Phase 1b Study of Tirabrutinib in Combination With Idelalisib or Entospletinib in Previously Treated Chronic Lymphocytic Leukemia

Short title: **Phase 1b Study of Tirabrutinib Combinations in CLL**

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Translational Relevance

Pharmacologic targeting of the B-cell receptor (BCR) signaling pathway is an active area of drug development in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma. However, few clinical trials have evaluated concurrent inhibition of multiple targets in this pathway and none have employed second-generation selective Bruton's tyrosine kinase (BTK) inhibitors in combination with alternative BCR-associated kinases.

This is the first study to evaluate tirabrutinib, a second-generation BTK inhibitor, combined with either the first-in-class PI3Kδ inhibitor idelalisib or the first-in-class spleen tyrosine kinase inhibitor entospletinib in patients with relapsed/refractory CLL. The trial demonstrated the safety of the regimen, a low treatment discontinuation rate, and high efficacy. This study paves the way for further investigations of concurrent targeting of multiple kinases within the BCR signaling pathway as part of multiagent therapeutic regimens poised to prolong and deepen responses and prevent emergence of resistance in CLL.

Abstract

Background: Bruton's tyrosine kinase (BTK) inhibition alone leads to incomplete responses in chronic lymphocytic leukemia (CLL). Combination therapy may reduce activation of escape pathways and deepen responses. This open-label, phase 1b, sequential dose-escalation and dose-expansion study evaluated the safety, tolerability, pharmacokinetics, and preliminary efficacy of the selective BTK inhibitor tirabrutinib (TIRA) alone, in combination with the phosphoinositide-3-kinase delta (PI3Kδ) inhibitor idelalisib (IDELA), or with the spleen tyrosine kinase (SYK) inhibitor entospletinib (ENTO) in patients with relapsed/refractory CLL.

Methods: Patients received either TIRA monotherapy (80 mg QD) or TIRA 20 mg to 150 mg QD in combination with either IDELA (50 mg BID or 100 mg QD) or ENTO (200 mg or 400 mg QD).

Findings: Fifty-three patients were included. Systemic TIRA exposure was comparable between monotherapy and combination therapy. No maximum tolerated dose was identified. Across all treatment groups, the most common adverse event was diarrhea (43%, 1 patient grade ≥3); discontinuation due to adverse events was uncommon (13%). Objective response rates were 83%, 93%, and 100%, and complete responses were 7%, 7%, and 10% in patients receiving TIRA, TIRA/IDELA, and TIRA/ENTO, respectively. As of February 21, 2019, 46/53 patients continue to receive treatment on study.

Interpretation: TIRA in combination with IDELA or ENTO was well tolerated in patients with CLL, establishing an acceptable safety profile for concurrent selective inhibition of BTK with either PI3Kδ or SYK. This small study did not establish a superior efficacy of the combinations over TIRA alone. This trial is registered at www.clinicaltrials.gov (NCT02457598).

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Introduction

In the past 2 decades, signaling through the B-cell receptor (BCR) has been a major focus of pharmacologic research. Several BCR-targeted agents are now approved for patients with chronic lymphocytic leukemia (CLL), including ibrutinib and acalabrutinib[1,2] (Bruton tyrosine kinase [BTK] inhibitors), idelalisib (IDELA) and duvelisib (phosphoinositide-3-kinase [PI3K] inhibitors), and venetoclax (a BCL2 inhibitor).

Ibrutinib, a first-generation BTK inhibitor, irreversibly inhibits at least 11 other kinases with an IC_{50} of approximately 11 nM or less: BTK, BLK, BMX, CSK, FGR, BRK, HCK, EGFR, YES, ErbB2, and ITK.[3,4] In addition, ibrutinib reversibly binds to other kinases that lack the active site cysteine residue, in some cases with comparable affinity as binding to BTK.[3-5] Binding of ibrutinib to these additional kinases may potentially be responsible for side effects such as rash, diarrhea, bleeding, and atrial fibrillation.[6-9]

Selective BTK inhibitors have been developed to minimize these off-target effects. Tirabrutinib (TIRA, formerly ONO/GS-4059) is a selective, irreversible, second-generation, small-molecule BTK inhibitor.[5,10] TIRA irreversibly binds to C481 of BTK with greater target selectivity. In a recent study, the IC_{50} values for inhibition of kinases by tirabrutinib were: BTK, 6.8 nM; BMX, 6 nM; BLK, 300 nM; TEC, 48 nM; EGFR, 3020 nM; ErbB2, 7313 nM; and ITK, >20,000 nM. TIRA showed a 440-fold and >2940-fold selectivity for BTK over EGFR and ITK, respectively.[11] In a phase 1 dose-escalation trial, TIRA demonstrated an overall response rate (ORR) of 96% in 28 patients with relapsed/refractory (R/R) CLL, with no maximum tolerated dose (MTD) identified up to 600 mg QD.[5] Long-term follow-up of that study (for a median of 32.5 months) demonstrated an estimated median progression-free survival (PFS) of 38.5 months and median overall survival of 44.9 months.[12] Despite the high ORR achieved with BTK inhibitors, most CLL patients will progress while on therapy. Thus, new therapeutic strategies are needed to achieve an increased depth of response to improve remission duration and reduce the emergence of resistant subclones, without additional toxicities.

The BCR signaling cascade consists of divergent signaling pathways. BCR cross-linking leads to activation of proximal tyrosine kinases, including BTK, PI3K, and spleen tyrosine kinase (SYK). The signal is further transmitted through multiple downstream mediators, leading to upregulation of antiapoptotic proteins such as MCL1 and BCL2.[13,14] The potential benefit of combining agents targeting BTK, PI3K, and SYK has been well documented in CLL and non-Hodgkin lymphoma (NHL) preclinical models. Concurrent targeting of BTK and PI3K in a murine CLL model led to improved survival and reduction in tumor burden compared with either agent alone.[15] Additive or synergistic effects of the combination of ibrutinib and IDELA have been reported in CLL, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) cell lines.[16,17] Combined inhibition of PI3K and BTK induced apoptosis of the DLBCL cell line TMD8, which was resistant to inhibition of either kinase alone.[18] Concurrent inhibition of alternative kinases may rely on unique mechanisms: unlike other BCR-signaling inhibitors, the selective reversible inhibitor of SYK entospletinib (ENTO) led to downregulation of MCL1 in CLL cells in microenvironment-mimicking conditions in vitro, thereby interrupting prosurvival signaling.[13]

Given this data, several clinical trials combining BTK and PI3K inhibitors in B-cell malignancies are ongoing. These include a phase 1 study of umbralisib + ibrutinib in patients with R/R CLL,[19] a phase 1 study of umbralisib, ublituximab, and ibrutinib in patients with CLL and non-Hodgkin lymphoma,[20] and a phase 1/2 study of pan-PI3K inhibitor copanlisib and ibrutinib in patients with MCL (NCT03877055).

These data provide a rationale for exploring combined inhibition of multiple kinases in the BCR pathway for treatment of CLL. In this study we evaluated the safety, tolerability, and preliminary efficacy of the combinations TIRA/IDELA and TIRA/ENTO, as well as TIRA monotherapy, in patients with relapsed/refractory CLL.

Materials and Methods

Study design

This was a phase 1b, open-label, multicenter, sequential, dose-escalation and dose-expansion study (NCT02457598) conducted in the United States, the United Kingdom, and France. Patients with CLL reported here represent one histological cohort of a larger study (Supplemental Figure 1) evaluating TIRA combinations in subjects with relapsed or refractory NHL. This manuscript reports safety and efficacy data only in patients with CLL. Eligible patients were age ≥18 years with Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and either documented disease progression or stable disease on the most recent of ≥1 chemotherapy- or immunotherapy-based CLL treatment regimen, and no prior exposure to AKT, BTK, PI3K, JAK, mTOR, or SYK inhibitors (see Supplemental Table 1 for more details). Institutional review boards at each of the study sites approved the protocols. All patients provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

A standard 3+3 dose-escalation schema was followed (Supplemental Table 2). Patients receiving the TIRA/IDELA combination were treated on 28-day cycles with either IDELA 50 mg BID or 100 mg QD and TIRA ranging from 20 mg to 160 mg QD. Patients receiving the TIRA/ENTO combination were treated with either ENTO 200 mg or 400 mg QD and TIRA ranging from 40 mg to 150 mg QD. TIRA monotherapy was given at 80 mg QD. Patients received a single dose of TIRA on cycle 1, day 1, before initiating IDELA or ENTO in combination with TIRA on cycle 1, day 2 (or continuation with TIRA monotherapy). After completion of study treatment, patients attended a 30-day safety follow-up visit.

Determination of CLL response and progression was based on the 2008 standardized International Workshop on CLL (iwCLL) Criteria, which were current at the time the study protocol was finalized.[21] CLL patients had CT or MRI scans performed at baseline, at 24 weeks, and at the time of progression. Bone marrow aspirates were collected at the time of suspected complete response (CR) for minimal residual disease (MRD) testing using the CLL ERIC MRD flow cytometry panel at Covance/Labcorp, Indianapolis, based on Rawstrom et al, 2007, and

Rawstrom et al, 2013.[22,23] For prognostic biomarkers, peripheral blood was collected prior to therapy at cycle 1, day 1, at disease progression, and at the time of suspected CR for MRD testing.

The primary endpoint of the dose-escalation phase was safety, evaluated by the occurrence of adverse events (AEs) and laboratory abnormalities defined as dose-limiting toxicities (DLTs) (see Supplemental Table 3). The disease and dose chosen for expansion cohorts were based on emerging safety, pharmacokinetics (PK), and pharmacodynamic results of the dose-escalation phase. In the dose-expansion phase (Supplemental Table 4), the primary endpoint was ORR, defined as the proportion of patients who achieve a CR (including those with CR with undetectable MRD), partial response (PR), or PR with lymphocytosis.[24] Secondary endpoints included PFS, duration of response, time to response, proportion of subjects who achieve undetectable MRD (defined as <1 leukemia cell/10,000 leukocytes), and PK parameters. Sum of the products of greatest perpendicular lesion diameters (SPD) change from baseline was evaluated as an exploratory endpoint.

Pharmacokinetic assessments

Blood samples were collected at protocol prespecified sampling times. Patients in the dose-escalation cohorts underwent intensive PK sampling on day 1, day 2, and day 8 of the first treatment cycle in order to assess potential drug-drug interactions between TIRA and IDELA or ENTO. Dose-escalation cohorts enrolled subjects with various B-cell malignancies, with the exception of the last dose-escalation cohort/highest TIRA dose (160 mg) that enrolled DLBCL subjects only. CLL patients in the dose-expansion cohorts had sparse PK samples collected at predose and 1.5–4.0 hours postdose of TIRA and ENTO or IDELA throughout the study.

Plasma concentrations of TIRA, ENTO, and IDELA were determined using validated bioanalytical assays. PK parameters were estimated by standard noncompartmental methods using Phoenix WinNonlin® 7.0 software (Certara, Princeton, NJ, US). PK parameters and concentrations were summarized using descriptive statistics.

Cytogenetic assessments

A panel of genetic aberrations common in CLL was assessed using next generation sequencing (NGS, CGI Focus CLL panel [NGS mutation panel consisting of 7 genes: *TP53, ATM, BIRC3, NOTCH1, SF3B1, CARD11,* and *MYD88*]), *IGVH* mutational status analysis, and FISH (both performed at Cancer Genetics; Rutherford, NJ, US). The following FISH probes were used: 11q22.3 (*ATM*); 17p13 (*TP53*); CEP12; 13q14(D13S319)/13q34; CEP6/6q23 (c-MYB); t(11;14)(CCND1/IGH). Cytogenetic risk was categorized as high for patients with *TP53* aberrations (deletions and/or mutations in the *TP53* gene determined by NGS or FISH panels), and standard risk for those with no detectable *TP53* aberrations.

BTK occupancy assay

BTK occupancy was evaluated in a duplexed, homogeneous Time-Resolved Fluorescence Resonance Energy Transfer assay that measures total and free BTK in peripheral blood mononuclear cells.[25]

Statistical analysis

Analysis results are presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category are presented; for continuous variables, this may include the number of subjects (n), mean, standard deviation (SD) or standard error, median, first quartile (Q1), third quartile (Q3), minimum, and maximum. Best overall response was defined as the best response recorded from the start of treatment until PD/recurrence. ORR is defined as the proportion of subjects who achieve CR or PR during the study based on iwCLL 2018 criteria.[24] PFS was analyzed by Kaplan-Meier methods and defined as the interval from the start of the study therapy to the earlier of the first documentation of definite disease progression (radiographic or clinical progression) or death from any cause.

The follow-up time for PFS was summarized using descriptive statistics and defined as the interval from the study therapy start date to the last follow-up date. For patients who were lost to follow-up without a PFS event, the last efficacy assessment date was used as the last follow-up date. All others were assigned the data extraction date (21 February 2019) as the follow-up date.

Results

A total of 53 patients with CLL were enrolled: 29 patients in the TIRA cohort, 14 in the TIRA/IDELA cohort, and 10 in the TIRA/ENTO cohort. Baseline demographics are summarized in Table 1. The median number of prior therapies was 1 in each treatment cohort. All patients in the combination therapy groups and 27 of 29 patients assigned to TIRA had an ECOG performance status of ≤1. There was a higher proportion of patients with Rai stage III-IV in the TIRA/ENTO cohort (50%), compared with the TIRA/IDELA (21%) and TIRA monotherapy (31%) cohorts.

As of 21 February 2019, 46 of 53 patients continue to receive treatment on study: 26 patients on TIRA, 10 patients on TIRA/IDELA, and all 10 patients assigned to TIRA/ENTO. Median (range) exposures were 67.4 (0.3, 104.6), 135.0 (36.0, 185.3), and 132.1 (107.6, 144.3) weeks in the 3 treatment cohorts, respectively (Figure 1, Supplemental Table 5). Three patients discontinued the study in the TIRA group (Supplemental Figure 2): 1 due to a treatment-emergent adverse event (TEAE, aphasia, deemed not related to study drug), 1 per investigator discretion, and 1 due to progressive disease. Four patients discontinued the study in the TIRA/IDELA group: 1 due to progressive disease, 2 per investigator discretion, and 1 death. There were no study discontinuations in the TIRA/ENTO cohort.

Safety

No DLTs were observed in CLL patients receiving either combination, and hence, no MTD was identified in any cohort at the doses evaluated. In each treatment cohort, all patients had at least 1 TEAE and/or at least 1 laboratory abnormality. Across all treatment cohorts, the most common TEAEs were diarrhea, constipation, nausea, neutropenia, and contusion (Table 2, Supplemental Table 6). Overall, neutropenia was the most common TEAE and the most common grade ≥3 laboratory abnormality (Table 3).

No patients receiving TIRA or TIRA/ENTO experienced pneumonitis; however, 2 patients on TIRA/IDELA developed grade 1–2 pneumonitis. One patient receiving TIRA/IDELA died; the patient was reported to have stopped breathing while on a long car ride. No autopsy was performed and the cause of death remains unknown. No patients receiving TIRA or TIRA/ENTO died during the study. There were no cases of Richter's transformation in this study.

TIRA

Diarrhea and nausea were the most common TEAEs with TIRA monotherapy (Table 2), occurring in 9 (31%) patients each. Six (21%) patients had neutropenia. Serious TEAEs occurred in 5 (17%) patients (Supplemental Table 6): these included pneumonia, pneumonia pseudomonal, and pneumonia staphylococcal (3 patients); aphasia, and lower respiratory tract infection (1 patient each). Grade ≥3 TEAEs were reported in 10 (35%) patients, most commonly neutropenia, occurring in 5 (17%) patients.

TIRA/IDELA

The most common TEAEs on TIRA/IDELA combination therapy were diarrhea in 8 (57%) patients, and neutropenia, cough, rash, and bronchitis, occurring in 5 (36%) patients each. Seven (50%) patients had serious TEAEs, the most common being pyrexia, pneumonia, and febrile neutropenia (2 patients each). Grade ≥3 TEAEs were reported in 10 (71%) patients, most commonly neutropenia, which occurred in 5 (36%) patients.

TIRA/ENTO

In the TIRA/ENTO cohort, the most common TEAEs were diarrhea, fatigue, and contusion, occurring in 6 (60%) patients each. Serious TEAEs were reported in 5 (50%) patients, the most common being upper respiratory tract infection (2 patients). Grade ≥3 TEAEs were reported in 7 (70%) patients, most commonly neutropenia in 3 (30%) and upper respiratory tract infection in 2 (20%).

TEAEs of special interest

Diarrhea and liver function test abnormalities are recognized complications of therapy with PI3K inhibitors, while hemorrhagic events, atrial fibrillation, and hypertension have been associated with BTK inhibitor therapy. In this study, only 1 patient receiving TIRA/IDELA experienced a

grade 3 AE of diarrhea, which resolved upon dose interruption. There was also 1 patient with a TEAE of diarrhea leading to treatment discontinuation in this study. Increases in alanine aminotransferase and aspartate aminotransferase and decreases in creatinine clearance occurred at higher rates in the combination cohorts. All such TEAEs resolved with treatment interruption.

Across treatment groups, the overall frequency of bleeding/hemorrhage was 53% (based on a broad medical search for terms such as contusion, petechiae, ecchymosis, conjunctival and hemorrhoidal hemorrhage, epistaxis, hematoma, and purpura). One patient receiving TIRA/IDELA had a grade 3 subdural hemorrhage. Atrial fibrillation was detected in 6% of patients on this study (none with grade ≥3). Meanwhile, the frequency of hypertension was 4%.

Efficacy

All patients were evaluable for response. Among all patients on study, ORR was 88.7% (47 out of 53 patients). Four patients achieved CR as defined by iwCLL criteria: 2 on TIRA and 1 each in the combination therapy groups. Of these, none had undetectable MRD. SPD reduction (best change from baseline) is shown in Figure 2. Out of the patients with valid baseline and post-baseline SPD measurements, only 1 patient in the TIRA arm and 2 patients treated with the combination of TIRA/IDELA did not reach a 50% decrease in SPD from baseline as the best response.

TIRA

The ORR in the TIRA group was 83% (Table 4). Median duration of response was not reached; mean (SD) time to response was 4.6 (1.3) months. Median PFS has not been reached; median (range) follow-up time of PFS was 15.5 (0.0, 24.0) months.

TIRA/IDELA

In patients treated with the TIRA/IDELA combination, the ORR was 93%. Median duration of response was 27 months (95% CI, 15 to 27 months). Mean (SD) time to response was 5.5 (1.1) months. Median PFS was 32 months (95% CI, 8 to 32 months), and the median (range) follow-up time of PFS was 34 (26, 43) months. Two patients had disease progression on TIRA/IDELA during the time course of this study.

TIRA/ENTO

Patients in the TIRA/ENTO treatment group had an ORR of 100%. Median duration of response was not reached, and the mean (SD) time to response was 5.8 (0.7) months. Median PFS also was not reached, and the median (range) follow-up time of PFS was 30.4 (24.7, 33.2) months.

Cytogenetic risk

Patients were classified as high risk if a *TP53* mutation and/or a del(17p) was detected, in contrast to patients with no aberration in *TP53* who were classified as standard risk. Data were available for all but 4 patients across all 3 arms. Based on the presence of *TP53* gene aberrations, 12 patients were categorized as high risk (Figure 2). Ten of these patients achieved either complete or partial response (responders), while 2 were nonresponders (Supplemental Table 7). Further, 37 patients were categorized as standard risk; 34 of these were responders, 3 were nonresponders. Reduction in tumor burden in response to TIRA alone or in combination with IDELA or ENTO was observed among patients with wild type as well as aberrant *TP53* (Figure 2). Across all treatment groups, only 7 patients had *IGHV* mutations; none of these patients achieved CR. Additional cytogenetic data correlated with treatment response can be found in Supplemental Table 8.

Pharmacokinetics and pharmacodynamics

The pharmacokinetics of TIRA were consistent with previous studies.[5] No accumulation of TIRA was observed after QD dosing, which is expected given the short TIRA half-life of 4–7 hours.[5] Systemic TIRA exposure in CLL patients is shown in Supplemental Table 9. TIRA plasma concentrations in CLL subjects were above levels required to inhibit BTK in peripheral blood (~20 ng/mL protein-adjusted IC50, see Supplemental Figure 3).[5]

Assessment of drug-drug interactions between TIRA and ENTO or IDELA was carried out in the dose-escalation cohorts, where intensive PK sampling was performed (see Methods). Based on these data we conclude that IDELA and ENTO did not affect TIRA PK (Supplemental Figure 3 and Supplemental Table 10). TIRA did not affect ENTO PK, but increased IDELA exposures at higher doses (TIRA 160 mg QD, see Supplemental Table 10). Note that patients treated at the TIRA 160 mg QD dose level were those with diffuse large B-cell lymphoma. This observation is consistent with a potential inhibitory effect of TIRA on the CYP3A metabolizing enzyme and/or the P-glycoprotein transporter for which IDELA is a substrate.[26,27]

Pharmacodynamic changes were assessed by measuring free and total BTK levels. Among the 25 CLL patients with evaluable data, the range of measured free BTK at baseline was 31−139 ng/mL. Free BTK levels decreased rapidly on treatment with 19 of 22 patients for whom assay data were available having no detectable free BTK (LLOQ, 12 ng/mL) 2 hours after the first dose. Free BTK levels were also not detectable in patients at trough. These observations were consistent across TIRA dose levels (20 mg BID, 40 mg QD, 80 mg QD); however, few samples were available at lower doses (Supplemental Table 11). Combining TIRA with IDELA or ENTO appeared to have the same effect on the free BTK levels as TIRA alone, although only limited data are available for combination treatment (Supplemental Figure 4).

Discussion

BTK inhibition in CLL is associated with an improved rate of PFS compared with standard chemoimmunotherapy regimens (bendamustine plus rituximab; fludarabine, cyclophosphamide, and rituximab; and chlorambucil), particularly in patients with unmutated *IGHV*[6,28] and

del(17p).[7,29] Recently the ELEVATE-TN study also showed that CLL patients with mutated *IGHV*, acalabrutinib+obinutuzumab led to significantly improved PFS when compared with obinutuzumab/chlorambucil.[2] However, there is a need for therapies for CLL patients that lead to deeper and longer remission. Complete responses with single-agent BCR pathway inhibitors are infrequent (<10%).[6,30-33] Persistent low-level residual disease allows the development of resistance, which can be difficult to treat. Combination therapy has the potential to meet these needs through broader elimination of B-cell clones, increased depth of response, and hence, shortened treatment duration. BTK, PI3K, and SYK are tractable targets within the BCR signaling cascade, and combining inhibitors of these pathways is a logical option to achieve those goals. The results presented here are the first to evaluate the combination of selective BTK inhibition with SYK or PI3K inhibition in patients with R/R CLL.

In this study, the objective was to evaluate the safety and preliminary efficacy of TIRA as monotherapy as well as in combination with ENTO or IDELA for patients with R/R CLL. The results demonstrate that TIRA in combination with IDELA or ENTO was well tolerated, with no significant potentiation of the previously characterized side effects associated with the individual agents. No DLTs were observed in patients receiving combination treatment, and no MTD was identified in any cohort at the doses evaluated. In previous studies, diarrhea and hepatic toxicity have been prevalent TEAEs observed with IDELA monotherapy or ENTO monotherapy, respectively.[5,34] In the present study, rates of grade 1–2 diarrhea were 31%, 57%, and 60% with TIRA, TIRA/IDELA, and TIRA/ENTO, respectively, but only 1 patient discontinued therapy due to this AE. A study evaluating dual therapy with IDELA/ENTO in CLL and NHL patients found severe treatment-emergent pneumonitis to be a prohibitive toxicity. Pneumonitis is a well-described complication of therapy with PI3Kδ inhibitors and has been reported in clinical trials of idelalisib, duvelisib, and umbralisib.[20,35,36] Cases of pneumonitis have been reported in CLL patients treated with ibrutinib.[37] Pneumonitis was also reported with the SYK inhibitor fostamatinib.[38] No patients receiving TIRA or TIRA/ENTO experienced pneumonitis; however, 2 patients on TIRA/IDELA developed grade 1–2 pneumonitis. Therefore, while uncommon, physicians treating patients with CLL should be aware of pulmonary complications that can arise when using novel agents.

These phase 1 safety findings are significant when put in context with use of currently approved BTK inhibitors. Between 12% and 21% of patients with R/R CLL have stopped therapy with ibrutinib due to adverse events when treated in clinical trials (with median follow-up between 9 and 62 months).[29,33,39] Furthermore, the overall ibrutinib discontinuation rate was as high as 41% in a real-world study (median follow-up 17 months), with drug-associated toxicity accountable for 50% of the discontinuations among the relapsed patients.[8] This is particularly important in CLL because the majority of these patients have multiple comorbidities,[40] which are known to negatively impact outcomes following chemoimmunotherapy[41] or treatment with ibrutinib.[42] For example, age is a significant independent risk factor for therapy discontinuation,[43] and higher comorbidity burden increases the likelihood of drug discontinuation and/or death.[42] Consistent with the favorable tolerability of TIRA monotherapy and combinations in the present

study, we observed low overall discontinuation rates (13%) due to AEs among all patients. TIRA monotherapy discontinuation was particularly infrequent (6%).

TIRA PK was consistent with previous reports. Pharmacodynamic data demonstrate that TIRA doses of 40 mg and above lead to full target occupancy, with no detectable free BTK, implying complete inhibition of BTK-mediated signaling. The reduction in free BTK was rapid (within hours of the first dose). Combining TIRA with either ENTO or IDELA did not influence the levels of free BTK. An objective response was achieved by 83%, 93%, and 100% of patients in the TIRA, TIRA/IDELA, and TIRA/ENTO treatment cohorts, respectively. The benefit of treatment is also evident in that responses to treatment are ongoing—46 patients still continue on study at the time of this report. Median PFS was 32 months in the TIRA/IDELA cohort and was not reached in CLL patients treated with TIRA or TIRA/ENTO. Based on the PD data showing that full BTK occupancy was achieved at 40 mg TIRA, and safety and efficacy data from the present study in conjunction with that of a previous study (Study ONO-4059POE001, NCT01659255),[5] the recommended phase 2 dose is 80 mg TIRA QD.

The preliminary efficacy findings of this study are consistent with the results of other early-phase clinical trials of BCR-signaling pathway inhibitors. A phase 1 study of the PI3K inhibitor umbralisib in combination with ibrutinib reported an overall response rate of 90% in patients (N=21) with R/R CLL.[19] In a combination phase 1 study of umbralisib, ublituximab (a second-generation anti-CD20 antibody), and ibrutinib in patients with CLL and NHL, ORR was 84%.[20] Meanwhile, an ORR of 95% was reported among patients with R/R CLL treated with acalabrutinib, a second-generation BCR-signaling inhibitor with relative selectivity toward BTK.[31]

Durable responses in patients with *TP53* aberrations continue to represent an unmet medical need in the era of targeted therapies. Presence of del(17p) was a statistically significant independent negative predictor of outcomes among patients treated with ibrutinib in a large cooperative group trial.[39,44] In the present data, responses were independent of *TP53* or del(17p) status. Among the 12 high-risk patients, 10 achieved a response. Thus, consistent with previous evaluation of TIRA as monotherapy, in this study TIRA given as monotherapy as well as in combination with IDELA or ENTO appears to benefit high-risk patients with *TP53* mutations or del(17p). This is consistent with the previously observed efficacy of BTK inhibition in patients with 17p/*TP53* aberrations.[7,29,31]

The limitations of this study include the short follow-up and the small number of patients, which make comparisons between treatment groups difficult. While a panel of mutations and other aberrations was assessed, due to the limited number of patients and the multiple combinations of these aberrations per patient, additional conclusions on the efficacy of TIRA in patients with specific aberrations besides *TP53*mt/17pdel could not be drawn.

BTK and in particular PI3K inhibition may increase genomic instability in preclinical models through enhanced expression of activation-induced cytidine deaminase, an enzyme involved in class switch recombination of the immunoglobulin genes.[45] It is possible that long-term therapy with BTK inhibitors alone or in combination with PI3K inhibitors may result in increased incidence of secondary cancers through this mechanism. This is particularly relevant in patients

with CLL who demonstrate an increased risk of secondary malignancies due to underlying immune dysregulation.[46] On the other hand, treatment with BTK inhibitors may lead to the reversal of the immunosuppressive state in CLL,[47] potentially enhancing antitumor immunity. Long-term follow-up will be needed to fully evaluate the risks of secondary malignancies among patients treated with BCR-signaling inhibitors.

While the preliminary efficacy data are promising, the reported combinations have not resulted in attaining rates of deeper responses that were hoped for in CLL. Whether a longer-term follow-up of these patients will result in higher rates of complete responses or undetectable MRD remains to be seen. A potential approach to further deepen responses is to add an anti-CD20 regimen with the current combinations. Phase 2 studies of triple-combination therapy to evaluate TIRA/ENTO ± obinutuzumab (NCT02983617) and TIRA/IDELA ± obinutuzumab (NCT02968563) in patients with R/R CLL are currently underway. Overall, we report the favorable safety profile, low rates of discontinuation, and promising preliminary efficacy data of TIRA both as monotherapy and in combination with other BCR signaling pathway inhibitors.

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Footnotes

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Data sharing statement: Anonymized individual patient data will be available upon request to qualified external researchers 6 months after FDA and European Medicines Agency approval per Gilead's Clinical Trial Disclosure & Data Transparency Policy as posted at https://www.gilead.com/research/disclosure-and-transparency.

Authorship

Contribution: A.V.D., C.H., S.S.M., S.A.R., R.H., P.C.Y., J.M.J., and X.H. designed and performed research; S.S.M., R.H., J.M.J., X.H., Z.Z., P.B., and P.C.Y. analyzed data; all authors participated in drafting, revising, and approving the final manuscript.

References

1. Project Orbis: FDA approves acalabrutinib for CLL and SLL. US Food and Drug Administration, 2019. (Accessed 12/12/2019, at https://www.fda.gov/drugs/resources-information-approved-drugs/project-orbis-fda-approves-acalabrutinib-cll-and-sll.)
2. Sharman JP, Banerji V, Fogliatto LM, et al. ELEVATE TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab (O) or Alone Vs O Plus Chlorambucil (Clb) in Patients (Pts) with Treatment-Naive Chronic Lymphocytic Leukemia (CLL). Blood 2019;134:31.
3. Berglof A, Hamasy A, Meinke S, et al. Targets for Ibrutinib Beyond B Cell Malignancies. Scand J Immunol 2015;82:208-17.
4. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci U S A 2010;107:13075-80.
5. Walter HS, Rule SA, Dyer MJ, et al. A phase 1 clinical trial of the selective BTK inhibitor ONO/GS-4059 in relapsed and refractory mature B-cell malignancies. Blood 2016;127:411-9.
6. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med 2015;373:2425-37.
7. Farooqui MZ, Valdez J, Martyr S, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. Lancet Oncol 2015;16:169-76.
8. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. Haematologica 2018;103:874-9.
9. Wu J, Liu C, Tsui ST, Liu D. Second-generation inhibitors of Bruton tyrosine kinase. J Hematol Oncol 2016;9:80.

10. Kozaki R, Vogler M, Walter HS, et al. Responses to the Selective Bruton's Tyrosine Kinase (BTK) Inhibitor Tirabrutinib (ONO/GS-4059) in Diffuse Large B-cell Lymphoma Cell Lines. Cancers (Basel) 2018;10.
11. Liclican A, Serafini L, Xing W, et al. Biochemical Characterization of Tirabrutinib and Other Irreversible Inhibitors of 1 Bruton's Tyrosine Kinase Reveals Differences in On- and Off-Target Inhibition. Biochimica et Biophysica Acta In Press 2020.
12. Walter HS, Jayne S, Rule SA, et al. Long-term follow-up of patients with CLL treated with the selective Bruton's tyrosine kinase inhibitor ONO/GS-4059. Blood 2017;129:2808-10.
13. Paiva C, Rowland TA, Sreekantham B, et al. SYK inhibition thwarts the BAFF - B-cell receptor crosstalk and thereby antagonizes Mcl-1 in chronic lymphocytic leukemia. Haematologica 2017;102:1890-900.
14. Packham G, Stevenson F. The role of the B-cell receptor in the pathogenesis of chronic lymphocytic leukaemia. Semin Cancer Biol 2010;20:391-9.
15. Niemann CU, Mora-Jensen HI, Dadashian EL, et al. Combined BTK and PI3Kdelta Inhibition with Acalabrutinib and ACP-319 Improves Survival and Tumor Control in CLL Mouse Model. Clin Cancer Res 2017;23:5814-23.
16. de Rooij MF, Kuil A, Kater AP, Kersten MJ, Pals ST, Spaargaren M. Ibrutinib and idelalisib synergistically target BCR-controlled adhesion in MCL and CLL: a rationale for combination therapy. Blood 2015;125:2306-9.
17. Mathews Griner LA, Guha R, Shinn P, et al. High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell-like diffuse large B-cell lymphoma cells. Proc Natl Acad Sci U S A 2014;111:2349-54.
18. Yahiaoui A, Meadows SA, Sorensen RA, et al. PI3Kdelta inhibitor idelalisib in combination with BTK inhibitor ONO/GS-4059 in diffuse large B cell lymphoma with acquired resistance to PI3Kdelta and BTK inhibitors. PLoS One 2017;12:e0171221.
19. Davids MS, Kim HT, Nicotra A, et al. Umbralisib in combination with ibrutinib in patients with relapsed or refractory chronic lymphocytic leukaemia or mantle cell lymphoma: a multicentre phase 1-1b study. Lancet Haematol 2019;6:e38-e47.
20. Nastoupil LJ, Lunning MA, Vose JM, et al. Tolerability and activity of ublituximab, umbralisib, and ibrutinib in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma: a phase 1 dose escalation and expansion trial. Lancet Haematol 2019;6:e100-e9.
21. Hallek M, Cheson BD, Catovsky D, 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.
22. Rawstron AC, Villamor N, Ritgen M, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia 2007;21:956-64.
23. Rawstron AC, Bottcher S, Letestu R, et al. Improving efficiency and sensitivity: European Research Initiative in CLL (ERIC) update on the international harmonised approach for flow cytometric residual disease monitoring in CLL. Leukemia 2013;27:142-9.
24. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-60.
25. Yu H, Truong H, Mitchell SA, et al. Homogeneous BTK Occupancy Assay for Pharmacodynamic Assessment of Tirabrutinib (GS-4059/ONO-4059) Target Engagement. SLAS Discov 2018;23:919-29.
26. Jin F, Robeson M, Zhou H, et al. Clinical drug interaction profile of idelalisib in healthy subjects. J Clin Pharmacol 2015;55:909-19.
27. Ramanathan S, Jin F, Sharma S, Kearney BP. Clinical Pharmacokinetic and Pharmacodynamic Profile of Idelalisib. Clin Pharmacokinet 2016;55:33-45.

28. Robak T, Burger JA, Tedeschi A, et al. Single-agent ibrutinib versus chemoimmunotherapy regimens for treatment-naive patients with chronic lymphocytic leukemia: A cross-trial comparison of phase 3 studies. Am J Hematol 2018;93:1402-10.
29. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol 2016;17:1409-18.
30. O'Brien SM, Jaglowski S, Byrd JC, et al. Prognostic Factors for Complete Response to Ibrutinib in Patients With Chronic Lymphocytic Leukemia: A Pooled Analysis of 2 Clinical Trials. JAMA Oncol 2018;4:712-6.
31. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2016;374:323-32.
32. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med 2014;370:997-1007.
33. Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood 2019;133:2031-42.
34. Awan FT, Thirman MJ, Patel-Donnelly D, et al. Entospletinib monotherapy in patients with relapsed or refractory chronic lymphocytic leukemia previously treated with B-cell receptor inhibitors: results of a phase 2 study. Leuk Lymphoma 2019:1-6.
35. Idelalisib (Zydelig) prescribing information. Available at: https://www.zydelig.com/. Last accessed February 4, 2019.
36. Duvelisib (Copiktra) prescribing information. Available at: http://www.verastem.com/wp-content/uploads/2018/08/prescribing-information.pdf. Last accessed December 18, 2019.
37. Mato AR, Islam P, Daniel C, et al. Ibrutinib-induced pneumonitis in patients with chronic lymphocytic leukemia. Blood 2016;127:1064-7.
38. Flinn IW, Bartlett NL, Blum KA, 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.
39. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood 2018;131:1910-9.
40. Thurmes P, Call T, Slager S, et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leuk Lymphoma 2008;49:49-56.
41. Rigolin GM, Cavallari M, Quaglia FM, et al. In CLL, comorbidities and the complex karyotype are associated with an inferior outcome independently of CLL-IPI. Blood 2017;129:3495-8.
42. Gordon MJ, Churnetski M, Alqahtani H, et al. Comorbidities predict inferior outcomes in chronic lymphocytic leukemia treated with ibrutinib. Cancer 2018;124:3192-200.
43. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. JAMA Oncol 2015;1:80-7.
44. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med 2018;379:2517-28.
45. Compagno M, Wang Q, Pighi C, et al. Phosphatidylinositol 3-kinase delta blockade increases genomic instability in B cells. Nature 2017;542:489-93.
46. Tsimberidou AM, Wen S, McLaughlin P, et al. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol 2009;27:904-10.
47. Long M, Beckwith K, Do P, et al. Ibrutinib treatment improves T cell number and function in CLL patients. J Clin Invest 2017;127:3052-64.

Table 1. Patient demographics and baseline characteristics

	TIRA (N=29)	TIRA/IDELA (N=14)	TIRA/ENTO (N=10)
Age, median (range) years	70 (52-91)	66 (50-79)	74 (61-82)
≥65 years of age, n (%)	21 (72.4)	8 (57.1)	9 (90)
Female	12 (41.4)	7 (50)	6 (60)
Time since diagnosis, median (range) years	10.5 (0.2, 22.4)	7.9 (1.4, 13.7)	7.7 (4.6, 13.7)
ECOG performance status, n (%)			
0	17 (58.6)	6 (42.9)	2 (20)
1	10 (34.5)	8 (57.1)	8 (80)
≥2	1 (3.4)	0	0
Missing	1	0	0
Rai staging at screening, n (%)			
Stage 0 (low risk)	0	1 (7.1)	0
Stage I-II (intermediate risk)	12 (41.4)	6 (42.9)	4 (40.0)
Stage III-IV (high risk)	9 (31.0)	3 (21.4)	5 (50.0)
Missing	8 (27.6)	4 (28.6)	1 (10)
Prior no. of anticancer therapies, median (range)	1 (1-6)	1 (1-4)	1 (1-3)
Best response to last regimen, n (%)			
Complete response	13 (44.8)	5 (35.7)	3 (30.0)
Partial response	7 (24.1)	4 (28.6)	5 (50.0)
Stable disease	1 (3.4)	2 (14.3)	0
Progressive disease	0	1 (7.1)	2 (20.0)
Other*	8 (27.6)	2 (14.3)	0

ECOG, Eastern Cooperative Oncology Group.

*Includes patients with unknown prior response, or unable to evaluate.

Table 2. Incidence of treatment-emergent adverse events

Category, n (%)	TIRA N=29	TIRA/IDELA N=14	TIRA/ENTO N=10	Overall N=53	Grade ≥3 (Overall) N=53
TEAEs by MedDRA-Preferred Term[a]					
Diarrhea	9 (31)	8 (57)	6 (60)	23 (43)	1 (2)[b]
Nausea	9 (31)	4 (29)	2 (20)	15 (28)	0
Contusion	4 (14)	3 (21)	6 (60)	13 (25)	0
Neutropenia	6 (21)	5 (36)	2 (20)	13 (25)	12 (23)
Constipation	6 (21)	4 (29)	2 (20)	12 (23)	0
Cough	2 (7)	5 (36)	5 (50)	12 (23)	0
Rash	4 (14)	5 (36)	2 (20)	11 (21)	0
Upper respiratory tract infection	3 (10)	4 (29)	4 (40)	11 (21)	2
Dyspepsia	3 (10)	4 (29)	3 (30)	10 (19)	0
Arthralgia	3 (10)	4 (29)	2 (20)	9 (17)	0
Fatigue	1 (3)	2 (14)	6 (60)	9 (17)	0
Petechia	4 (14)	3 (21)	2 (20)	9 (17)	0
Rhinitis	2 (7)	4 (29)	3 (30)	9 (17)	0
Back pain	3 (10)	4 (29)	1 (10)	8 (15)	0
Bronchitis	3 (10)	5 (36)	0	8 (15)	0
Dizziness	4 (14)	2 (14)	2 (20)	8 (15)	0
Muscle spasms	3 (10)	4 (29)	1 (10)	8 (15)	0
Vomiting	1 (3)	3 (21)	4 (40)	8 (15)	0

MedDRA, Medical Dictionary for Regulatory Activities.
[a]TEAEs of any grade occurring in ≥15% of patients overall.
[b]One patient receiving TIRA/IDELA experienced a grade 3 AE of diarrhea, which resolved upon dose interruption.

Table 3. Incidence of ≥grade 3 laboratory abnormalities of interest

Category, n (%)	TIRA (N=29)	TIRA/IDELA (N=14)	TIRA/ENTO (N=10)
≥Grade 3 laboratory abnormalities of interest	19 (68)	14 (100)	7 (70)
Hematology			
Neutrophils decreased	4 (14)	6 (43)	3 (30)
Platelets decreased	4 (14)	2 (14)	2 (20)
Hemoglobin decreased	2 (7)	0	1 (10)
Lymphocytes decreased	0	1 (7)	2 (20)
Chemistry			
Triglycerides increased	3 (11)	2 (14)	0
Hyperuricemia	0	3 (21)	0
Lipase increased	1 (4)	2 (14)	0
g-glutamyl transferase increased	1 (4)	0	1 (10)

Table 4. Best overall response

	TIRA	TIRA/IDELA	TIRA/ENTO
All patients, N	29	14	10
Overall response rate*, n (%)	24 (83)	13 (93)	10 (100)
Best overall response, n (%)			
Complete response	2 (7)	1 (7)	1 (10)
Partial response	19 (66)	11 (79)	9 (90)
Partial response with lymphocytosis	3 (10)	1 (7)	0
Stable disease	2 (7)	1 (7)	0
Progressive disease	0	0	0
Nonevaluable	0	0	0
Discontinued study‡	3 (10)	0	0
High cytogenetic risk,† N	6	5	1
Overall response rate,* n (%)	5 (83)	4 (80)	1 (100)
Best overall response			
Complete response	1 (17)	0	0
Partial response	4 (67)	4 (80)	1 (100)
Partial response with lymphocytosis	0	0	0
Stable disease	1 (17)	1 (20)	0
Progressive disease	0	0	0
Nonevaluable	0	0	0
Discontinued study‡	0	0	0
Standard cytogenetic risk,† N	21	9	7
Overall response rate,* n (%)	18 (86)	9 (100)	7 (100)
Best overall response, n (%)			
Complete response	1 (5)	1 (11)	1 (14)
Partial response	15 (71)	7 (78)	6 (86)
Partial response with lymphocytosis	2 (10)	1 (11)	0
Stable disease	0	0	0
Progressive disease	0	0	0
Nonevaluable	0	0	0
Discontinued study‡	3 (14)	0	0

*Overall response rate = complete response + partial response + partial response with lymphocytosis.

†Cytogenetic risk was categorized as high for patients with *TP53* aberrations (deletions and/or mutations in the *TP53* gene determined by NGS or FISH panels), and standard risk for those with no detectable *TP53* aberrations.

‡Discontinued study or started new anticancer therapy before first assessment.

Figure Legend

Figure 1. Patient exposure and disposition in A) TIRA monotherapy, B) TIRA/IDELA, and C) TIRA/ENTO treatment groups

Figure 2. Best percentage change from baseline in SPD by treatment, dose level, and risk status

[FIG 2 FOOTNOTES]
High-risk CLL patients are defined as patients with p53 mutation and/or FISH del(17p) at baseline or early on-treatment time points.

SPD, sum of the products of the greatest perpendicular diameters.

Figure 1A

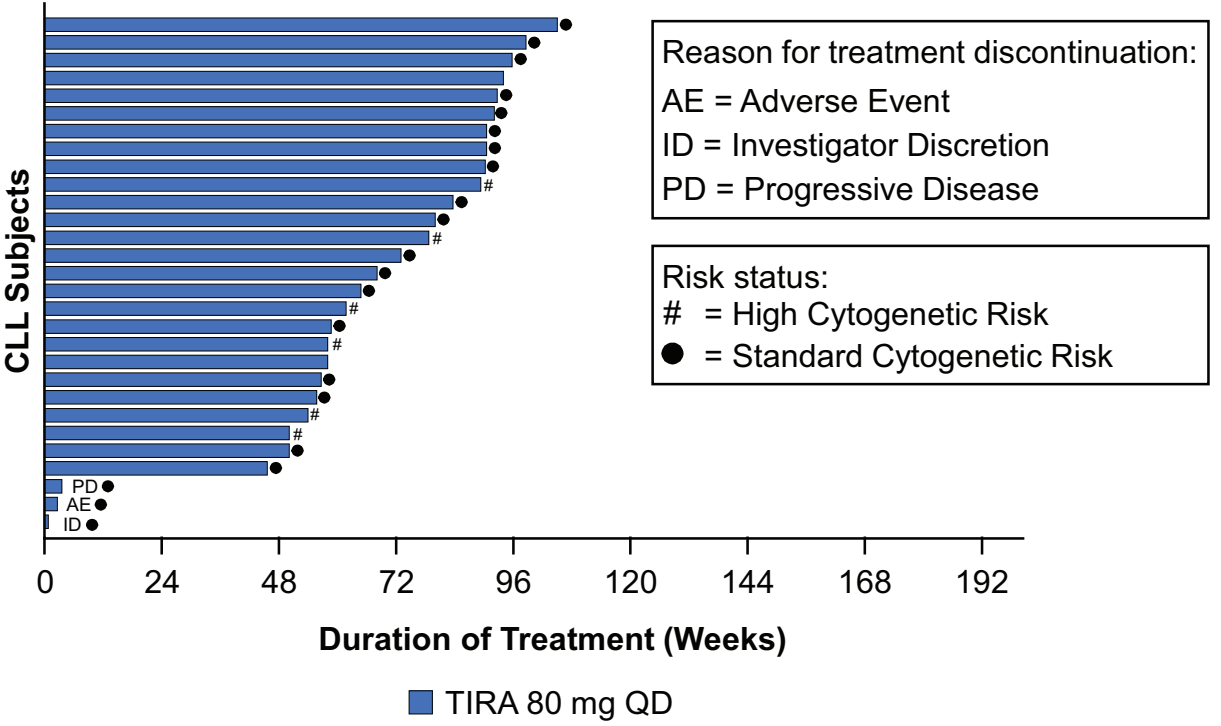
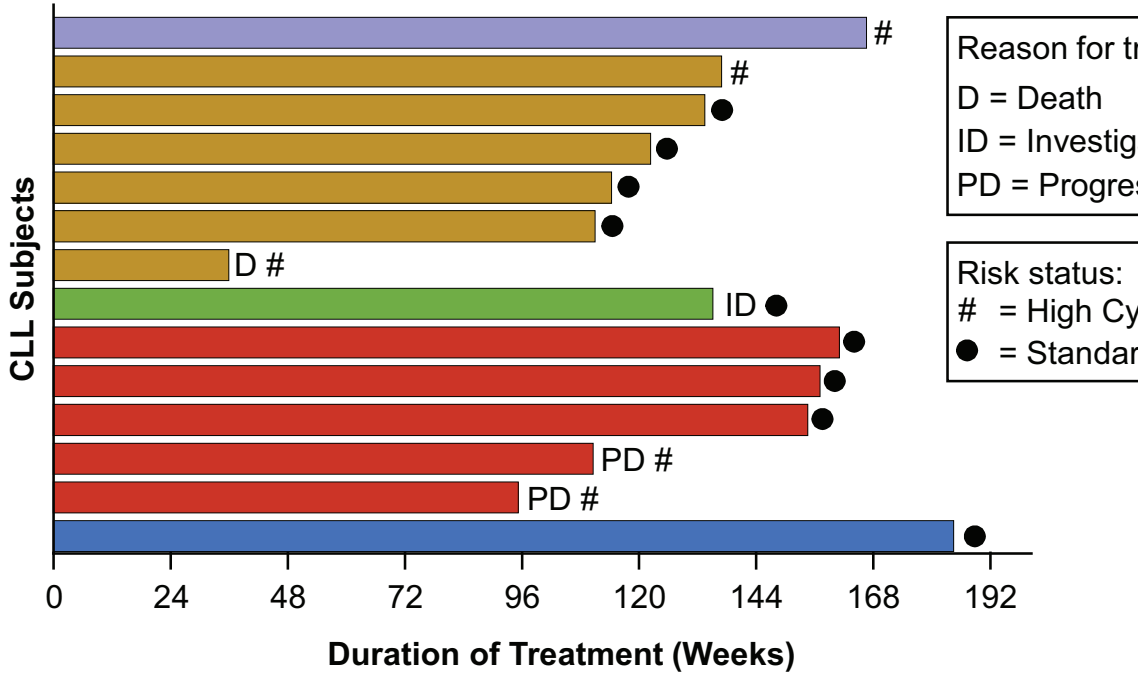

CLL Subjects
PD
AE
ID
0
24
48
72
96
120
144
168
192
Duration of Treatment (Weeks)
TIRA 80 mg QD
Reason for treatment discontinuation:
AE = Adverse Event
ID = Investigator Discretion
PD = Progressive Disease
Risk status:
= High Cytogenetic Risk
● = Standard Cytogenetic Risk

Figure 1B



Reason for treatment discontinuation:
D = Death
ID = Investigator Discretion
PD = Progressive Disease

Risk status:
= High Cytogenetic Risk
● = Standard Cytogenetic Risk

Figure 1C

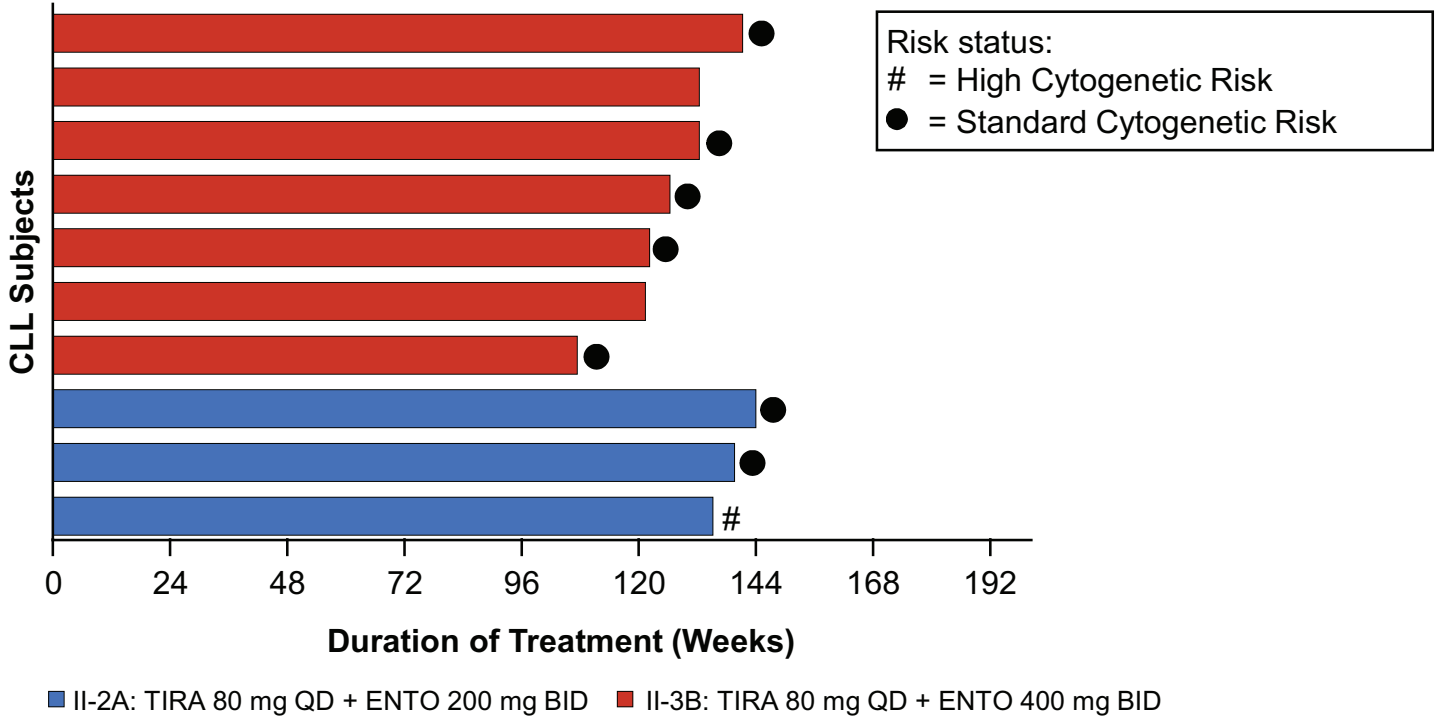
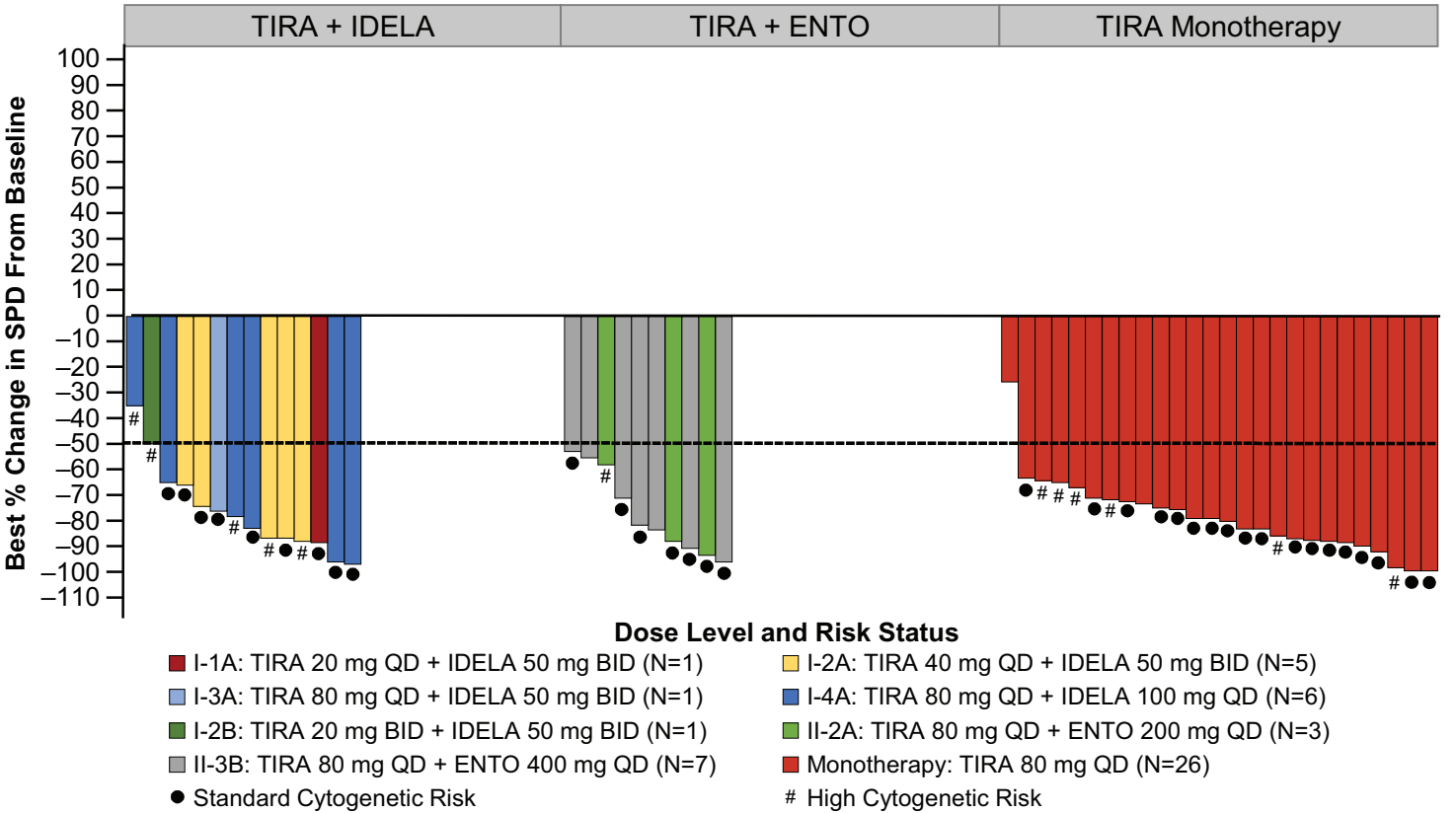

Risk status:
= High Cytogenetic Risk
● = Standard Cytogenetic Risk
CLL Subjects
#
0
24
48
72
96
120
144
168
192
Duration of Treatment (Weeks)
II-2A: TIRA 80 mg QD + ENTO 200 mg BID
II-3B: TIRA 80 mg QD + ENTO 400 mg BID

Figure 2


TIRA + IDELA
TIRA + ENTO
TIRA Monotherapy
Best % Change in SPD From Baseline
100
90
80
70
60
50
40
30
20
10
0
–10
–20
–30
–40
–50
–60
–70
–80
–90
–100
–110
Dose Level and Risk Status
I-1A: TIRA 20 mg QD + IDELA 50 mg BID (N=1)
I-2A: TIRA 40 mg QD + IDELA 50 mg BID (N=5)
I-3A: TIRA 80 mg QD + IDELA 50 mg BID (N=1)
I-4A: TIRA 80 mg QD + IDELA 100 mg QD (N=6)
I-2B: TIRA 20 mg BID + IDELA 50 mg BID (N=1)
II-2A: TIRA 80 mg QD + ENTO 200 mg QD (N=3)
II-3B: TIRA 80 mg QD + ENTO 400 mg QD (N=7)
Monotherapy: TIRA 80 mg QD (N=26)
Standard Cytogenetic Risk
High Cytogenetic Risk