Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) (IOV-CLL-01)

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, patients may derive primary or acquired resistance due to tumor evasion and 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.

- 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).

- Computed with pre-British and treatment-naïve PBLs, the PBLs derived from BTK– inhibitor-treated blood samples demonstrated higher fold expansion from limited clinical starting material (simple blood, no apheresis needed) 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.

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: 3 to 15 patients per cohort

- Primary endpoints:
  - Phase 1 (Cohorts 1a and 1b): Recommended Phase 2 dose (RP2D) of IOV-2001 and 8.2–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

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study Population</th>
<th>Cohort Test Product, Dose Regimen, and Route of Administration</th>
<th>Dose-finding with IOV-2001 dose de-escalation guided by DLT observations (n=6 to 48):</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>CLL / SLL that has relapsed or is relapsing on or after BTK inhibitor</td>
<td>Cohort 5: IOV-2001, followed by 6 doses of SC low-dose IL-2 (800,000 IU/kg) every 8–12 hours (600,000 IU/kg) every 8–12 hours</td>
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<tr>
<td>2</td>
<td>CLL / SLL that has relapsed or is relapsing on or after BTK inhibitor</td>
<td>Cohort 6: IOV-2001, followed by 6 doses of IV high-dose IL-2 (800,000 IU/kg) every 8–12 hours</td>
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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 brutinib or acalabrutinib for ≥4 weeks prior to blood sample collection for PBL manufacturing

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 biological agents (except brutinib 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, antiviral monotherapy or thrombocytopenia, coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system
- Sanitogenic test suggesting reinfusion 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
- Receiving 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

- This study and poster are sponsored by Iovance Biotherapeutics, Inc. San Carlos, CA, USA.
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