

2 NON-TECHNICAL ABSTRACT

Malignant mesothelioma, non-small cell lung cancer and cancers of the pancreatic and ovary are among the most aggressive and lethal malignancies. Collectively, new cases of these cancers are diagnosed in approximately 200,000 Americans each year and cause nearly as many deaths. These high mortality rates provide unquestionable evidence that effective new therapies are urgently needed for these malignancies. In addition to their severity, these tumors share the common feature of high level expression of a protein known as Mesothelin on their cell surface. Cerus Corporation has developed a novel vaccine-based approach that is designed to stimulate the immune response to Mesothelin in patients given this candidate therapy to target and kill malignant cells that over-express Mesothelin. This vaccine, termed “CRS-207”, is based upon the demonstrated anti-tumor activity in animal models of cancer. A phase I study has been designed to evaluate the safety, tolerability, and the immune response to CRS-207 in adult subjects who have malignant mesothelioma, advanced non-small cell lung cancer or advanced carcinoma of the ovary or pancreas, refractory to standard treatment.

Unlike conventional vaccines that are given during childhood to prevent subsequent infections with viruses that cause mumps or chicken pox, CRS-207 has been designed for administration to subjects that actually have the disease, in this case, specific cancers that express Mesothelin to a high extent. Such therapeutic vaccines or active immunotherapy agents are used to specifically stimulate the subject’s immune response to attack and kill the cancerous cells, and as a result stem progression of the malignancy, with the ultimate goal to provide patient benefit. In this case, CRS-207 will be administered to patients with malignant mesothelioma, non-small cell lung cancer, or advanced cancers of the pancreas or ovary to stimulate specific immunity to these malignancies that over-express Mesothelin.

The CRS-207 vaccine is based on a live-attenuated form of a bacterium known as *Listeria monocytogenes* (*Lm*) that is often found as a food borne contaminant. *Lm* has also been studied for decades as a model to understand basic aspects of cellular immunology and microbial pathogenesis. However, in addition to causing a generally mild and self-limited form of gastrointestinal disease, the form of *Lm* usually found in nature can also occasionally cause a more severe illness known as listeriosis. Cancer patients, particularly those with hematologic malignancies or severe immunosuppression of their immune system (e.g., if given corticosteroids as part of their chemotherapy regimen) may be at increased risk for this disease. To address this potential safety issue in the proposed clinical trial, Cerus has developed a live-attenuated strain of *Lm* that is more than 1,000-fold less virulent when

administered to mice. The safety and tolerability of this attenuated strain, known as CRS-100, is currently being evaluated in a Phase I clinical trial under a U.S. IND application (clinicaltrials.gov identifier NCT00327652). *Lm* is recognized as a powerful activator of non-specific immune responses known as innate immunity, which in turn facilitates development of specific or adaptive immunity. Adaptive immunity comes in 2 forms: humoral, otherwise known as antibody immunity; and, cellular immunity. *Lm* principally activates the cellular arm of the immune response, comprised of cytotoxic T lymphocytes (CTLs) and helper T lymphocytes. In particular, CTLs stimulated in response to *Lm* recognize *Lm*-infected host cells in the infected animal as foreign, and kill them. Similarly, the goal of therapeutic cancer vaccines is to induce the generation of CTLs to specifically recognize the cancerous cells as foreign, and kill them. Thus, by engineering *Lm* to express proteins – known as antigens – that are highly prominent on the surface of tumor cells, CTLs induced in response to immunization with this recombinant *Lm* vaccine are specifically designed to recognize and destroy in a selective manner both *Lm* infected cells and, significantly, tumor cells that over-express the antigen. The CRS-207 vaccine is a recombinant live-attenuated *Lm* strain that has been engineered to express Mesothelin. Studies conducted in the laboratory have demonstrated that treatment of mice bearing Mesothelin expressing tumors with CRS-207 induces Mesothelin-specific cellular immunity and reduction of tumor burden, resulting in increased survival relative to controls.

There exists a strong rationale to stimulate the immune system to generate CTLs that specifically seek out and destroy malignant mesothelioma and pancreatic carcinomas, as well as NSCLC and ovarian cancer cells that express Mesothelin. Studies conducted to evaluate the expression of Mesothelin in normal and cancerous cells have demonstrated limited expression of this protein in normal cells, principally located in the lining of the chest, heart, and gut. On the other hand, high-level expression of Mesothelin is observed in cancerous cells of these tumor types, but not in normal pancreas or ovarian tissues. Expression in normal tissues of the lung is low in comparison to the expression on the cell surface of these tumors. A previous early-phase clinical study with a different experimental vaccine has demonstrated a correlation between cytotoxic T lymphocytes specific for Mesothelin that were induced in response to treatment, and benefit in patients with advanced stage pancreatic cancer. Taken together, these observations indicate that Mesothelin meets three important criteria that strongly favor potential use as an immune target in the development of therapeutic vaccines for patients with malignant mesothelioma, NSCLC and carcinomas of the pancreas or ovary: (1) Mesothelin is widely shared by most ovarian and pancreatic cancers; (2) it has a limited expression in normal tissues

and CTL responses can be induced following vaccination, and (3) these responses correlate with clinical benefit in patients at high risk for disease recurrence.

Cerus proposes to conduct a Phase 1, pen-label, dose-escalation, multiple dose study of the safety, tolerability, and immune response of CRS-207 in adult subjects with malignant mesothelioma, non-small cell lung cancer or advanced carcinoma of the ovary or pancreas, who have failed standard therapy or who are not candidates for standard treatment. The primary study objective is to determine the maximum tolerated dose (MTD) of CRS-207 and to gather data regarding the safety profile following a multiple dose regimen of administration of CRS-207 in study subjects with these advanced carcinomas. The secondary study objective is to explore the immunological response to CRS-207, the biodistribution and clearance of CRS-207, and to evaluate tumor status prior to and after administration of the investigational agent. Subjects must meet a number of specific inclusion and exclusion criteria for study enrollment. CRS-207 will be administered by intravenous infusion every 21 days up to a total of 4 treatments. Each study subject will receive multiple intravenous injections (a total of four injections; once every three weeks) of CRS-207 at one of three dose levels (either 1×10^8 colony forming units (cfu), 1×10^9 cfu or 1×10^{10} cfu). Each injection will take approximately 2-hours to complete, and patients will be closely observed during and after each injection. Beginning on Day 7 after the last study dose, a 10-day course of oral antibiotics will be provided for all study subjects.