ASX ANNOUNCEMENT **7 October 2024**

AML patient achieves Complete Response in CHM CORE-NK Combination Phase 1b trial

Sydney, Australia, 7 October 2024: Chimeric Therapeutics (ASX:CHM, "Chimeric" or the "Company"), an Australian leader in cell therapy, is pleased to provide an update on the CHM CORE-NK + Vactosertib Phase 1b clinical trial, after a Complete Response from an Acute Myelogenous Leukemia (AML) patient participating in the trial.

The ongoing Phase 1b study is building upon the clinical activity seen in the initial CHM CORE-NK Phase 1a clinical trial by adding Vactosertib, an oral TGF-β receptor inhibitor that was designed to disrupt the inhibitory TGF-β signaling pathway.

The trial is the first ever to assess NK cells in combination with Vactosertib in patients with advanced colorectal and blood cancers. This is the first and currently only patient treated in the blood cancer arm of the Phase 1b trial.

This trial is being led by Dr Eva Selfridge at UH Seidman Cancer Center in Ohio.

Chimeric COO Dr Rebecca McQualter said: "As the study continues to enrol subjects with advanced cancer, we are pleased to see the clinical combination can be delivered safely, and we are very happy to report that one study subject with advanced Acute Myelogenous Leukemia (AML) experienced a Complete Response at Day 28 after starting treatment with the CHM CORE-NK + Vactosertib combination." The patient will continue on study and be monitored for up to 15 years, a standard FDA requirement for all cell therapy trials. 3 patients are currently enrolled in the Phase 1b study with the goal to enrol 12 patients.

This new result is in addition to the previous result from the Phase 1a clinical trial announced on 16 May 2024, where a different patient in that trial also achieved a complete response that has now been sustained for 48 months (was 15 months complete response at time of the initial CORE-NK study publication).

CHM CORE-NK is a universal off-the-shelf NK cell therapy manufactured with the CORE-NK platform, which can produce hundreds of doses in a single manufacturing run. CHM CORE-NK was previously studied in a Phase 1a clinical trial that established safety with no GvHD (Graft versus Host Disease), prolonged NK cell persistence at 28 days, and an encouraging early efficacy signal, particularly in blood cancers where all patients achieved disease control.

The Phase 1b study (clinicaltrials.gov/study/NCT05400122) is designed to treat 12 patients with either locally advanced/metastatic colorectal cancer or relapsed/refractory blood cancers. An overview of the study is attached.

The Phase 1b study is funded without financial support from Chimeric Therapeutics; CHM CORE-NK is manufactured at a cost to Chimeric and supplied for the clinical trial.

The company confirms that this trial is unblinded with one participant in the blood cancer arm to date. The complete response was determined by the absence of cancer through standard laboratory testing. The combination therapy is administered intravenously on day 1. Updates will be provided when all subjects are enrolled and the data is collated.

ABOUT the CHM CORE NK Platform

The CHM CORE NK platform is a **C**linically validated, **O**ff the shelf, **R**obust and **E**nhanced **N**atural **K**iller (NK) cell platform. The platform uses a novel, proprietary genetically-modified feeder cell line to activate and expand universal off-the-shelf allogeneic NK cell products derived from healthy donors. The expanded CORE-NK cells exhibit enhanced cytotoxicity, metabolism, and expression of activating receptors compared to fresh, activated NK cells. From the CORE-NK platform, Chimeric is developing next generation NK and CAR NK assets with plans for phase 1 clinical trials in solid tumours and blood cancers.

ABOUT CHIMERIC THERAPEUTICS

Chimeric Therapeutics, a clinical stage cell therapy company and an Australian leader in cell therapy, is focused on bringing the promise of cell therapy to life for more patients with cancer. To bring that promise to life for more patients, Chimeric's world class team of cell therapy pioneers and experts is focused on the discovery, development, and commercialization of the most innovative and promising cell therapies.

Chimeric currently has a diversified portfolio that includes first in class autologous CAR T cell therapies and best in class allogeneic NK cell therapies. Chimeric assets are being developed across multiple different disease areas in oncology with 3 clinical stage programs.

CHM CDH17 is a first-in-class, 3rd generation CDH17 CAR T invented at the world-renowned cell therapy centre, the University of Pennsylvania (Penn) in the laboratory of Dr. Xianxin Hua, professor in the Department of Cancer Biology in the Abramson Family Cancer Research Institute at Penn. Preclinical evidence for CDH17 CAR T was published by Dr. Hua and his colleagues in March 2022 in Nature Cancer demonstrating complete eradication of tumours in 7 types of cancer in mice. CHM CDH17 is currently being studied in a phase 1/2 clinical trial in gastrointestinal and neuroendocrine tumours that was initiated in 2024.

CHM CLTX is a novel and promising CAR T therapy developed for the treatment of patients with solid tumours. CLTX CAR T is currently being studied in a phase 1B clinical trial in recurrent / progressive glioblastoma. Positive preliminary data from the investigator-initiated phase 1A trial in glioblastoma was announced in October 2023.

CHM CORE-NK is a potentially best-in-class, clinically validated NK cell platform. Data from the complete phase 1A clinical trial was published in March 2022, demonstrating safety and efficacy in blood cancers and solid tumours. Based on the promising activity signal demonstrated in that trial, two additional Phase 1B clinical trials investigating CORE-NK in combination regimens have been initiated. From the CORE-NK platform, Chimeric has initiated development of new next generation NK and CAR NK assets.

Authorised on behalf of the Chimeric Therapeutics board of directors by Chairman Paul Hopper.

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Overview of study

Title:	**Natural Killer (NK) Cells in Combination With Interleukin-2 (IL-2) and Transforming Growth Factor Beta (TGFbeta) Receptor I Inhibitor Vactosertib in Cancer**
ClinicalTrials.gov ID	**NCT05400122** clinicaltrials.gov/study/NCT05400122

Brief Summary

One of the ways that cancer grows and spreads is by avoiding the immune system. NK cells are immune cells that kill cancer cells, but are often malfunctioning in people with colorectal cancer and blood cancers. A safe way to give people with colorectal cancer and blood cancers fresh NK cells from a healthy donor has recently been discovered. The purpose of this study is to show that using two medicines (vactosertib and IL-2) with NK cells will be safe and will activate the donor NK cells. NK cells and vactosertib are experimental because they are not approved by the Food and Drug Administration (FDA). IL-2 (Proleukin®) has been approved by the FDA for treating other cancers, but the doses used in this study are lower than the approved doses and it is not approved to treat colorectal cancer or blood cancers.

Detailed Description

The objective of this research is to demonstrate that natural killer (NK) cells from non-Human Leukocyte Antigen (HLA)-matched donors can be safely infused into colorectal cancer patients and patients with relapsed/refractory hematologic malignancies in combination with IL-2 and the oral transforming growth factor beta (TGFβ) receptor I inhibitor vactosertib to improve the persistence of donor NK cells.

Official Title

A Phase Ib Study to Evaluate Safety and Persistence of ex Vivo Expanded Universal Donor NK Cells in Combination With IL-2 and TGFbeta Receptor I Inhibitor Vactosertib in Patients With Locally Advanced/Metastatic Colorectal Cancer and Relapsed/Refractory Hematologic Malignancies

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Incidence of Treatment-Emergent Adverse Events [Safety and Tolerability])	This will be defined as the incidence of Grade ≥ 2 treatment-related adverse events	Within 28 days of NK cell infusion
Persistence of donor NK cells	This will be defined as the presence of donor NK cells in recipient blood as determined by short tandem repeat (STR)-chimerism at a frequency of >10%.	7 days post-treatment

Secondary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Persistence of donor NK cells	This will be defined as the presence of donor NK cells in recipient blood as determined by STR-chimerism at a frequency of >10%.	14 days post-treatment
Persistence of donor NK cells	This will be defined as the presence of donor NK cells in recipient blood as determined by STR-chimerism at a frequency of >10%.	21 days post-treatment
Persistence of donor NK cells	This will be defined as the presence of donor NK cells in recipient blood as determined by STR-chimerism at a frequency of >10%.	28 days post-treatment
Clinical Response	This will be defined as a change in size of measurable disease on CT scans (colorectal cancer) or by standard methods for hematologic malignancies (e.g. bone marrow biopsy for AML)	28 days post-treatment

Intervention / Treatment

- Drug: Vactosertib
- Drug: Fludarabine Phosphate
- Drug: Cyclophosphamide
- Drug: IL-2
- Drug: Natural Killer Cells

Participation Criteria

Researchers look for people who fit a certain description, called eligibility criteria. Some examples of these criteria are a person's general health condition or prior treatments.

Eligibility Criteria

Description

Inclusion Criteria:

- Subjects must have histologically confirmed locally advanced or metastatic colorectal adenocarcinoma or relapsed or refractory hematologic malignancy and have failed at least one standard line of chemotherapy. Participants will be eligible if they have either refused standard treatment regimens or if there is no standard approach to curative salvage therapy per National Comprehensive Cancer Network (NCCN) guidelines in the setting of relapsed/refractory disease.

Malignancies can include:

- Acute myeloid leukemia
- Myelodysplastic syndrome
- Acute lymphoblastic leukemia
- Chronic myeloid leukemia
- Chronic lymphocytic leukemia
- Non Hodgkin Lymphoma
- Hodgkin Lymphoma
- Myeloproliferative syndromes
- Plasma cell myeloma
- Colon and/or rectal adenocarcinoma
    - Subjects must have recovered from acute toxicities of prior chemotherapy or stem cell transplant. Any prior non-hematologic vital organ toxicity (cardiac, pulmonary, hepatic, renal) of previous therapy must have resolved to grade 1 or less. Exceptions: Alopecia; subjects with chemotherapy-induced sensory neuropathy must have grade ≤ 3
    - Age ≥18 years. Because no dosing or adverse event data are currently available on the use of NK cells in subjects ≤18 years of age, children are excluded from this study.
    - Eastern Cooperative Oncology Group (ECOG) Performance status ≤2
    - Subjects must have normal organ and marrow function as defined below:
        - Serum total bilirubin <2 mg/dl. If known Gilbert syndrome, total bilirubin must be <3mg/dl
        - Aspartate aminotransferase (AST) < 2.5 X institutional upper limit of normal
        - Alanine Aminotransferase (ALT) < 2.5 X institutional upper limit of normal
        - Pulmonary function (DLCO) >40% of the expected value corrected for alveolar volume and hemoglobin
        - Serum Creatinine ≤ 1.5 X institutional upper limit of normal
        - Hemoglobin ≥ 7.5 g/dL

        - Absolute neutrophil count ≥ 1,250/mcL for colorectal cancer (CRC) patients or ≥ 1,000/mcL for patients with hematologic malignancies unless patient has bone marrow involvement of hematological malignancy
        - Platelet count ≥ 50,000/mcL
    - Women of child-bearing potential and men must agree to use adequate contraception (double barrier method of birth control or abstinence) 4 weeks prior to study entry and for the duration of study participation. Women of child-bearing age must have documented negative pregnancy test prior to start of lymphodepleting regimen.
    - Subjects must have the ability to understand and the willingness to sign a written informed consent document.
    - Subjects must have at least 3 weeks between last cytotoxic anti-neoplastic medication and initiation of preparative regimen.

Exclusion Criteria:

- Subjects receiving any other investigational agents
- Subjects requiring systemic corticosteroid therapy (10mg or less of prednisone or equivalent doses of other systemic steroids are permitted).
- Subjects for whom a potential 29-day delay in treatment will interfere with their potential therapeutic options
- Patients with active, untreated malignant involvement of the central nervous system (CNS) should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. If clinical suspicion for CNS involvement head imaging will be necessary to document absence of active CNS involvement in patients with colon/rectal cancer. Patients with hematologic malignancies who have undergone treatment for malignant involvement of the CNS must have no evidence of residual disease by imaging or cerebrospinal fluid (CSF) sampling prior to study enrollment.
- History of allergic reactions to fludarabine or cyclophosphamide
- Subjects with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant or breastfeeding women are excluded from this study because cytotoxic agents used as part of the lymphodepleting regimen have the potential for teratogenic or abortifacient effects. Because there is an unknown, but potential risk for adverse events in nursing infants secondary to treatment of the mother with lymphodepleting chemotherapy, breastfeeding should be discontinued if the mother participates in the trial. These potential risks may also apply to other agents used in this study.
- HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with chemotherapeutic agents. In addition, these patients are at increased risk of lethal infections when treated with marrow suppressive therapy.
- Chronic active untreated hepatitis B or C infection. (Assessments should include Hepatitis B Surface Ab, Hepatitis B Surface Ag, Hepatitis B Core Ab - Total, Hepatitis B Core Ab, IGM, Hepatitis C Ab).
- Recipients of previous allogeneic transplants who have rash involving more than 10% body surface area attributed to graft versus host disease (GVHD). Stem cell transplant recipients will be excluded if they are still receiving immunosuppression including steroids for GVHD or have active GVHD in any organ (except for 10% BSA of skin, not requiring treatment).
- Subject who is taking prohibited medications when using vactosertib as following (refer to APPENDIX III). A minimal washout period of 5 half-lives for the following drugs is recommended prior to the first dosing.
    - Concurrent use of drugs or foods that are known strong CYP3A4 inhibitors including but not limited to grapefruit juice, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, voriconazole. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed.

- Concurrent use of drugs that are known potent CYP3A4 inducers including but not limited to phenytoin, rifampin, St. John's wort.
- Concurrent use of drugs that are CYP3A4, CYP1A2, CYP2B6 substrates with narrow therapeutic indices including but not limited to theophylline, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, sirolimus, tacrolimus, terfenadine (astemizole, cisapride, and terfenadine have been withdrawn from the US market).
- Concurrent use of drugs that are sensitive CYP3A4, CYP1A2, CYP2B6 substrates including but not limited to efavirenz, darunavir, dasatinib, everolimus, lopinavir, midazolam, sirolimus, ticagrelor.

- QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 12-lead ECGs

Study Plan

This section provides details of the study plan, including how the study is designed and what the study is measuring.

Design Details

Primary Purpose	Treatment
Interventional Model	Single Group Assignment
Interventional Model Description	Approximately 12 subjects will be enrolled in this trial and all will receive a preparative regimen consisting of lymphodepleting chemotherapy agents followed by two infusions of ex vivo-expanded NK cells in combination with vactosertib and IL-2 (Proleukin®).
Masking	Open Label

Arms and Interventions

Participant Group/Arm	**Intervention/Treatment**
Experimental: Experimental Infusion Preparative Regimen Administration: • Fludarabine will be given at a dose of 30mg/m2 intravenously daily • Cyclophosphamide will be given at a dose of 500mg/m2 intravenously daily Investigational Agent Administration: • NK Cell Product will be given per institutional standard of care (at a rate no faster than 250mL per hour or 3-4 ml per minute) as two doses by intravenous infusion on Days 0 (+2 days acceptable) and 14 (+/- 3 days acceptable) • IL-2 will be administered at a flat dose of 2.2 million IU subcutaneously starting on the same day as the first NK	Drug: Vactosertib • Vactosertib is a highly selective, potent inhibitor of the protein serine/threonine kinase activity of transforming growth factor (TGF)-β receptor type 1 (TGFBR1; also known as activin receptor-like kinase 5 [ALK5]). Vactosertib inhibits the phosphorylation of the ALK5 substrates Smad2 and Smad3, as well as the intracellular signalling of TGF-β. • Other Names: ○ TEW-7197 ○ EW-7197 ○ EW7197 Drug: Fludarabine Phosphate • Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoroara-ATP. This metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. • Other Names: ○ Fludara Drug: Cyclophosphamide • Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA

Participant Group/Arm	Intervention/Treatment
cell infusion and will be administered three times weekly (dose level 1) or twice weekly (dose level -1) for up to four weeks total • Vactosertib will be administered at a dose of 200mg twice daily for 5 consecutive days per week, for up to four weeks total.	synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. • Other Names: ○ Cytoxan ○ 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate Drug: IL-2 • Proleukin® (aldesleukin) has been shown to possess the biological activities of human native interleukin-2. In vitro studies performed on human cell lines demonstrate the immunoregulatory properties of Proleukin, including: a) enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human interleukin-2 dependent cell lines; b) enhancement of lymphocyte cytotoxicity; c) induction of killer cell (lymphokine-activated (LAK) and natural (NK)) activity; and d) induction of interferon-gamma production. The in vivo administration of Proleukin in animals and humans produces multiple immunological effects in a dose dependent manner. These effects include activation of cellular immunity with profound lymphocytosis, eosinophilia, and thrombocytopenia, and the production of cytokines including tumor necrosis factor, IL-1 and gamma interferon. In vivo experiments in murine tumor models have shown inhibition of tumor growth • Other Names: ○ Proleukin Drug: Natural Killer Cells • Adoptive NK cell therapy has demonstrated the potential for cancer immunotherapy in various malignancies with particular potential in hematologic malignancies including acute myeloid leukemia (AML), and colon cancer [14, 19-23]. This therapeutic approach is extremely well tolerated in patients even when massive numbers of cells are utilized (~109 NK cells/kg). In fact, studies suggest that high doses of NK cells are not only well tolerated but have potential to lead to higher levels of efficacy.