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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

A Phase (Ph) 2 Study of TL-895, a Highly Selective, Novel Covalent BTK Inhibitor (BTKi), in Patients (pts) with Treatment-Naïve (TN) and Relapsed/Refractory (R/R) BTKi-Naïve Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

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Background:
Covalent BTKi have become the backbone of CLL/SLL therapy. Through improved target kinase selectivity, second generation BTKi offer improved safety with potentially better efficacy, yet compartmental clearance leading to complete remission (CR) remains elusive.
TL-895 is a potent, second generation, irreversible, oral BTKi with best-in-class selectivity (Gulrajani 2023) over other second generation BTKi; which may lead to improved safety and clearance of leukemic disease to induce deeper and more durable responses.

Methods:
This multicenter Ph 2 study (NCT02825836) enrolled symptomatic, BTKi-naïve CLL/SLL pts ≥18 years with ECOG PS 0-2. The R/R and TN arms enrolled sequentially and pts were randomly assigned to receive TL-895 at 100 mg (Arm 1 [R/R] and Arm 4 [TN]) or 150 mg (Arm 2 [R/R] and Arm 3 [TN]) twice a day continuously until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR: partial remission [PR], nodular PR [nPR], or CR) per iwCLL 2018 criteria and key secondary were CR rate, safety and BTK occupancy.

Results:
As of 11 July 2023, 84 pts were enrolled at 12 sites throughout the US and Europe. In TN Arms 3 and 4 (n=21 each), 57% of pts were *IGHV* ^{UNMUT}, 14% had del17p/ *TP53* ^{MUT} and 29% bulky (≥5 cm) adenopathy. Median baseline ALC was 77x10 ^{9}/L (range 2-444) in Arm 3 and 46x10 ^{9}/L (range 3-215) in Arm 4. In R/R Arms 1 and 2 (n=21 each), pts received a median of 2 prior therapies (range 1-5), 69% of pts were *IGHV* ^{UNMUT}, 48% had del17p/ *TP53* ^{MUT} and 52% bulky adenopathy. Median baseline ALC was 21x10 ^{9}/L (range 1-235) in Arm 1 and 34x10 ^{9}/L (range 2-178) in Arm 2.
In TN Arms 3 and 4, at a median follow-up of 8 months ([mo] range 1-10), the ORR was 86%. In the R/R Arms 1 and 2, at a median follow-up of 23 mo (range 1-26), the ORR was 86% and 81%, respectively. At the 100 mg dose, two unconfirmed CRs

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(uCR) pending bone marrow (BM) biopsy were reported in R/R Arm 1. At the 150 mg dose, one CR, one uCR pending BM biopsy and two nPRs were reported, two each in R/R Arm 2 and TN Arm 3. All CRs/uCRs and nPRs occurred by week 48.
In TN Arm 3 150 mg dose, a faster time to response was observed compared to TN Arm 4 100 mg dose (**Figure 1**), with a median ALC reduction of 50% by 3 mo compared to 6 mo, respectively **(Figure 2)**. Additionally, at a median of only 5 mo (range 0.3-8.3), 62% (13/21) of pts in Arm 3 compared with 20% (4/21) of pts in Arm 4 had complete resolution of lymphocytosis in their blood (<4 x10 ^{9}/L). Full trough target occupancy (median ≥95%) was achieved in both TN and R/R pts, with low intrapatient variability and near complete inhibition of signaling proteins downstream of BTK by FACS analysis.
In the TN arms, treatment-emergent adverse events (TEAEs) regardless of causality were reported in 88% of pts (36% grade [Gr] 3, 0% Gr 4). Most common TEAEs (>10%), were anemia (21%), neutropenia (14%), COVID-19 and upper respiratory tract infection (URTI; 12% each). Most common Gr 3/4 TEAEs (>10%) were anemia and neutropenia (12% each). In the R/R arms, TEAEs were reported in 98% of pts (31% Gr 3, 14% Gr 4). Most common TEAEs were neutropenia (31%) and COVID-19 (21%), thrombocytopenia (19%), diarrhea (17%), anemia, hypertension (HTN) and URTI (14% each), sinusitis and pneumonia (12% each). Most common Gr 3/4 TEAE was neutropenia (26%).
In the TN arms, incidence of TEAEs of interest (any Gr; Gr 3/4) were rash (2%; 0%), HTN (5%; 2%), and headache (2%; 0%) with no events of atrial fibrillation (AFib) or major hemorrhage. In the R/R arms, incidence of TEAEs of interest (any Gr; Gr 3/4) were rash (5%; 0%), HTN (14%; 5%), headache (5%; 0%), AFib (5%; 5%) and major hemorrhage (2%, 2%). Gr 5 TEAEs occurred in six R/R pts (three in each arm) and one TN Arm 4 pt, including three COVID-related deaths; none were considered related to TL-895. Excluding COVID-related deaths, median progression free survival (PFS) was not reached with an estimated 8 mos PFS rate of 93% (95% CI, 79-95) in TN pts and 84% (95% CI, 69-93) at 22 mos in R/R pts. Treatment discontinuations included 2 Richter's transformations, one each in TN Arms 3 and 4.

Conclusion:

Treatment with TL-895 resulted in rapid clearance of leukemic compartments, particularly in TN pts, leading to earlier and deeper responses than expected with monotherapy BTKi. In R/R pts with a very high frequency of del17p/ *TP53*^{MUT}, remissions have been durable. With a very low incidence of AEs typical of less selective BTKi (e.g., AFib, major hemorrhage, rash and headache), TL-895 has the potential to be a best-in-class backbone BTKi.

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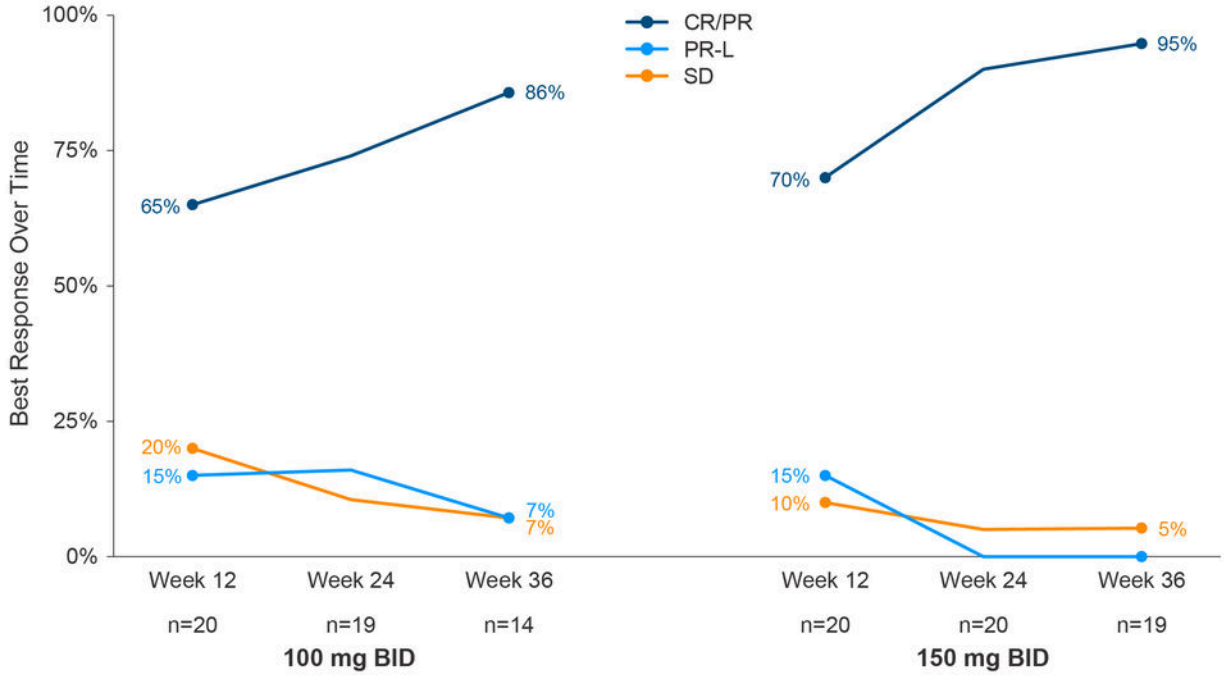
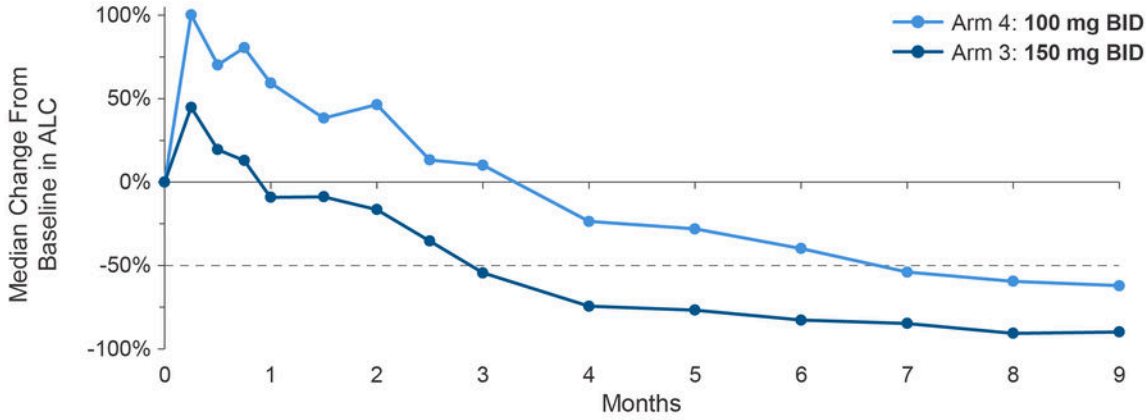
Figure 1: Treatment-Naïve Best Response Over Time



Data cut-off: 11 July 2023 (9-month cut-off).
Best response over time among all patients who could be evaluated at the respective time point.
Abbreviations: BID, twice-a-day; CR, complete remission; PR, partial remission; PR-L, partial remission with lymphocytosis; SD, stable disease.

Figure 2: Treatment-Naïve Median Change in ALC From Baseline



100 mg BID, n	21	20	20	20	20	19	19	19	19	19
Median ALC	46	89	77	44	36	25	22	14	16	16
150 mg BID, n	21	21	19	20	19	20	20	20	20	19
Median ALC	77	61	48	23	15	10	9	7	3	5

Data cut-off: 11 July 2023 (9-month cut-off).
Abbreviations: ALC, absolute lymphocyte count ($x10^9$/L); BID, twice-a-day.

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Figure 1

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