Elenagen, a novel DNA immunotherapy for ovarian cancer, found to delay disease progression

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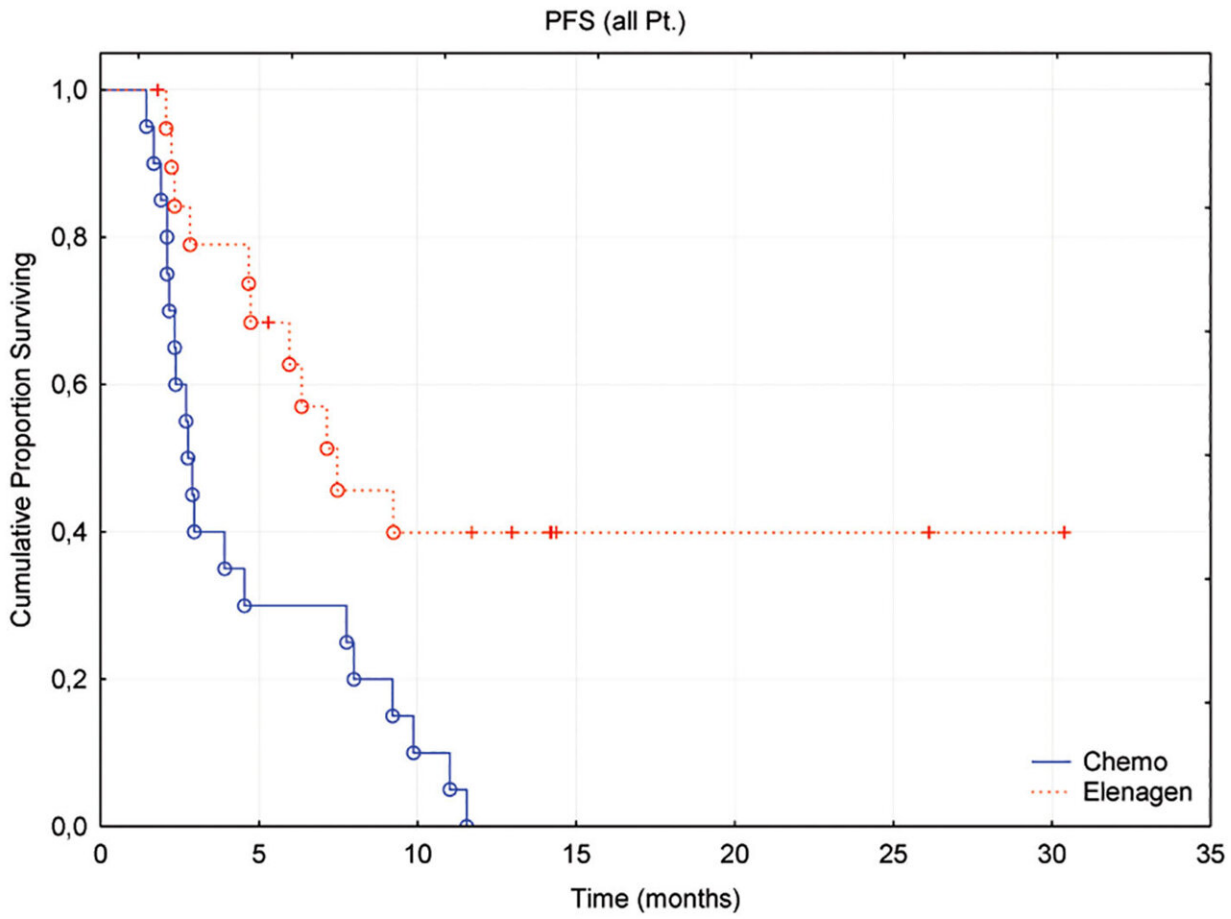

Progression-free survival of patients treated with chemo+ELENAGEN or chemo only. Credit: CureLab Oncology Inc.

CureLab Oncology, a clinical-stage, pre-IPO biotech company, announced that its novel biological agent, Elenagen, has been shown to significantly enhance standard chemotherapy and provides clinical benefits for the patients with the deadliest form ovarian cancer. Elenagen belongs to a novel class of biological agents, supercoiled circular DNA (plasmids).

The study, published in *Frontiers in Oncology*, shows that disease progression was significantly delayed in a group of stage III and IV platinum-resistant ovarian cancer (PROC) patients who received gemcitabine in combination with Elenagen, compared to the group who received gemcitabine alone.

Almost 1 in 80 women will be diagnosed with ovarian cancer during their lifetime. Today, the majority of newly diagnosed ovarian cancer patients are initially treated with platinum-based chemotherapy (such as cisplatin and carboplatin), a therapy that halts disease progression over a prolonged period. Sooner or later, however, most patients stop responding to platinum therapies, joining those who had a platinum-resistant form of ovarian cancer from the beginning.

Treatment options for these patients are limited, which makes it especially important to improve the efficacy of available non-platinum-based chemotherapies. The short lifespan of platinum-resistant ovarian cancer (PROC) patients is further exacerbated by their reduced life quality associated with disease progression.

Currently available chemotherapies provide only a short period of progression-free survival (PFS), during which time neither the primary tumor nor a metastatic process exacerbate the patient's symptoms. Also, these therapies may cause toxic side effects. The search for non-toxic adjuvants that could extend PFS for PROC patients is a major medical need for oncology and women's health because almost 1/110 women will

die of PROC.

Gemcitabine is among the most-often prescribed PROC chemotherapies—and it's an interesting example of how mechanism-based drug development is often failing as a model.

"Perhaps, gemcitabine is teaching us to be skeptical of the dominant biotech dogma," said Dr. Alexander Shneider, the primary author of the paper and CureLab's founder. "In 1971, when President Nixon declared a 'war on cancer,' scientists made an honest and probably inevitable mistake: they proposed that new drugs should come from a deeper understanding of the molecular mechanisms of the disease.

"Thus, it became 'cool' for top academic institutions and the most prestigious journals to pursue only mechanism-based drug development, undermining and ignoring the traditional way that brought us most of the lifesaving drugs in use today. After five decades and hundreds of billions spent, relatively few drugs have made it to medical practice using the mechanism-based approach. Gemcitabine is a classic example of one of the pitfalls of mechanism-based drug development. What we consider the mechanism of action today may tomorrow turn out to be just one of the mechanisms—and maybe not even the most important one."

The original purpose of gemcitabine was to mimic the nucleotides necessary to build DNA. Since cancer cells divide more rapidly than normal cells, they must build more DNA. Therefore, molecules that act as "defective" nucleotides will cause greater damage to cancer cells that are rapidly dividing. Scientists were extremely proficient at measuring DNA replication and cell division at the time but were less effective at assessing different types of immune response.

Later, it was found that gemcitabine and some other chemotherapies have a crucial effect (if not a more important effect) on cancer patients'

immune system as they have on their ability to halt cell division. This is one of the typical situations analyzed by Shneider in his paper "Mental inertia in the biological sciences," published in *Trends in Biochemical Sciences,* where he attempted to systemize and classify types of mental inertia common in science. Another paper published by Shneider in *TIBS* titled "Four stages of a scientific discipline; four types of scientist", was initially rejected by 12 journals and then held the #1 position as the most-read paper, according to Faculty 1000.

"I did not analyze mental inertia in science and evolution of scientific disciplines to publish papers," said Shneider. "To me, publishing is not that important. In fact, this work liberated the CureLab team—and me—from dominant dogmas. In a way, one might say that the Elenagen journey is an exercise in overcoming mental inertia, which makes us somewhat outsiders to the mainstream."

The first papers published by the team on Elenagen, however, did not promise to lead to anything contrarian. Rather, Shneider opted for a more typical therapeutic vaccine approach.

Shneider explained, "The p62 protein is present in all cells. Cancer cells, however, cannot survive without it. Moreover, cancer cells overexpress p62, which protects them from chemo- and radiation therapy. We can induce an immune response when we inject a DNA or RNA drug with a gene encoding p62 into a muscle. Then, a vaccine-induced immune response would find and eliminate in the body the cells that express elevated levels of p62—i.e., the cancer cells. In addition, if cancer cells were to lose their p62 under an immune selection or if some subgroup of cancer cells stopped producing p62 due to a mutation, these cancer cells would be very susceptible to therapies."

The original logic worked in multiple rodent cancer models and in dogs; in eleven cases of breast cancer, CureLab saved ten dogs. Then,

serendipity intervened. Elenagen altered tumor structure in a way that could not be explained by an anti-cancer DNA vaccine alone. Due to changes in tumor structure, immune cells entered the tumor and remained active to a much greater extent.

Elenagen's novel way of increasing anti-tumor immunity cannot be attributed to the fact that it serves as yet another anti-cancer vaccine, because in a classic definition of the word "vaccine," a vaccine presents a specific antigen against which to elicit an immune response, whereas the tumor is not altered to enhance an immune response to multiple antigens not included in vaccines. Also, in mice, Elenagen prevented and even reverted osteoporosis, and also demonstrated multiple other effects unrelated to a cancer vaccine modality.

Soon, it became clear that CureLab had stumbled upon a serendipitous discovery of a systemic anti-inflammatory drug acting through a yet unknown mechanism. Shneider assembled the team and announced, "We won't be going from a mechanism to a drug; we'll go from a drug to a mechanism. Our goal is to provide patients with clinical benefits—nothing else matters. Therefore, we will not publish in prestigious journals, because this will require unnecessary auxiliary experiments. Plus, no NIH grants as they expect mechanism-based applications. Lastly, we will go ex-US, and return when/if we succeed in clinic."

In the article published in *Frontiers in Oncology*, CureLab Oncology, the N.N. Alexandrov National Cancer Center, and Minsk City Oncology Center treated 20 PROC patients with gemcitabine alone and 20 with gemcitabine plus weekly injections of Elenagen. Patients were randomly assigned to these groups and observed for up to thirty months before the study was stopped due to the war. There were no serious adverse events (SAEs) reported in patients receiving Elenagen. It is noteworthy that many cancer immunotherapies show SAEs, which significantly limit

their use.

Gemcitabine alone had an average progression-free survival (PFS) similar to previously reported durations: 2.7 months. In contrast, fifty percent of women who received the combination of gemcitabine and Elenagen demonstrated a PFS of 7.2 months. This difference between the two groups was highly statistically significant. Importantly, nine out of twenty patients in the Elenagen group remained free of disease progression for the entire duration of observation (the longest scoring 30 months), whereas no patient receiving chemotherapy without Elenagen remained progression-free for even 12 months.

According to Shneider, these studies have taught him not to assume, but rather to observe.

"We discussed whether the patients with the worst prognosis factors would be too late to help, and whether we should include them in the study. Now, we are glad we did because Elenagen demonstrated the best results with people with the worst prognosis factors," he said.

Indeed, the gemcitabine-Elenagen combination demonstrated greater benefits for patients with an elevated blood level of CA 125, an ovarian cancer marker. Oncologists generally consider CA 125 a negative prognosis factor.

The same was true for patients demonstrating disease progression after one course of platinum chemotherapy compared with those remaining progression-free for multiple platinum courses. In theory, a more severe cancer should not respond to platinum drugs even for a relatively short period of time, and a less severe cancer should respond to platinum drugs over multiple courses. Despite this, the most receptive to gemcitabine-Elenagen were the patients with progressive disease after a single platinum chemotherapy course.

CureLab plans to conduct Phase II/III studies in the U.S., testing the same gemcitabine-Elenagen combination on a larger number of patients. An IND pre-application package has already been submitted to the FDA, and the principal investigator for the study will be Prof. Bhavana Pothuri, MD of NYU. At the same time, the company plans to carry out additional international collaborations to test whether Elenagen also enhances doxil, paclitaxel, and other PROC treatments.

"For me, it is imperative to publish in *Frontiers in Oncology* at a time when our society is in desperate need of major adjustments that challenge the dominant dogmas and hierarchies," added Shneider. "I hope this will be our contribution to the cause."

More information: Sergei Krasny et al, Clinical efficacy of plasmid encoding p62/SQSTM1 (Elenagen) in combination with gemcitabine in patients with platinum-resistant ovarian cancer: a randomized controlled trial, *Frontiers in Oncology* (2024). DOI: 10.3389/fonc.2024.1343023

Provided by CureLab Oncology Inc.