

**PROTOCOL SYNOPSIS**

<b>PROTOCOL No:</b> CM-2015-01	
<b>STUDY TITLE:</b> A Phase 2 open label study to investigate the safety and clinical activity of autologous EBV-specific T cells (CMD-003) for the treatment of patients with EBV positive lymphomas	
<b>STUDY ACRONYM:</b> CIVIC ( <u>C</u> ellular <u>I</u> mmunotherapy for <u>V</u> iral- <u>I</u> nduced <u>C</u> ancer)	
<b>INVESTIGATIONAL PRODUCT (CMD-003):</b> Autologous LMP1, LMP2, EBNA1 and BARF1 EBV-specific T cells. Treatment consists of up to 5 doses administered over a 2-month period. Each dose is comprised of $2 \times 10^7$ cells/m <sup>2</sup> given every 2 weeks intravenously via a peripheral or central line over a 1 to 10-minute period for a maximum of 5 doses.	
<b>PHASE OF DEVELOPMENT:</b> Phase 2	
<b>NUMBER OF SITES:</b> Approximately 12-15 US sites.	<b>NUMBER OF PATIENTS</b> Up to 70 patients
<b>LENGTH OF STUDY:</b> Each patient will be monitored for safety and efficacy for 1 year after the first CMD-003 dose administration. This study is expected to complete patient enrollment in 24 months, for a total study duration of 3 years from the first patient in to the last patient study visit. Long-term survival information will be collected for an additional 12 months following the Final Study Visit.	
<b>STUDY OBJECTIVES:</b> To evaluate the safety and efficacy of EBV-specific autologous T cells (CMD-003) in the treatment of EBV+ DLBCL, HL and PTLD after failing first-line treatment.	
<b>STUDY DESIGN:</b> This is an open label, Phase 2 multicenter trial. Up to 70 patients with 3 types of EBV positive tumors will be enrolled and treated with autologous EBV-specific T cell infusion (CMD-003). The study is composed of 2 phases: Screening and Treatment. In the Screening Phase, patients with history of EBV positive lymphoma or active post-transplant lymphoproliferative disease (PTLD) will be screened for this trial. Patients must have documentation of Epstein-Barr early	

RNA (EBER) positive tumor based on a report from a certified laboratory to be considered for screening in this study. Informed consent and if applicable, assent will be obtained before any study procedures are performed. A 200 mL whole blood sample will be obtained as starting material for the GMP manufacture of CMD-003. The manufacturing and product release time for CMD-003 is approximately 40 days from the initial blood procurement.

The Treatment Phase of the study will commence with the initiation of lymphodepleting therapy in the HL and DLBCL cohorts, followed by the infusion of CMD-003. Baseline assessments will include, but not be limited to: PET-CT imaging to document disease status, documentation of medications and interim medical history changes, plus the evaluation of clinical status and standard safety laboratory tests. Lymphodepleting therapy consisting of cyclophosphamide and fludarabine, will be administered during the week prior to the first CMD-003 infusion, unless in the judgment of the Investigator, patients are unable to tolerate lymphodepletion. Modification or omission of the lymphodepletion regimen requires prior approval of the Medical Monitor. The investigational cell product, CMD-003 will be administered every 2 weeks for a maximum of 5 doses.

During the study, there will be an assessment of adverse events (AEs) and concomitant medications at every study visit. Patients will be assessed at periodic study visits for 1 year from their first CMD-003 administration. Patients receiving  $\leq 2$  doses of CMD-003 will undergo their first disease response assessment at Week 8. Patients receiving  $\geq 3$  doses of CMD-003 will undergo their first disease response assessment at Month 3. Additional response assessments will be repeated every 3 months beginning at Month 6 through the Final Study Visit (Month 12). Tumor response will be evaluated based on Lugano 2014 Criteria by an independent radiological review committee. Individual sites will be allowed to use other imaging techniques for medical management in addition to the Lugano mandated procedures.

The patients' plasma and whole blood EBV DNA viral load and EBV-specific T cell activity will be assessed at Screening, Baseline (prior to lymphodepletion) and all study visits from Day 1 through the Final Study Visit (Month 12). Survival status and disease status will be captured using telephone and/or medical record based data capture out to Month 24.

A central pathology laboratory provided by the Sponsor will perform EBER (ISH) and test for other relevant biomarkers on tumor tissue samples obtained in this study. Pre-treatment and post-treatment tumor tissue will be batched and tested under a separate laboratory protocol. The testing is being performed centrally to reduce testing variability, to investigate the CMD-003 mechanism of action and support the development of a companion diagnostic.

#### **SELECTION CRITERIA FOR SCREENING PHASE:**

##### **FOR INCLUSION**

1. The study will include 3 primary cohorts, with any of the following EBV+ diseases:

- **Cohort A:** Diffuse large B-cell lymphoma (DLBCL), 1) in first or subsequent relapse, not eligible for autologous transplantation following salvage therapy OR 2) relapse following autologous transplantation.
  - **Cohort B:** Hodgkin lymphoma (HL), post brentuximab vedotin (BV) treatment, with progressive disease, relapse, partial response, stable disease or unable to tolerate BV.
  - **Cohort C:** Solid organ transplant patients with post-transplant lymphoproliferative disorder (PTLD) with progressive disease, relapse, partial response or stable disease following rituximab and chemotherapy treatment or following rituximab therapy alone if not able to tolerate chemotherapy.
2. Presence of active lymphoma or active PTLD, based on imaging performed within the previous 3 months.
  3. Tumor positive for EBER based on report from certified laboratory.
  4. Absolute lymphocyte count (ALC) > 500/ $\mu$ L.
  5. Male or female  $\geq$  12 years of age.
  6. Weight  $\geq$  35 kg.
  7. ECOG performance score 0-2, inclusively or Lansky score  $\geq$  60, as age appropriate.
  8. Able to understand and comply with the requirements of the study and to provide written informed consent or age appropriate assent for pediatric patients.

**FOR EXCLUSION**

1. Known CNS lymphoma.
2. Primary refractory HL or DLBC, defined either by progression at any time during first-line chemotherapy and up to 3 months after end of first-line chemotherapy, or by failure to achieve at least PR with first-line therapy.
3. Bulky disease, defined as, any site of disease > 5 cm diameter.
4. Relapse or progression following previous autologous EBV-specific T cell treatment.
5. Use of systemic corticosteroids > 0.5 mg/kg/day prednisolone or equivalent dose of alternative corticosteroid within 10 days prior to obtaining 200 mL starting material.
6. Known hypersensitivity to the investigational cell product or any components in the final formulation (e.g. DMSO and/or HSA).
7. Positive laboratory test for anti-HIV 1, 2; HBsAg, anti-HTLV-I; anti-HCV, or syphilis (Patients with anti-hepatitis B core antibody are eligible if negative for HBsAg; patients positive for anti-HCV may be enrolled if negative by nucleic acid amplification test).
8. Positive  $\beta$ -hCG test in females of childbearing potential.
9. Patient is pregnant or lactating.

10. Female patients of childbearing potential and male patients with partners of childbearing potential unwilling to use a highly effective method of birth control during the study and for 6 months after the study treatment is concluded.
11. Systemic fungal, bacterial, viral or other infection that is not controlled.
12. History of any of the following cardiovascular conditions within the past 3 months:
  - a. Class III or IV heart failure as defined by the New York Heart Association,
  - b. Cardiac angioplasty or stenting,
  - c. Documented myocardial infarction, or
  - d. Unstable angina.
13. Cardiac ejection fraction < 35%.
14. Prior allogeneic hematopoietic stem cell transplantation (allo HSCT).
15. Known history of primary immunodeficiency.
16. Active second malignancy, except for basal cell carcinoma of skin, squamous cell carcinoma of the skin or cervical carcinoma in situ.
17. Previous non-hematologic malignancy, unless the tumor was treated with curative intent more than 5 years prior to study entry.
18. Clinically significant medical condition e.g. pulmonary, neurologic, cardiovascular, metabolic, hepatic or hematologic that could jeopardize patient safety, interfere with the objectives of the protocol, or limit patient compliance with study requirements, as determined by the Investigator.

**SELECTION CRITERIA FOR TREATMENT PHASE:****FOR INCLUSION**

1. Presence of active lymphoma or PTLN, based on baseline imaging.
2. Recovery from acute hematologic, hepatic and renal chemotherapy-related toxicities as defined by  $\leq$  Grade 1 according to NCI CTCAE v4.0. (Transfusion to achieve the hematologic criteria is acceptable.)
3. Estimated life expectancy  $\geq$  14 weeks.
4. ECOG performance score 0-2, inclusively or Lansky score  $\geq$  60, as age appropriate.
5. Able to understand and comply with the requirements of the study and to provide written informed consent or age appropriate assent for pediatric patients.

**FOR EXCLUSION**

1. Systemic corticosteroids within 24 hours prior to study product administration.
2. Use of any chemotherapy agent (apart from the lymphodepletion regimen required by this protocol) within 2 weeks prior to first study product dose.
3. Major surgery within prior 2 weeks.
4. Radiotherapy within prior 3 weeks.

5. Investigational agents within prior 4 weeks.
6. Use of any antibody therapy within prior 6 weeks.
7. Systemic fungal, bacterial, viral or other infection that is not controlled.
8. History of any of the following cardiovascular conditions within the past 3 months:
  - a. Class III or IV heart failure as defined by the New York Heart Association,
  - b. Cardiac angioplasty or stenting,
  - c. Documented myocardial infarction, or
  - d. Unstable angina.
9. Prior allogeneic hematopoietic stem cell transplantation (allo HSCT).
10. Active second malignancy, except for basal cell carcinoma of skin, squamous cell carcinoma of the skin or cervical carcinoma in situ.
11. Clinically significant medical condition e.g. pulmonary, neurologic, cardiovascular, metabolic, hepatic or hematologic that could jeopardize patient safety, interfere with the objectives of the protocol, or limit patient compliance with study requirements, as determined by the Investigator.

**STUDY TREATMENTS:**

For patients with HL or DLBCL, a lymphodepletion regimen consisting of a single dose of cyclophosphamide 900 mg/m<sup>2</sup>, administered IV on Day -4 and fludarabine 25 mg/m<sup>2</sup>, administered in 3 separate IV doses on Days -3, -2 and -1, will be given prior to the first CMD-003 infusion on Day 1. The lymphodepletion regimen should be omitted or modified if:

- the patient has ≥ Grade 2 hematologic and/or renal toxicities, or
- in the Investigator's judgment, the patient is already lymphodepleted, or
- the patient is unlikely to tolerate lymphodepletion.

Modification or omission of this lymphodepletion regimen requires prior approval of the Medical Monitor.

For patients with PTLD receiving immune suppression, the immune suppression regimen will be based on the Investigator's choice. Reduction of immune suppression beginning before whole blood collection and before the first CMD-003 infusion is recommended if in the Investigator's judgment such reduction in immune suppression will not jeopardize the function of the solid organ graft or medical condition of the patient.

CMD-003 treatment will consist of up to 5 doses given over a 2-month period. Each dose is comprised of  $2 \times 10^7$  CD3+ cells/m<sup>2</sup> administered intravenously over a 1 to 10-minute period via a peripheral or existing central line.

**STUDY ENDPOINTS:****PRIMARY**

- Overall response rate (ORR), defined as best single observed response (CR or PR)

**SECONDARY**

- Complete response rate (CR)
- Duration of response (DoR)
- Disease control (CR+PR+SD)
- Time to response (TTR)
- Progression free survival (PFS)
- Disease free survival (DFS)
- Overall survival (OS)
- Adverse events (AEs)

**EXPLORATORY**

- Virological response based on reduction in EBV DNA levels as measured by PCR.
- Peripheral blood EBV-antigen-specific T cell activity based on ELISpot activity.
- ORR based on LYRIC criteria as assessed centrally by independent radiology committee.

**CRITERIA FOR EVALUATION:****EFFICACY**

Disease response will be assessed per Lugano 2014 Criteria at Baseline, Week 8 or Month 3 (as determined by the number of administered CMD-003 doses), and then every 3 months beginning at Month 6 through the Final Study Visit (Month 12). Patient response to treatment will be determined by an independent review committee.

**SAFETY**

Safety assessments will include:

- Adverse event assessments (NCI CTCAE v4.0). AEs will be recorded from the time of the first investigational cell product dose until 30 days after the last investigational cell product dose. SAEs will be recorded for up to 1 year following first CMD-003 infusion.
- Physical examination, vital signs, weight and pulse oximetry. (Vital signs and pulse oximetry obtained before and up to 1 hour following CMD-003 infusion.)
- Serum chemistry, hematology, coagulation and urinalysis laboratory evaluations.

**MECHANISM OF ACTION/IMMUNE FUNCTION**

- Immunological assessment of EBV-specific T cell activity and phenotyping.
- Levels of plasma and whole blood EBV DNA (viral load). Tumor and peri-tumor biomarker analysis

**STATISTICAL METHODS:**

## SAFETY ANALYSES

All recorded AEs will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of MedDRA. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. Any significant physical examination findings and results of clinical laboratory tests will be listed. All safety data will be analysed for the entire safety population as well as by disease cohort.

## EFFICACY ANALYSES

The primary efficacy endpoint is ORR as defined as the proportion of evaluable patients with a best response of CR or PR from a single observation. Evaluable patients are defined in this protocol, as all patients with baseline PET-CT assessable or CT measurable disease (as determined by the Independent Radiology Review Committee (IRRC)), who received at least 1 dose of CMD-003, and whose formal disease response has been determined at a scheduled study visit (including early termination visits).

In addition to ORR, CR, Disease Control, DoR, TTR, PFS, DFS and OS will be analyzed to determine clinical benefit durability in evaluable patients. For ORR in each disease cohort, an exact binomial 90% confidence interval will be determined by the Clopper-Pearson method. Median time to response and DoR will be summarized for those patients with confirmed responses, using the Kaplan-Meier method; PFS, DFS and OS will be similarly summarized.

In each disease cohort after 7 evaluable patients have completed the 8 week or 3 month (as applicable) assessment, the IDSMC will review safety and response data. Within each cohort, if 0 responses (CR or PR) are observed, the cohort will be closed to further accrual. If  $\geq 1$  response (CR or PR) is observed, up to 7 additional patients may be enrolled in that cohort, for a total of 14 patients.

The final analysis will be conducted when the last enrolled patient has an event or has completed at least 12 months of study participation, whichever occurs first. Patients alive at data cut-off are censored at the last date the patient is known to be alive. Long-term patient survival will be collected for up to 1 year following the Final Study Visit.

An ORR at the final analysis in a given disease cohort of 3/14 or higher will support a conclusion that a true ORR in that cohort is higher than 5% ( $\alpha=0.05$ , 1-sided). Additional patients may be added to improve the precision of the estimates of the various endpoint response rates.

**SAMPLE SIZE JUSTIFICATION:**

The CIVIC study is based on a Simon two-stage (minimax) design for each disease cohort. The Futility Boundary is set at 5% (the response threshold below which the treatment would not be developed further) and the Success Boundary at 30% (the response threshold at which the treatment is considered successful), with power at 80% (20% chance of false negative or type II error, within cohort), and the false positive rate or type I error is set at 5% within each cohort. Therefore, the total number of patients used for sample size assumption in each cohort is 14 evaluable patients (7 in the first stage and 7 in the second stage).

In Stage I, 1 or more responses in a cohort must be seen to continue to Stage II. For Stages I and II combined, 3 or more responses in a cohort are required to support the conclusion that the true response rate exceeds 5% and a true response rate of 30% cannot be ruled out.

Assuming there are a minimum of 7 and a maximum of 14 evaluable patients across Cohorts A-C, the sample size (total evaluable patients) will range from 21-42.

In addition, it is estimated that up to 50% of the patients enrolled and treated will not fulfil the evaluable patient definition for ORR primary efficacy analysis. Possible reasons include but are not limited to, patients with non-measurable/non-assessable disease baseline and/or not completing a study specific tumor assessment.

**INDEPENDENT REVIEW OF DATA**

An Independent Radiology Review Committee (IRRC) will assess all study images according to international consensus standards (Lugano 2014 Criteria). An Independent Data and Safety Monitoring Committee (IDSMC) will review safety data.

The IDSMC will have the ability to recommend stopping or modifying the study based on safety data. The IDSMC will also review the assessments of the IRRC to adjudicate the overall response status of each patient. The IDSMC will review each patient disease cohort after 7 evaluable patients are enrolled (Stage I), and recommend whether enrolment in that disease cohort should be continued (Stage II). The IRRC and IDSMC procedures will be documented in charters.