **Fig. 3**. TAK-659 exposure generally increased with dose over the 60–120-mg range. Median time to maximum plasma concentration (T_{max}) was approximately 2 hours. Variability of dose-normalized, steady-state exposure [area under the concentration–time curve for a dosing interval (AUC_{tau})/dose] was 20%.

Following oral once-daily administration of TAK-659 for 15 days, the overall mean accumulation was 1.90-fold (range, 1.42–2.41) and

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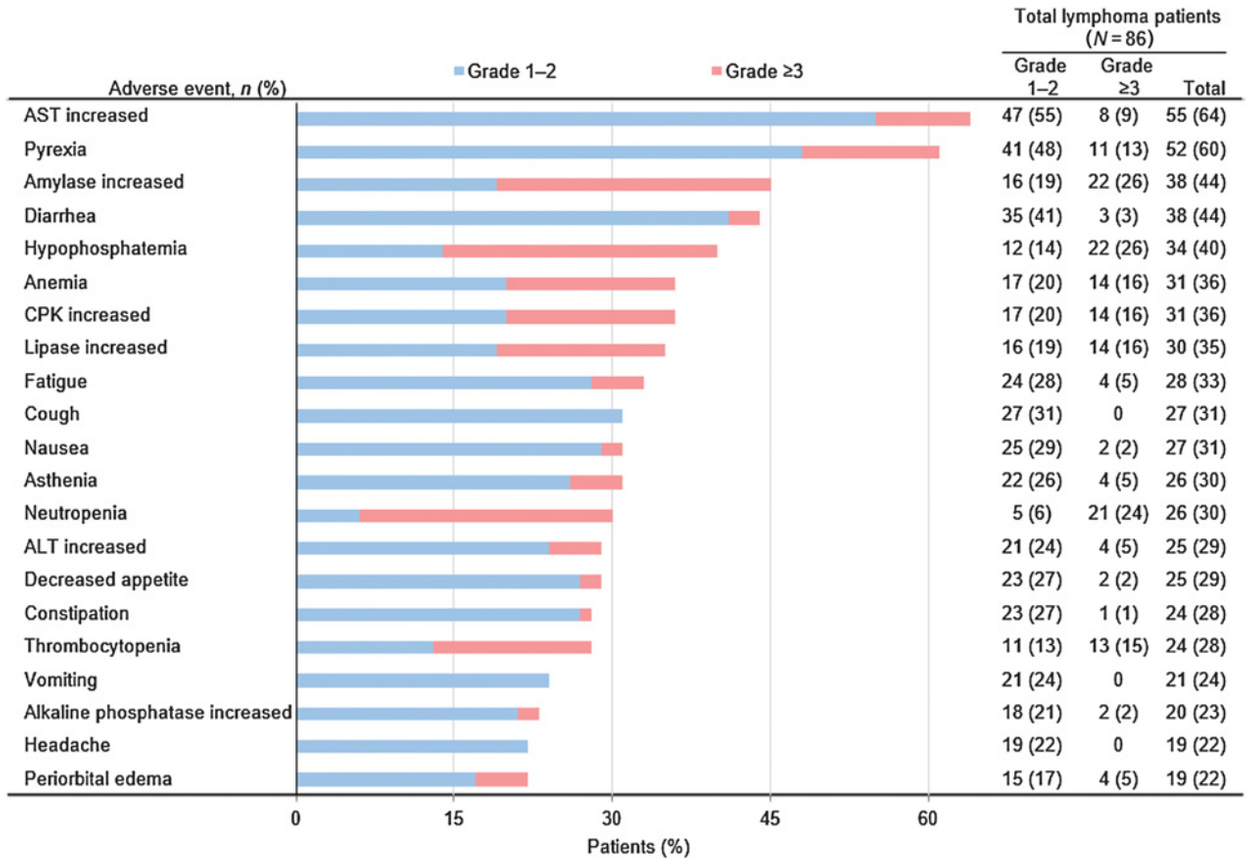

Figure 1.
Most common TEAEs in patients with lymphoma. Bar lengths may appear different than the corresponding values of frequency due to rounding. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

the overall mean peak/trough ratio on day 15 of cycle 1 was 4.85 (range, 2.33–10.2). Approximate steady-state pharmacokinetic conditions were reached by day 8, based on visual inspection of trough concentrations obtained during cycle 1. Overall geometric mean renal clearance was 12.1 L/hour (range, 2.95–25.6), and mean ratio of TAK-659 renal clearance to apparent clearance was 0.306 (range, 0.070–0.530), indicating that renal clearance accounted for at least 30% of systemic clearance. Geometric mean terminal half-life was approximately 36.6 hours based on data from 14 iNHL run-in patients with serial pharmacokinetic sampling up to 168 hours after a single oral dose of TAK-659 100 mg.

Antitumor activity

Response to TAK-659 was evaluated in the response-evaluable population (defined as those who received at least one dose of TAK-659 and had at least one follow-up assessment), per the statistical analysis plan and is shown in **Table 2** along with response in the intent-to-treat (ITT) lymphoma population. Eight of 43 response-evaluable patients with DLBCL (19%) achieved a complete response (CR) and 4 (9%) achieved a partial response (PR), resulting in an ORR (CR+PR) of 28% in response-evaluable patients (**Fig. 4A**) and 23% in the ITT population. Median time to response was 53 days (range, 27–168). Among the 12 responders, 9 had a response lasting for ≥16 weeks and 4 were ongoing on study at the data cutoff; median duration of response was not estimable (NE; range, 1–1,182) and median duration of treatment in patients with DLBCL with an objective response was 435.5 days (range, 53–1,354; **Fig. 4B**). Two patients with DLBCL with an objective response stopped treatment to undergo allogeneic hematopoietic stem cell transplantation (one after cycle 4, one after cycle 7). Median PFS was 50 days [95% confidence interval (CI), 44–62] in all patients with DLBCL; median was not reached in DLBCL responders (95% CI, 279–NE; one progressive disease event and the remaining patients were censored) and was 50 days (95% CI, 34–54) in DLBCL nonresponders (Supplementary Fig. S1). Responses were seen in patients with *de novo* DLBCL and in patients with transformed DLBCL; responses appeared to be independent of DLBCL cell-of-origin classification (Supplementary Table S6).

Among 15 evaluable patients with iNHL, 4 achieved CR [mucosa-associated lymphoid tissue lymphoma ($n = 1$), FL ($n = 2$), small lymphocytic lymphoma ($n = 1$)] and 7 achieved PR [FL ($n = 6$), nodal marginal zone B-cell lymphoma ($n = 1$)] resulting in an ORR of 73% in response-evaluable patients and 52% in the ITT population. Of the 11 responders, 5 had a response lasting ≥16 weeks. Among the 9 response-evaluable patients with FL, the ORR was 89% (CR, $n = 2$; PR, $n = 6$; 57% in the ITT population). Median time to response was 58.5 days (range, 52–148), median duration of response was 137 days (range, 1–856), and median duration of treatment in responding patients was 174 days (range, 84–896). At the time of data cutoff, 1 patient was still

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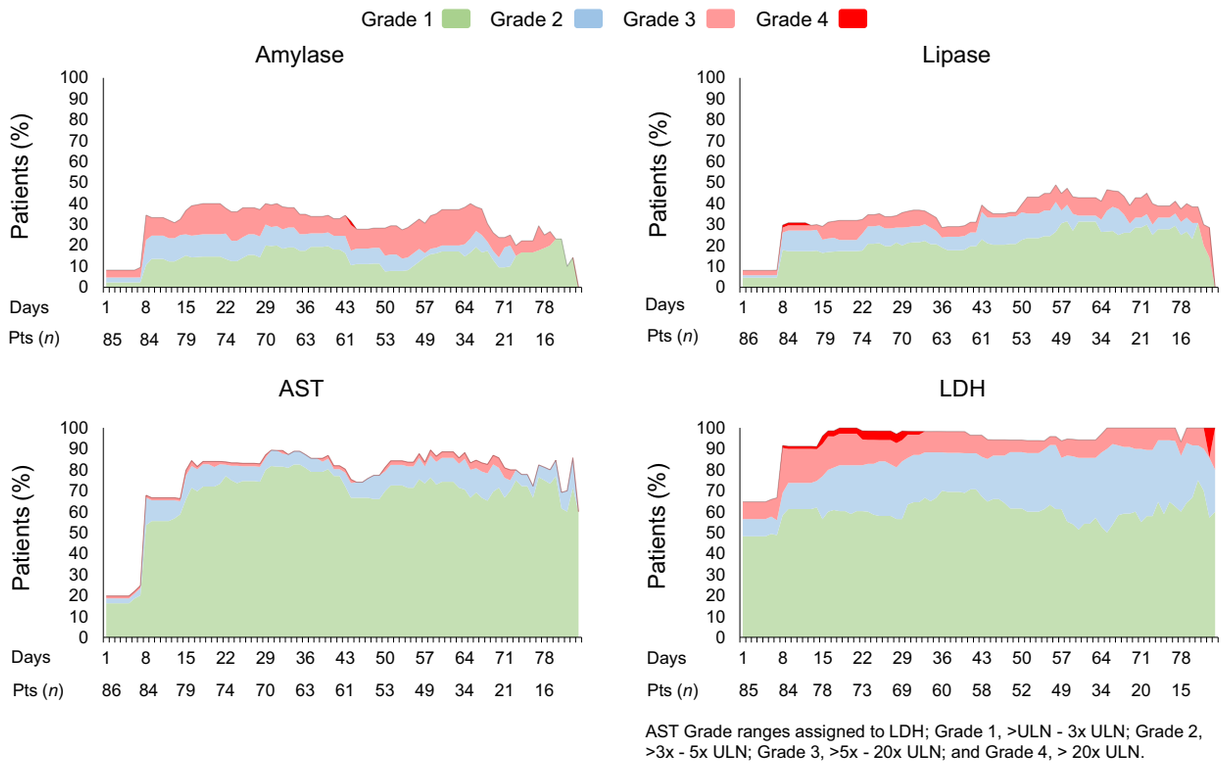

Figure 2.

Laboratory-parameter grade changes over three cycles in patients with lymphoma receiving TAK-659. AST, aspartate aminotransferase; LDH, lactate dehydrogenase; Pts, patients; ULN, upper limit of normal.

on study and 1 patient had transitioned to hematopoietic stem cell transplantation after 8 months on treatment. Median PFS was 201 days (95% CI, 61–907) in all patients with FL with 3 patients censored due to the date of the last adequate assessment (Supplementary Fig. S2). Of 5 evaluable patients with CLL, 3 (60%) achieved PR and 2 had stable disease (ORR of 50% in the ITT population).

Of the 6 enrolled patients with CLL, 5 were tested for mutations. None of the 5 patients had *BTK* mutations and 2 had a *PLC-γ2* mutation (one S707F mutation and one T706I mutation). All 3 CLL responders had prior ibrutinib and/or idelalisib exposure, including the patient with the *PLC-γ2* S707F mutation. The first responder achieved a best response of PR to ibrutinib in the fourth line and was refractory to idelalisib in the fifth line. The second responder was refractory to ibrutinib in the second line of treatment. The last responder had received rituximab and venetoclax as a second-line treatment with a best response of CR and was later refractory to ibrutinib in the fourth line.

Discussion

We conducted a phase I, first-in-human study of TAK-659 in patients with advanced solid tumors or lymphoma. The rationale for inclusion of patients with solid tumors in dose-escalation only was multifold: (i) it was exploratory based on emerging data; (ii) it expedited enrollment and completion of the escalation phase; and (iii) the results of the solid tumor response assessment, with only 1 of 19 patients responding, did not justify opening a dedicated solid tumor cohort in expansion. The role of SYK in the pathogenesis of B-cell malignancies is well established (4–10), and targeting SYK was expected to drive clinical benefit in the target study population of this trial (patients with lymphoma). However, it is uncertain whether antagonizing FLT3 signaling in parallel would contribute further to the clinical activity of TAK-659 in B-cell malignancies.

The MTD of TAK-659 was determined to be 100 mg once daily, and this dose was selected for expansion. Clinical responses were observed at all four doses evaluated, suggesting the therapeutic window of TAK-659 ranges from 60 to 100 mg once daily. Toxicity was manageable and there was single-agent antitumor activity in patients with relapsed/refractory B-cell lymphoma across different histologic subtypes. In particular, TAK-659 demonstrated a relatively high rate of CR (two-thirds of responders achieved CR), a long duration of treatment (median of 435.5 days among responders at data cutoff), and a median response duration that was NE (range, 1–1182) in later-line DLBCL. TAK-659 also showed encouraging single-agent antitumor activity in response-evaluable patients with FL with an ORR of 89% (57% ITT), albeit in a small group of patients and with short duration of response.

The contribution of dual SYK and FLT-3 inhibition to the toxicity profile of TAK-659 versus SYK inhibition alone is difficult to ascertain based on the available data from this study. The most common nonlaboratory AEs that occurred in at least 30% of patients included pyrexia, diarrhea, fatigue, cough, nausea, and asthenia; these events were largely grade 1 and 2. The laboratory elevations in transaminase, pancreatic enzymes, and CPK were not associated with symptoms, and were manageable with dose interruptions and modifications.

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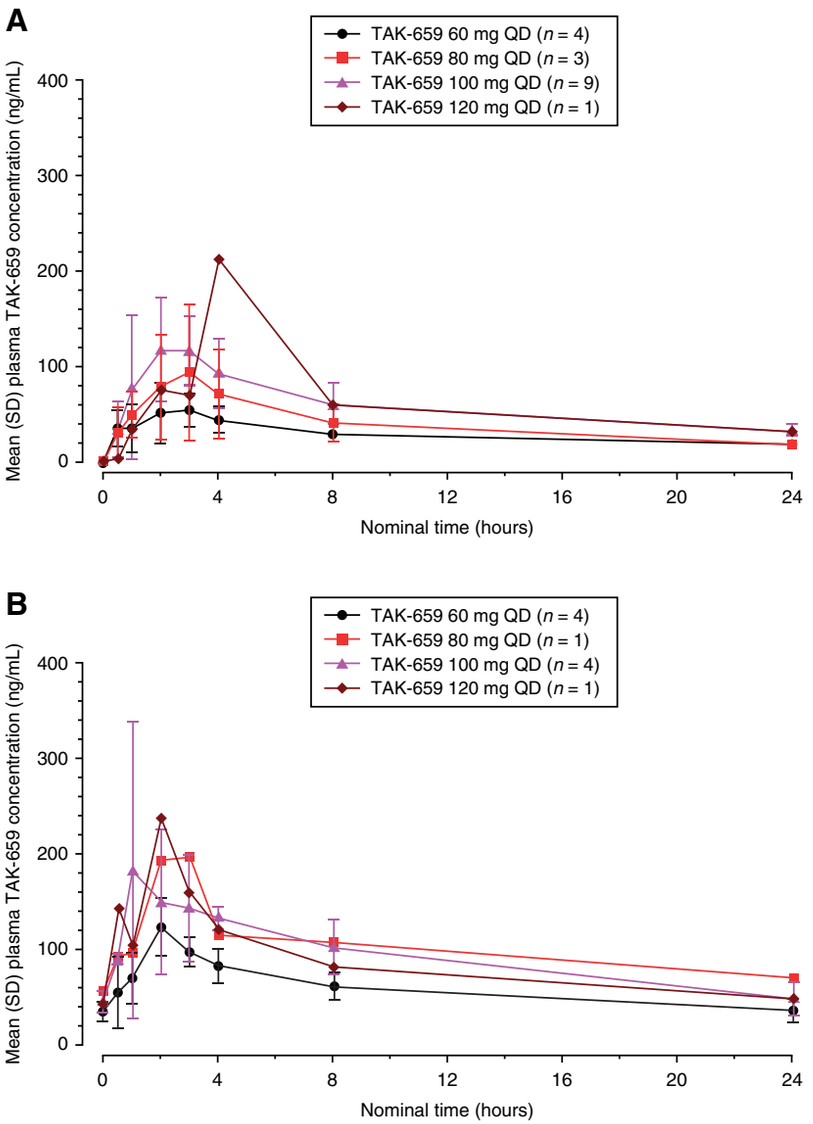

Figure 3.
Plasma concentration–time profiles of TAK-659 in patients with lymphoma following oral once-daily administration on cycle 1 day 1 (**A**) and cycle 1 day 15 (**B**). QD, once daily.

LDH was universally elevated in patients treated with TAK-659 and the mechanism is not known. Although asymptomatic elevation of these enzymes was also reported with the SYK inhibitor entospletinib (26–28), it is unclear whether this is a target-based class effect or an individual drug effect. The most common hematologic AE was neutropenia, though a significant number of patients had marrow involvement at baseline. Most patients (94%) experienced a treatment-related AE; however, the overall incidence of hematologic treatment-related AEs reported in this study was relatively low. Treatment-related grade ≥3 neutropenia and thrombocytopenia was reported in 17% and 6% of patients, respectively, and treatment-related grade ≥3 anemia was reported in 1 patient only.

Increased susceptibility to infection was identified as a potential risk with TAK-659 based on the nonclinical toxicology findings of lymphoid depletion and myelosuppression (Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, data on file). In this study, opportunistic infection and viral reactivation events were seen, including 4 patients (5%) with treatment-emergent PJP (all grade 3 and related) and 12 (14%) with treatment-emergent CMV infection, of which 9 (11%) were considered related to TAK-659. In the 12 patients with CMV reactivation, 1 patient had concurrent grade 2 pneumonia, 1 patient had concurrent grade 1 pneumonia/grade 2 pneumonitis, and another patient had concurrent grade 3 PJP; however, there were no associated reports of retinitis, esophagitis, colitis, hepatitis, or encephalitis. Interestingly, the incidence of CMV reactivation was higher in Europe (all 12 cases were reported in either Spain or Italy) compared with the United States where no cases were reported for the duration of the study. To manage the risk of infection, we initiated prophylactic measures during the study against PJP in high-risk patients, as well as CMV monitoring and preemptive treatment, as clinically indicated following local standard practice.

TAK-659 showed encouraging single-agent clinical activity in patients with lymphomas of different histologies, including DLBCL, iNHL (FL), CLL, and MCL. Durable and deep responses were observed in approximately 20% of patients with DLBCL, which is not insignificant in this

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Table 2. Best antitumor response and duration of treatment.

	ITT		Response-evaluable patients						
Tumor type	*n*	ORR, *n* (%)	*n*	ORR, *n* (%)	CR, *n* (%)	PR, *n* (%)	Median time to response, days (range)	Median duration of response, days (range)	Median duration of treatment in responding patients, days (range)
All lymphoma	86	27 (31)	67	27 (40)	12 (18)	15 (22)	57 (27–168)	856 (1–1182)	189 (53–1354)
DLBCL	53	12 (23)	43	12 (28)	8 (19)	4 (9)	53 (27–168)	NE (1–1182)	435.5 (53–1354)
iNHL[a]	21	11 (52)	15	11 (73)	4 (27)	7 (47)	60 (52–148)	176 (1–856)	185 (64–896)
FL	14	8 (57)	9	8 (89)	2 (22)	6 (67)	58.5 (52–148)	137 (1–856)	174 (84–896)
CLL	6	3 (50)	5	3 (60)	0	3 (60)	57 (56–107)	NE (1–59)	138 (104–155)
MCL	5	1 (20)	3	1 (33)	0	1 (33)	54 (54–54)	109 (109–109)	149 (149–149)
PTLD	1	0	1	0	0	0	-	-	-

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; ITT, intent-to-treat; MCL, mantle cell lymphoma; NE, not estimable; ORR, overall response rate; PR, partial response; PTLD, posttransplant lymphoproliferative disease.

[a]Includes nodal marginal zone B-cell lymphoma ($n = 2$), mucosa-associated lymphoid tissue, B-cell lymphoplasmacytic lymphoma/immunocytoma, B-cell small lymphocytic lymphoma, and splenic marginal zone lymphoma ($n = 1$ each).

heavily pretreated patient population (**Fig. 4B**). The longer than 12-month duration of treatment in responding patients by the data cutoff, and the CR rate of 19% (two-thirds of responders had CR; 15% ITT) reported here for DLBCL could be attributable to the role of SYK, not only in the direct targeting of tumor cells but also in local immunity, a hypothesis supported by preclinical data, which demonstrate that TAK-659 exhibits immunomodulatory effects that control tumor growth (19). These effects include inhibition of tumor-associated T-regulatory cells and MDSCs, as well as upregulation of antitumorigenic macrophages (19). Furthermore, responses to TAK-659 in patients with DLBCL appeared to be independent of cell-of-origin classification, as responses were observed in both patients with GCB and non-GCB; however, more data are needed before making confirmatory statements about where this agent would fit in lymphoma treatment with respect to cell of origin. Antitumor activity was also observed in patients with CLL who received prior ibrutinib and/or prior idelalisib therapy, suggesting that TAK-659 could be beneficial in treating B-cell malignancies less sensitive to BTK inhibitors, although larger studies are needed to confirm this observation.

For TAK-659–treated response-evaluable patients with lymphoma, the ORR of 40% (31% ITT), including the 12 patients (18%; 14% ITT) who achieved CR, is notable; response-evaluable patients with FL responded particularly well, with an ORR of 89% (57% ITT). While cross-study comparisons have major limitations, in an initial phase II study of the SYK inhibitor fostamatinib (29), activity was limited, with an ORR of 3% reported in relapsed/refractory patients with DLBCL; 13% of patients reported at least stable disease (30). In a phase II study of entospletinib (800 mg twice a day), no patients achieved CR and 61% achieved PR in relapsed/refractory CLL (26), and the ORR in iNHL was reported to be 13% (26). In a similar phase II study of entospletinib (800 mg twice a day), the ORR in patients with FL was 17% (all were PRs) with 51% achieving stable disease (27). In a phase I, dose-escalation study of cerdulatinib in patients with relapsed/refractory B-cell malignancies, of 13 patients with FL, 1 patient achieved CR and 1 achieved PR; none of the 16 patients with DLBCL responded (31). In a phase II study, cerdulatinib has demonstrated response rates of 43%–61% in relapsed/refractory B- and T-cell NHL [61% in CLL/SLL, 50% in FL, and 43% in PTCL (4 CRs and 2 PRs in 14 patients; ref. 31)]. Moreover, preliminary phase II data of cerdulatinib in relapsed/refractory FL have demonstrated an ORR of 46% as a single-agent and 67% in combination with rituximab (32).

The pharmacokinetic properties of TAK-659 in this study supported continuous, oral once-daily dosing. However, later studies of TAK-659 are investigating alternative dosing schedules (e.g., intermittent). TAK-659 has favorable pharmaceutical properties, namely, low protein binding (free fraction of 0.55 in human plasma), good solubility, fast absorption (T_{max} ~2 hours), and a relatively long terminal half-life in humans (~37 hours).

Unfortunately, no informative pharmacodynamic data were generated in this study to support the dose determination. SYK and FLT3 inhibition by TAK-659 and correlation with response could not be assessed in this study. Details of our efforts to evaluate downstream signaling of SYK and FLT-3 as potential pharmacodynamic markers of TAK-659 activity are provided in the Supplementary Materials. To study the pharmacodynamic effects of TAK-659 inhibition of BCR and FLT3 signaling, modulation of multiple proximal signal transducers was evaluated in cell lines by flow cytometry, including phosphorylated SYK, FLT3, BLNK, and BTK. Only modest regulation by TAK-659 was observed (Supplementary Fig. S3A–S3D), which limited their utility as a pharmacodynamic measure of activity in a clinical application. Both SYK and FLT3 are known to regulate AKT/mammalian target of rapamycin signaling (33, 34); thus, the phosphorylation of S6 kinase on serine 235/236 was also evaluated as a potential TAK-659 pharmacodynamic readout. TAK-659 treatment was shown to decrease the phosphorylation of S6 kinase in multiple cell lines constitutively expressing phosphorylated SYK, with maximal inhibition seen in cell lines also harboring a *FLT3-internal tandem deletion* mutation (Supplementary Fig. S3E). Thus, there was a lack of significant change compared with dimethyl sulfoxide, but TAK-659 treatment decreased the phosphorylation of S6 kinase. In primary human samples, this assay was shown to be variable due to the quality and handling of the primary samples and, therefore, the data were not conclusive.

Although TAK-659 100 mg once daily was determined as the MTD, it remains an open question whether this is a biologically optimal dose and safest long-term dose. Due to the aggressive nature of DLBCL and the need for immediate disease control, the level of dose interruption in the first two cycles may greatly influence efficacy. Only 29% of patients with lymphoma dosed at TAK-659 100 mg proceeded through cycle 1 without dose modification. Common reasons for dose modification included neutropenia, hypophosphatemia, blood CPK increased, amylase increased, periorbital edema, and pyrexia. A dose of TAK-659 that

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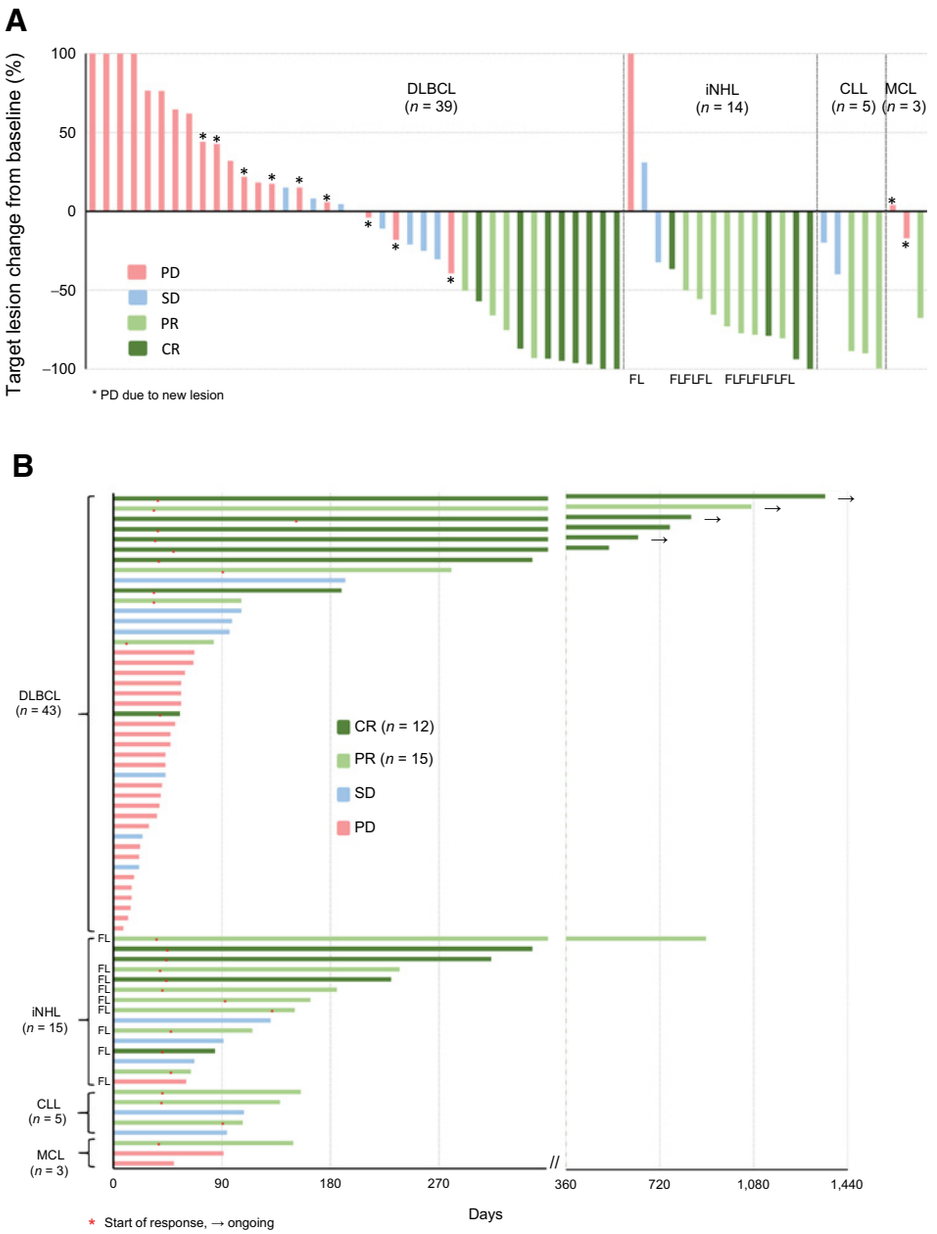

Figure 4.

A, Antitumor response to TAK-659 in response-evaluable patients: best percentage change from baseline in the sum of the products of the diameters among all patients with lymphoma who received at least one dose of study drug and at least one follow-up assessment. **B,** Response and time on study by patient. CLL, chronic lymphocytic lymphoma; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

results in substantial dose modification during initial treatment—and thus potentially compromises efficacy—may be suboptimal. To address this, lower doses and/or intermittent schedules are being investigated (NCT03123393, NCT03357627, NCT02954406).

On the basis of these findings, further investigation of TAK-659 is warranted in patients with relapsed/refractory B-cell lymphoma (NCT02954406, NCT03357627), and in early-line combination with standard chemotherapy (NCT03742258). Given the established role of SYK in BCR-driven pathogenesis of B-cell malignancies, additional translational research to identify potential patient selection markers may also prove productive.

Disclosure of Potential Conflicts of Interest

R. Popat is an employee/paid consultant for, reports receiving speakers' bureau honoraria from, and reports receiving other remuneration from Takeda. S. Madan reports receiving speakers' bureau honoraria from and is an advisory board member/unpaid consultant for Takeda. G. Gritti reports receiving speakers' bureau honoraria from IQVIA. D. El-Sharkawi reports receiving speakers' bureau honoraria from Abbvie and Janssen, and is an advisory board member/unpaid consultant for Abbvie. I. Chau is an employee/paid consultant for Bristol-Myers Squibb, Eli-Lilly, MSD, AstraZeneca, Roche, Merck-Serono, Oncologie International, Pierre Fabre, and Bayer; and reports receiving commercial research grants from Eli-Lilly and Janssen Cilag. J.A. Radford reports receiving commercial research grants from Takeda and reports receiving speakers bureau honoraria from speaker engagements. J.P. de Oteyza is an employee/paid consultant for and reports receiving commercial research grants from Takeda. S. Iyer reports receiving commercial research grants from Takeda, Rhizen, Seattle Genetics, and Merck. R. Karmali reports receiving other commercial research support from Takeda, BMS, Kite/Gilead, BMS/Celgene/Juno; reports receiving speakers bureau honoraria from Kite/Gilead, AstraZeneca, BeiGene; and is an advisory board member/unpaid consultant for BMS/Celgene/Juno, Kite/Gilead, and Karyopharm. H. Miao, I. Proscurshim, and S. Wang are employees/paid consultants for Millennium Pharmaceuticals Inc., Cambridge, MA, USA, a

wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Y. Wu is an employee/paid consultant for Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company. K. Stumpo is an employee/paid consultant for Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company, and holds ownership interest (including patents) in AstraZeneca, Teva Pharmaceuticals, GSK, BMS, and Pfizer. C. Carpio reports receiving speakers bureau honoraria from Takeda. F. Bosch reports receiving commercial research grants from Hoffman La Roche, Janssen, Celgene, Gilead, and Novartis; reports receiving speakers' bureau honoraria from Abbvie, Janssen, AstraZeneca, and Roche; and is an advisory board member/unpaid consultant for Abbvie, Janssen, AstraZeneca, and Gilead. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.I. Gordon, J.B. Kaplan, H.A. Burris, M.R. Patel, G. Gritti, I. Chau, S. Iyer, W. Townsend, R. Karmali, H. Miao, I. Proscurshim, S. Wang, Y. Wu, Y. Shou, F. Bosch
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Other (clinical care of patients and delivery of treatment): W. Townsend

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References

1. Cheng AM, Rowley B, Pao W, Hayday A, Bolen JB, Pawson T. SYK tyrosine kinase required for mouse viability and B-cell development. Nature 1995;378:303–6.
2. Cornall RJ, Cheng AM, Pawson T, Goodnow CC. Role of Syk in B-cell development and antigen-receptor signaling. Proc Natl Acad Sci U S A 2000;97:1713–8.
3. Turner M, Mee PJ, Costello PS, Williams O, Price AA, Duddy LP, et al. Perinatal lethality and blocked B-cell development in mice lacking the tyrosine kinase Syk. Nature 1995;378:298–302.
4. Buchner M, Fuchs S, Prinz G, Pfeifer D, Bartholome K, Burger M, et al. Spleen tyrosine kinase is overexpressed and represents a potential therapeutic target in chronic lymphocytic leukemia. Cancer Res 2009;69:5424–32.
5. Cheng S, Coffey G, Zhang XH, Shaknovich R, Song Z, Lu P, et al. SYK inhibition and response prediction in diffuse large B-cell lymphoma. Blood 2011;118:6342–52.
6. Mocsai A, Ruland J, Tybulewicz VL. The SYK tyrosine kinase: a crucial player in diverse biological functions. Nat Rev Immunol 2010;10:387–402.
7. Gururajan M, Jennings CD, Bondada S. Cutting edge: constitutive B cell receptor signaling is critical for basal growth of B lymphoma. J Immunol 2006;176:5715–9.
8. Leseux L, Hamdi SM, Al Saati T, Capilla F, Recher C, Laurent G, et al. Syk-dependent mTOR activation in follicular lymphoma cells. Blood 2006;108:4156–62.
9. Gobessi S, Laurenti L, Longo PG, Carsetti L, Berno V, Sica S, et al. Inhibition of constitutive and BCR-induced Syk activation downregulates Mcl-1 and induces apoptosis in chronic lymphocytic leukemia B cells. Leukemia 2009;23:686–97.
10. Chen L, Monti S, Juszczynski P, Daley J, Chen W, Witzig TE, et al. SYK-dependent tonic B-cell receptor signaling is a rational treatment target in diffuse large B-cell lymphoma. Blood 2008;111:2230–7.
11. Cen O, Kannan K, Huck Sappal J, Yu J, Zhang M, Arikan M, et al. Spleen tyrosine kinase inhibitor TAK-659 prevents splenomegaly and tumor development in a murine model of Epstein-Barr virus-associated lymphoma. mSphere 2018;3:e00378–18.
12. Du ZM, Kou CW, Wang HY, Huang MY, Liao DZ, Hu CF, et al. Clinical significance of elevated spleen tyrosine kinase expression in nasopharyngeal carcinoma. Head Neck 2012;34:1456–64.
13. Hao YT, Peng CL, Zhao YP, Sun QF, Zhao XG, Cong B. Effect of spleen tyrosine kinase on nonsmall cell lung cancer. J Cancer Res Ther 2018;14:S100–4.
14. Katz E, Dubois-Marshall S, Sims AH, Faratian D, Li J, Smith ES, et al. A gene on the HER2 amplicon, C35, is an oncogene in breast cancer whose actions are prevented by inhibition of Syk. Br J Cancer 2010;103:401–10.
15. Yu Y, Suryo Rahmanto Y, Shen YA, Ardighieri L, Davidson B, Gaillard S, et al. Spleen tyrosine kinase activity regulates epidermal growth factor receptor signaling pathway in ovarian cancer. EBioMedicine 2019;47:184–94.
16. Lam B, Arikawa Y, Cramlett J, Dong Q, de Jong R, Feher V, et al. Discovery of TAK-659 an orally available investigational inhibitor of spleen tyrosine kinase (SYK). Bioorg Med Chem Lett 2016;26:5947–50.
17. Huck J, Kabir S, Kuida K, Kannan K, Shou Y, Petrich A. Preclinical and clinical development of TAK-659: an investigational SYK and FLT3 kinase inhibitor. Paper presented at 12th International Ultmann Chicago Lymphoma Symposium; 24–25 April 2015; W Chicago City Center, Chicago, IL.
18. Purroy N, Carabia J, Abrisqueta P, Egia L, Aguilo M, Carpio C, et al. Inhibition of BCR signaling using the Syk inhibitor TAK-659 prevents stroma-mediated signaling in chronic lymphocytic leukemia cells. Oncotarget 2017;8:742–56.
19. Kannan K, Riley J, Zhang M, Farrell P, Bailey B, Creson J, et al. TAK-659, a dual SYK/FLT3 inhibitor, leads to complete and sustained tumor regression and immune memory against tumor cells upon combination with anti-PD-1 agent. Eur J Cancer 2016;69:S92.
20. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009;9:162–74.
21. Pan PY, Wang GX, Yin B, Ozao J, Ku T, Divino CM, et al. Reversion of immune tolerance in advanced malignancy: modulation of myeloid-derived suppressor cell development by blockade of stem-cell factor function. Blood 2008;111:219–28.
22. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446–56.
23. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.
24. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
25. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275–82.

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26. Sharman J, Hawkins M, Kolibaba K, Boxer M, Klein L, Wu M, et al. An open-label phase 2 trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in chronic lymphocytic leukemia. Blood 2015;125:2336–43.
27. Andorsky DJ, Kolibaba KS, Assouline S, Forero-Torres A, Jones V, Klein LM, et al. An open-label phase 2 trial of entospletinib in indolent non-Hodgkin lymphoma and mantle cell lymphoma. Br J Haematol 2019;184:215–22.
28. Burke JM, Shustov A, Essell J, Patel-Donnelly D, Yang J, Chen R, et al. An open-label, phase II trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in diffuse large B-cell lymphoma. Clin Lymphoma Myeloma Leuk 2018;18:e327–31.
29. Friedberg JW, Sharman J, Sweetenham J, Johnston PB, Vose JM, Lacasce A, et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. Blood 2010;115:2578–85.
30. Flinn IW, Bartlett NL, Blum KA, Ardeshna KM, LaCasce AS, Flowers CR, et al. A phase II trial to evaluate the efficacy of fostamatinib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Eur J Cancer 2016;54:11–7.
31. Hamlin PA, Flinn IW, Wagner-Johnston N, Burger JA, Coffey GP, Conley PB, et al. Efficacy and safety of the dual SYK/JAK inhibitor cerdulatinib in patients with relapsed or refractory B-cell malignancies: results of a phase I study. Am J Hematol 2019;94:E90–93.
32. Smith SD, Munoz J, Stevens DA, Smith SM, Feldman TA, Ye JC, et al. Rapid and durable responses with the SYK/JAK Inhibitor cerdulatinib in a phase 2 study in relapsed/refractory follicular lymphoma—alone or in combination with rituximab. Hematol Oncol 2019;37:61–62.
33. Kazi JU, Ronnstrand L. FMS-like tyrosine kinase 3/FLT3: from basic science to clinical implications. Physiol Rev 2019;99:1433–66.
34. Chen L, Monti S, Juszczynski P, Ouyang J, Chapuy B, Neuberg D, et al. SYK inhibition modulates distinct PI3K/AKT- dependent survival pathways and cholesterol biosynthesis in diffuse large B cell lymphomas. Cancer Cell 2013;23:826–38.

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Clinical Cancer Research

Phase I Study of TAK-659, an Investigational, Dual SYK/FLT3 Inhibitor, in Patients with B-Cell Lymphoma

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