Trial in Progress: Phase 1/2 Study Evaluating the Safety and Efficacy of IOV-2001, an Autologous, Non-Genetically Modified, Polyclonal T-Cell Product, in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) (IOV-CLL-01)

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Background

- Bruton tyrosine kinase (BTK) inhibitors (ie, ibrutinib, acalabrutinib) are approved for treating patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), and can mediate durable responses in some patients; however, relapses may occur, primarily due to acquired mutations in BTK enzyme and/or phospholipase C gamma 2
- Preclinical studies demonstrated successful generation of a T-cell product (IOV-2001) from BTK–inhibitor-treated patients with CLL:[1]
  - IOV-2001, a non-genetically modified, polyclonal T-cell product, was reproducibly generated from 50 mL of blood over a 9-day manufacturing duration to yield billions of peripheral blood lymphocytes (PBLs)
  - Compared with pre-ibrutinib and treatment-naïve PBLs, the PBLs derived from post-ibrutinib blood samples demonstrated higher-fold expansion from limited clinical starting material (simple blood draw, no apheresis required) and produced higher levels of IFNγ in response to non-specific T-cell receptor stimulation
  - IOV-2001 demonstrated robust cytotoxicity against autologous tumor (leukemia) cells

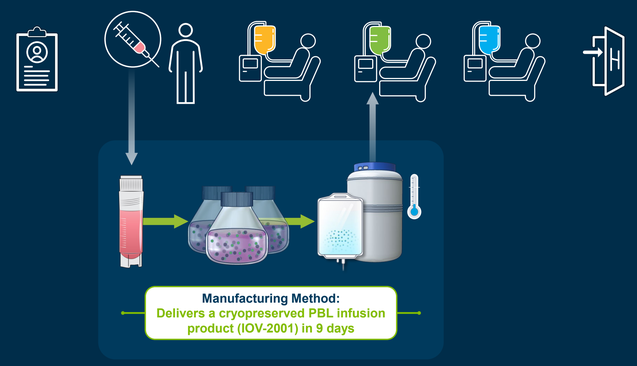
IOV-CLL-01

- **IOV-CLL-01 (NCT04155710)** is an ongoing first-in-patient, Phase 1/2, open-label, multi-cohort, dose-finding study designed to evaluate the safety and efficacy of IOV-2001 in patients with CLL/SLL who are progressing or have progressed with ibrutinib or acalabrutinib treatment

IOV-2001 Manufacturing

- **The one-time IOV-2001** cell therapy uses 50 mL of blood obtained from the patient to generate PBLs in a 9-day manufacturing process at a central GMP manufacturing facility

Figure 1. Patient Journey and Central GMP Manufacturing



Study Overview & Endpoints

- The study will enroll approximately 39 to 70 patients; 4 US sites are currently active and enrolling patients
  - Cohorts 1a and 1b: 9 to 40 dose-limiting toxicity (DLT)-evaluable patients
  - Cohorts 2 and 3: ~15 patients per cohort

Primary endpoints:
- Phase 1 (Cohorts 1a and 1b): Recommended Phase 2 dose (RP2D) of IOV-2001 and IL-2 dose selected for the RP2D
- Phase 2 (Cohorts 2 and 3): Efficacy of IOV-2001 at the RP2D followed by selected IL-2 dose, as measured by objective response rate (ORR) per investigator assessment

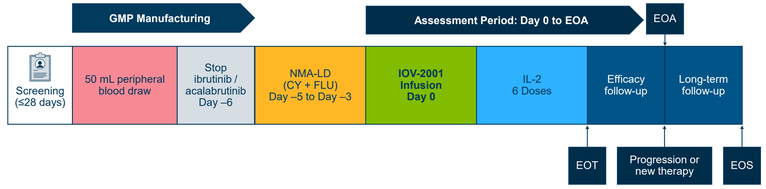
Secondary endpoints:
- ORR (Cohorts 1a and 1b)
- PFS, OS, DCR, DOR, CR, CRi, PR, SD, CR/CRi rate per investigator, as defined by iwCLL 2018 criteria
- MRD-negative rate
- Additional safety endpoints

Study Cohorts

Phase	Study Population	Cohort Test Product, Dose Regimen, and Route of Administration
1	CLL / SLL that has relapsed or is relapsing on ibrutinib or acalabrutinib	**Dose-finding with IOV-2001 dose de-escalation guided by DLT observations (n=9 to 40):** • **Cohort 1a**: IOV-2001, followed by 6 doses of SC low-dose IL-2 (9 MIU) every 8–12 hours (Completed) • **Cohort 1b:** IOV-2001, followed by 6 doses of IV high-dose IL-2 (600,000 IU/kg) every 8–12 hours
2		IOV-2001 RP2D, followed by 6 doses of the selected IL-2 dose: • **Cohort 2 (n≈15):** with del(17p) and/or *TP53* mutation progressed or progressing on first-line therapy • **Cohort 3 (n≈15):** without del(17p) and/or *TP53* mutation progressed or progressing on ≥1 additional line of therapy

IOV-CLL-01 Treatment Regimen

Figure 2. Cohort 2 and Cohort 3 Patient Treatment Schema



Abbreviations: ACT, adoptive cell therapy; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CR, complete response; CRi, complete remission with incomplete marrow recovery; CY, cyclophosphamide; DCR, disease control rate; DLT, dose-limiting toxicity; DOR: duration of response; ECOG, Eastern Cooperative Oncology Group; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FLU, fludarabine; GMP, good manufacturing practice; HD-IL-2, high-dose IL-2; HIV, human immunodeficiency virus; IL-2, interleukin-2; IU, international units; IV, intravenous; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; LD-IL-2, low-dose IL-2; MIU, million international units, MRD, minimal residual disease; NMA-LD, nonmyeloablative lymphodepletion; ORR, objective response rate; OS, overall survival; PBL, peripheral blood lymphocytes; PFS, progression-free survival; RP2D, recommended Phase 2 dose; SC, subcutaneous; SLL, small lymphocytic lymphoma.

Key Inclusion & Exclusion Criteria

Inclusion Criteria – All Patients

- ≥18 years of age, ECOG performance status of 0 or 1, and an estimated life expectancy of ≥3 months
- Adequate bone marrow function to receive NMA-LD
- Adequate pulmonary function, as assessed by spirometry
- Adequate cardiac function
- Radiographically measurable disease
- Receiving ibrutinib or acalabrutinib for ≥4 weeks prior to blood sample collection for PBL manufacturing

Prior Therapy Criteria

Cohort*	Del(17p) and/or *TP53* mutation	Number of prior lines of therapy (including BTK inhibitor)†
1a / 1b	Yes	≥1
	No	≥2
2	Yes	≥1
3	No	≥2

*All relapsed or relapsing on ibrutinib or acalabrutinib treatment.
†Most recent line of therapy must include ibrutinib or acalabrutinib.

Exclusion Criteria – All Patients

- Received an organ allograft or prior cell transfer therapy within the past 20 years
- Known or suspected transformed disease (ie, Richter transformation)
- Received treatment with any systemic chemotherapy, immunotherapy, targeted small molecule inhibitors, or other biologic agents (except ibrutinib or acalabrutinib) within 30 days or 5 half-lives, whichever is shorter, of IOV-2001 infusion
- Known involvement of CNS by lymphoma or leukemia
- Receiving chronic systemic steroid therapy (>5 mg/day prednisone equivalent)
- Active infection requiring systemic antibiotics, autoimmune anemia or thrombocytopenia, coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system
- Serologic test suggesting recent/active infection for any of the following:
  - Human immunodeficiency virus (HIV)-1 or HIV-2 antibodies
  - Hepatitis B antigen or anti-hepatitis B core total antibodies, or hepatitis C antibody
- Requiring treatment for anti-coagulation with a vitamin K antagonist (eg, warfarin)
- Received a live or attenuated vaccine within 28 days of beginning the preparative NMA-LD regimen

References
[1]Karyampudi L, et al. *HemaSphere*. 2019; 3(suppl 1; abstract PF447).

Disclosures
- This study and poster are sponsored by Iovance Biotherapeutics, Inc. San Carlos, CA, USA.
- FGF, MJ, SS, BY, and HL are current or former employees of Iovance Biotherapeutics, Inc., and have stock options.
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