### Title

Phase 1/2 Study of Zilovertamab and Ibrutinib in Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL), or Marginal Zone Lymphoma (MZL)




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## 440 | PHASE 1/2 STUDY OF ZILOVERTAMAB AND IBRUTINIB IN MANTLE CELL LYMPHOMA (MCL), CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), OR MARGINAL ZONE LYMPHOMA (MZL)

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**Background:** Zilovertamab (Zilo) is a humanized monoclonal antibody that inhibits the tumor promoting activity of the cancer stem cell receptor, ROR1, which is highly expressed in many hematologic malignancies but not on normal adult tissues.

**Methods:** Patients (Pts) with relapsed or refractory (RR) MCL or MZL or treatment-naïve (TN) or RR CLL were enrolled. Part 1 (Dose Escalation in CLL & MCL) evaluated multiple doses up to Zilo 600 mg IV q4wks + Ibr 420 mg (CLL) or 560 mg (MCL) daily which was selected for Part 2 (Dose Expansion in CLL, MCL & MZL) and Part 3 (CLL only; pts randomized 2:1 to Zilo+Ibr vs. Ibr alone).

**Results:** To date, 33 MCL, 62 CLL & 4 MZL (99) pts were treated in Parts 1, 2 & 3. In Parts 1&2, 28 RR MCL and 34 CLL (12 TN and 22 RR) on zilo+ibr were efficacy evaluable (MZL not yet evaluable). In Part 3, 23 CLL pts on Zilo+Ibr (16) or Ibr (7) were evaluable. Safety & efficacy results were as of 11 October 2022.

**Safety in MCL and CLL:** The most frequent (≥30%) treatment emergent adverse events (TEAEs) for all MCL & CLL pts on Zilo +Ibr ($n$ = 85) were diarrhea & fatigue (45.9%), contusion (38.8%) and cough (30.6%). The most frequent (≥5%) grade ≥3 TEAEs were hypertension (10.6%), pneumonia (8.2%), atrial fibrillation (AF) & neutropenia (7.1%), and fatigue (5.9%). For all MCL & CLL pts on zilo+ibr, grade ≥3 hematologic lab abnormalities were decreases in neutrophils (11.8%), platelets (4.7%), and hemoglobin (3.5%).

**Efficacy in MCL:** The ORR was 89.3% (42.9% CR); 18% had achieved CR at 3 mos which suggests rapid response; median duration of response (mDOR) was 34.1 mos. Median PFS (mPFS) was not reached (NR) (95% CI: 33.2, NE) with median follow-up (mf/u) of 19.5 mos. Pts with 1 prior line of therapy (LOT) and >1 prior LOT had mPFS of 33.2 mos and NR, respectively. In pts with poor prognostic factors, 7 pts with TP53 mutation had ORR of 85.7% with mPFS NR and 14 pts with Ki-67 ≥30% had ORR of 85.7% with mPFS 33.2 mos. Overall, median OS was NR (95% CI: 22.46, NE).

**Efficacy in CLL:** In parts 1–3, mPFS was NR with mf/u of 40 mos for parts 1&2 and ~30 mos in part 3. In pooled analysis of all parts, mPFS in 10 pts (5 TN, 5 R/R) with TP53/del(17p) was NR and landmark PFS and OS were 100% at 42 & 40 mos, respectively.

**Conclusions:** Zilo+Ibr is well-tolerated with a safety profile that is comparable to Ibr alone. AF (all grades) occurred in 9.4% of all pts treated which appears lower than rate in Ibr alone studies. The combination is very promising in pts with RR MCL (ORR 89.3%, CR 42.9%, mPFS NR). For CLL pts with TP53 mut/del(17p), Zilo+Ibr is also very active, maintaining 100% PFS and OS at ~42 mos. This Zilo + Ibr data after >3 years of f/u is very encouraging in reference to the ALPINE results which reported estimated PFS at 36 mos of ~55% for Zanubrutinib and ~42% for Ibr in RR CLL pts with TP53 mutation. The study is currently enrolling MZL pts and has provided a strong rationale for conducting a Phase 3 pivotal study in RR MCL (ZILO-301).

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chronic Lymphocytic Leukemia (CLL), Molecular Targeted Therapies

**Conflicts of interests pertinent to the abstract.**

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## 441 | CCTG LY18-A PHASE I MASTER PROTOCOL OF NOVEL COMBINATION THERAPY FOR PATIENTS WITH RELAPSED OR REFRACTORY LYMPHOMA - THE RGDP-VENETOCLAX SUBSTUDY

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**Introduction:** Therapies for relapsed/refractory (r/r) large B cell lymphomas are expanding. Chemo-immunotherapy and autologous stem cell transplant (ASCT) remains an important therapeutic option with survival benefit. About 50% of patients (pts) have an adequate response to salvage therapy which is required to proceed to ASCT. Novel salvage regimens may increase response and transplantation rate.

**Methods:** LY.18 is a Canadian Cancer Trials Group Phase I platform trial of novel salvage regimens for patients with r/r large B cell lymphoma. RGDP (rituximab, gemcitabine, dexamethasone, cisplatin) plus venetoclax (RGDP-V) was evaluated in adult pts with diffuse large B cell lymphoma, primary mediastinal B cell lymphoma, transformed follicular lymphoma, or high-grade B cell lymphoma after one prior line of therapy. RGDP was administered at standard doses (Crump, JCO, 2014) for up to 3 cycles pre-transplant. V was administered at increasing dose levels (200–800 mg) according to a 3 +3 design, with dose limiting toxicity (DLT) assessed in cycle one. The recommended Phase 2 dose (RP2D) was the primary outcome. Pts with a partial or complete response (PR or CR) could proceed to ASCT. Response was assessed using both the Lugano criteria and RECIL.

**Results:** Since Sept 2020, 18 pts have been treated at 5 dose levels. Severe myelotoxicity was noted in the first dose level with 2 DLTs observed in the first 4 pts. The trial was amended to mandate G-CSF days 9 to 14 with each cycle of therapy (Table 1). Median age was 59, 4 pts were ≥65 years, 8 were female, median ECOG was 1 (range 0 to 3). Two of 3 pts experienced a DLT at the 800 mg dose. The recommended phase 2 dose (RP2D) is RGDP-V 400 mg days 4 to 10 of cycle 1, and days 1 to 10 of cycles 2 and 3. There were 7 serious adverse events in 5 pts, including febrile neutropenia ($n = 3$); grade 2 bacteremia ($n = 1$); and grade 3 abdominal pain, C2 fracture from fall, and supraventricular tachycardia ($n = 1$ each), all unrelated. There were 4 deaths on trial; 3 disease related, 1 from transplant-related complications. All grade treatment emergent adverse events occurring in at least 20% of patients were tinnitus, abdominal pain,

Table 1

| Dose Level | Regimen RGDP plus Ven | Patients* n=18 | DLT n=4 | Nature of DLT | Best Response (Lugano) | ORR (CR+PR) |
|---|---|---|---|---|---|---|
| Dose level 1 | Ven 200mg/day C1: days 4-10 C2,3: days 1-10 | 4 | 2 | • Grade 4 neutropenia >7 days<br>• Grade 4 neutropenia, thrombocytopenia >7 days | 2 PR<br>1 PD<br>1 INEVAL | 50% |
| Dose level -1 | Ven 200mg/day C1: days 4-8 C2,3: days 1-5 G-CSF | 3 | 0 | N/A | 1 CR<br>2 PR | 100% |
| Modified Dose llevel 1 | Ven 200mg/day C1: days 4-10 C2,3: days 1-10 G-CSF | 5 | 0 | N/A | 1 CR<br>3 PR<br>1 INEVAL | 80% |
| Modified Dose level 2 | Ven 400mg/day C1: days 4-10 C2,3: days 1-10 G-CSF | 3 | 0 | N/A | 3 PR | 100% |
| Modified Dose llevel 3 | Ven 800mg/day C1: days 4-10 C2,3: days 1-10 G-CSF | 3 | 2 | • Grade 4 neutropenia >7 days<br>• Febrile Neutropenia | 1 PD<br>2 still on treatment | |

*17 diffuse large B Cell Lymphoma, 1 mixed follicular/high grade B cell
DLT dose limiting toxicity; CR complete response; PR partial response; progressive disease; ORR overall response rate; INEVAL inevaluable; Ven venetoclax; RGDP rituximab gemcitabine, dexamethasone, cisplatin;
G-CSF granulocyte colony stimulating factor