Report On FDA's Go-Ahead Of A Path Forward For Multikine

May 8, 2024

Contents

Our Mission-Critical Progress With FDA

I am excited to share that we have reached an agreement with the United States Food and Drug Administration (FDA) for a clear path forward to bring our first-line investigational cancer drug Multikine to the market, marking a critical milestone.

Agreement On 212-Patient Confirmatory Study Based On The Strong Survival Benefit Seen In Our Completed 928-Patient Phase 3 Study

The point of this letter is to apprise you of the breakthrough we have made with FDA since we announced at ESMO 2023 the clinical data that supports our cancer drug Multikine.[1] We now have agency support to conduct a "Registration Study" to confirm Multikine's efficacy and safety in a targeted patient population that saw a much higher survival rate than the control group in our completed 928-patient Phase 3 trial. Favorably for us, the confirmatory Registration Study needs only 212 patients (because of the strength of the existing data), and enrollment should proceed much more quickly than the prior study. This achievement is a huge deal for the Company, because we now have FDA's agreement on how to move Multikine forward on a path towards approval.

A "Registration Study" means the trial is intended to obtain sufficient data to support an application for regulatory approval. The target population for this study represents a subgroup of patients from our completed Phase 3 trial who showed the most survival benefit from Multikine and who can be selected prior to surgery, when Multikine is given. In the prior study, those patients saw their ***5-year death rate cut in half vs control***.

FDA Has Accepted Our Registration Study Design

In April 2024, CEL-SCI met with fourteen FDA regulators and scientists to discuss Multikine, including senior FDA oncology leadership. The discussion was extremely positive and collaborative. The FDA stated in a written meeting summary that:

- "eligibility criteria are generally acceptable" for this study
- nonclinical data package "appears sufficient to support the proposed clinical study"
- proposed stratification factors "appear reasonable" for analysis
- CEL-SCI's approach for the product specifications "is deemed acceptable."

The FDA had no safety objections to the further treatment of patients with Multikine, and also acknowledged the unmet medical need for improved therapies in this space. CEL-SCI is incorporating the FDA's comments into the Registration Study protocol and intends to submit a final protocol by this summer so that the study can begin as soon as possible.

[1] https://cel-sci.com/wp-content/uploads/2023/10/CEL-SCI_shareholder_letter_from_CEO_Oct2023.pdf

OUR MISSION-CRITICAL PROGRESS WITH FDA

BEING FIRST MEANS THE BAR IS HIGHER

This breakthrough did not come easy for us, because we are targeting "newly-diagnosed" head and neck cancer patients prior to surgery. Currently approved head and neck cancer immunotherapies are for recurrent cancer patients who have failed the standard treatments and are expected to die soon from the cancer. In those "late-stage" patients, it is acceptable to administer medicines that are toxic—and that may even kill some patients—as long as there is a quantifiable and proven benefit to the group as a whole.

The benefit/risk balance must be stricter for our patients who are newly diagnosed and have not yet received treatment for their cancer. One regulator called such patients "much more delicate" than late-stage patients, because newly diagnosed patients have a much higher chance of surviving if treated with the current standard of care. In the newly diagnosed patient context, like ours, a drug can be approved only if (1) there was no harm to patients who are expected to survive and (2) there was a high likelihood that the drug would improve outcomes for those who are expected to die. Therefore, to be allowed to run our confirmatory Registration Study, we had a far more difficult path than expected, requiring biological justifications, deep research of the literature, and stronger clinical evidence. Further, the rationale for approving Multikine must be tied, with evidence, to its biological mechanism of action and cannot be based solely on Multikine's clinical performance. That is, the regulators demanded not only that we show positive clinical outcomes from Multikine (which we believe we have done), but we also had to provide explanations and evidence as to ***why*** Multikine performed as it did in the clinical trials.

Despite these high hurdles, we successfully demonstrated to the FDA that:

(i) We can select patients before surgery using selection criteria at the time of diagnosis—by contrast, for the standard of care, this is done only after surgery;
(ii) The selection criteria arise from Multikine's biological mechanism of action;
(iii) Treating patients with Multikine is safe; and
(iv) Patients meeting the selection criteria are likely to see a significant survival benefit.

Our Registration Study Is Likely To Succeed

We Have Already Shown That Multikine Improves Survival

Certain facts about Multikine cannot be denied. First, Multikine leads to pre-surgical responses, meaning that Multikine's benefits become immediately apparent for many within just a few weeks of treatment. Second, if one has a pre-surgical response, then their chance of survival is greatly improved. ***Therefore, we know that Multikine improves survival for those with pre-surgical responses.***

The biological mechanism of action—literally, ***why*** Multikine works—suggests that Multikine should have the greatest activity in patients whose local immune architecture (e.g. lymph nodes) has not been compromised by disease. The mechanism of action also suggests that tumors with low PD-L1, which have lower defenses to the immune system, will be more vulnerable to an immune attack versus tumors with high PD-L1, which have greater defenses to an immune attack. Thus, the Multikine target population is restricted to patients with no lymph node involvement of the disease and with low PD-L1 tumor expression. These features can be assessed right at diagnosis with a PET scan and a biopsy.

Patients in our completed Phase 3 trial who fit these selection criteria had the following results, which we presented at the ESMO cancer conference in October 2023:[2]

- ✓ ***risk of death cut in half*** at five years versus control;
- ✓ 28.6% absolute 5-year overall survival benefit versus control (p=0.0015);
- ✓ 0.349 hazard ratio vs control (95% CIs [0.18, 0.66], Wald p=0.0012);
- ✓ >35% rate of pre-surgery tumor reductions and/or disease downstages (p<0.01).

These results are very strong. This is why we believe the chance of success in our Registration Study is high and, in fact, even higher than in a normal confirmatory study:

[2] https://cel-sci.com/wp-content/uploads/2023/10/ESMO-2023-Poster_893P_FINAL.pdf. Unstratified log rank p-value is presented for 5-year absolute OS, and Fisher Exact p-value is presented for pre-surgical responses.

OUR REGISTRATION STUDY IS LIKELY TO SUCCEED

- In general, confirmatory studies typically have a higher chance of success than original Phase 3 studies, and we believe our confirmatory study has an even higher chance of success than normal confirmatory studies. Confirmatory studies usually involve a drug that has already shown tumor responses, and the question is whether that tumor response will translate into increased survival. In the case of our confirmatory study, we already know that Multikine leads to pre-surgical responses, and we know that patients with such responses live far longer than those without. Now, we need to prospectively show the FDA that these pre-surgical responses lead to survival benefit in the target population.

- "Success" in a clinical study like ours means showing an absolute 10% improvement in overall survival (OS) versus control. In our completed Phase 3 trial, the selected target population saw an absolute 28.5% improvement at 5 years, which is much higher than the absolute 10% we need for success. That is a solid cushion.

- Success also means showing a hazard ratio of 0.72 or less, and the selected target population saw a hazard ratio of 0.349 in the completed study, which is again much better than the level typically needed to show success. That is another solid cushion.

- The hazard ratio's "upper confidence interval," considered to be the worst-case scenario statistically, was 0.66. That too is better than levels needed for success.

- The study needs to enroll only 212 patients, because the survival benefit of the selected Phase 3 patients was so large and the statistical significance was so high.

These reasons give us confidence that the Registration Study is likely to succeed.

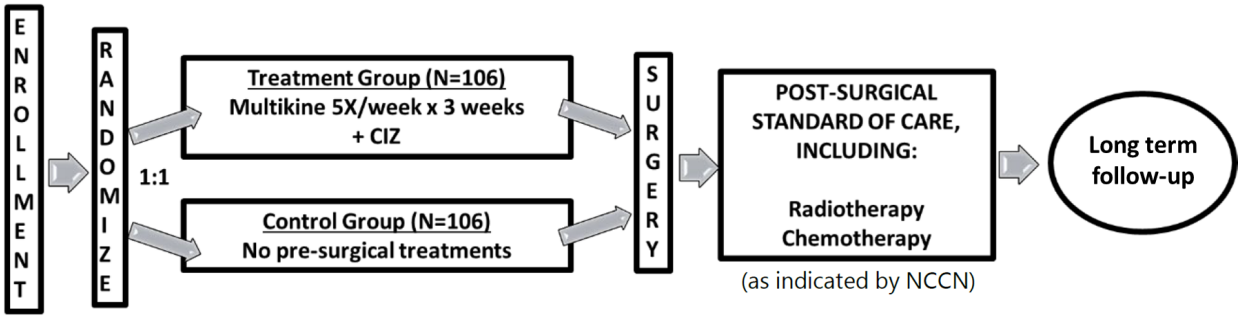
OUR REGISTRATION STUDY DESIGN IS STRAIGHTFORWARD

The Registration Study will be a randomized controlled trial with two equally sized arms: one treatment arm with Multikine and one control arm without Multikine. Both arms would receive the current standard of care following surgery.

Enrollment will be completed in a first stage (Stage 1), and subjects will be followed for long-term survival in a second stage (Stage 2). Stage 1 subjects will be randomized 1:1 between the treatment arm and the control arm. Stage 1 will look at pre-surgical response rates, which can be determined almost immediately after enrollment is completed, because pre-surgical responses occur within just a few weeks of Multikine treatment. As explained later on in this letter, patients who have pre-surgical responses saw much better survival in the completed Phase 3 study. Stage 2 of the confirmatory study will assess overall survival as the primary efficacy endpoint. Histopathology biomarkers will be assessed as well.

OUR REGISTRATION STUDY IS LIKELY TO SUCCEED

The Registration Study design is shown graphically below:



FOCUSED ON SUCCESS: OUR TARGET POPULATION FOR MULTIKINE

Our completed a 928-patient Phase 3 head and neck cancer study focused on very sick newly-diagnosed patients, hoping to make their survival better by treating them with Multikine. The idea was to give immunotherapy ***first***, before the immune system is damaged by standard treatments (surgery, radiotherapy and/or chemotherapy). The survival outcomes were excellent for the Multikine-treated patients who were deemed "low risk for recurrence" (as defined by NCCN Guidelines) by their doctors after surgery. However, patients deemed "high risk for recurrence" after surgery, who receive chemotherapy on top of the other treatments, did not see a benefit from Multikine.

We therefore sought to focus the Multikine target population on those patients who would most benefit from it. The challenge we faced was that the "low risk" and "high risk" patients were identified by doctors ***after surgery***, but because Multikine is given ***before surgery***, we had to find a way to identify the "low risk" patients right at diagnosis. This had never been done before in head and neck cancer, and so we had to blaze our own trail to find selection criteria that did two things: (1) include the patients most likely to benefit from Multikine, and also (2) exclude patients who were not likely to benefit from Multikine. These criteria could not be overinclusive nor underinclusive—they had to be just right. Moreover, because we were the first ones to do this, we had to provide a mountain of evidence to support the criteria before the FDA would accept it for future use of Multikine.

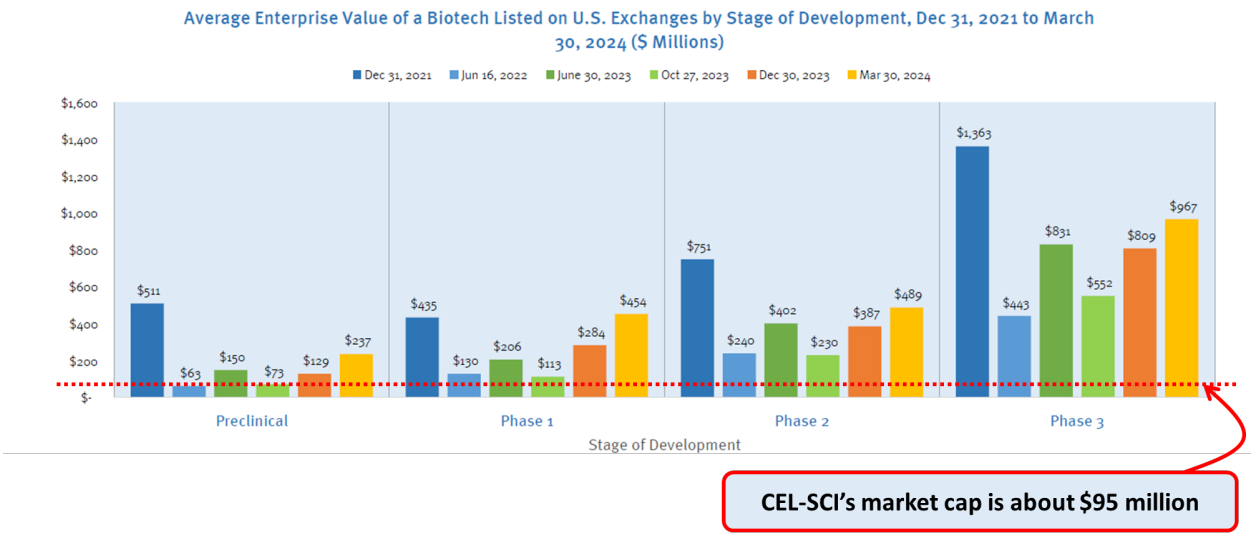
Last fall, we presented at a major cancer conference that we had achieved a definition of the Multikine selection criteria that we believed FDA would accept. We did so by looking at ***why*** Multikine works, which is called its "mechanism of action." We performed cellular analysis, researched the literature, and took advice from regulators and top consultants, including several of the most respected head and neck immuno-oncologists in the world. We confirmed the selection criteria by selecting patients from our completed Phase 3 trial who fit the criteria to see how they fared—the survival improvement vs control was very large, cutting the 5-year rate of death in half. We did everything right, and FDA has now accepted the selection criteria for the confirmatory Registration Study.

Our Value Proposition For Investors

We believe CEL-SCI provides a de-risked value proposition for investors because the path forward is positive and has been accepted by the FDA. In the confirmatory study, Multikine will be given to the kind of patients who have already seen excellent survival in the completed Phase 3 study. This confirmation is required only because the regulations require that a benefit be defined prospectively. This is a rare opportunity for investors to bet on the success of a cancer drug that has already produced a great amount of data demonstrating a significant survival benefit in the target population.

We Are Undervalued

CEL-SCI is currently valued very low in part because its path to bringing Multikine to market was unclear despite the good data. An April 2024 report by the brokerage firm Stifel shows that Phase 3 biotech companies are valued $967 million on average, and Phase 2 companies are valued at $489 million on average, as shown in the excerpt below:



As of today, CEL-SCI sits at the red dotted line and is valued far below the averages even of Phase 1 companies, despite having been through Phase 3 and showing that its drug is safe and active in a large group of patients. This low valuation might make sense if CEL-SCI could not figure out how to select the patients before surgery for the confirmatory study—but we did figure it out and the FDA accepted our solution. We now have a clear path to the market and, based on the data we have, we believe that we have a very good chance of being successful. Many successful companies had to do confirmatory studies to gain full approvals for their drugs. By working with the FDA, we are walking the same path.

When a cancer drug is shown to be effective at prolonging life, it should become part of the standard of care, which means it would then be unethical for a physician not to give Multkine to eligible patients. The success of our confirmatory study would mean great

success for CEL-SCI. Current cancer immunotherapies are reimbursed in the U.S. at about $150,000 per treatment and more. I just saw that one new cancer drug is planning to charge over $500,000. Considering the large number of head and neck cancer patients, the absence of other therapies in our space, and our target population of approximately 100,000 cases annually worldwide, even a small penetration would mean billions of dollars of annual revenue with no competition.

My Personal Perspective On Value

Obviously, I am biased, since I am the long-term CEO and a major shareholder of CEL-SCI. But I am these things because I truly believe in Multikine and the idea that the immune system must be activated right away, before it has been ravaged by the standard of care. My thinking is logical, data-driven, and based on three decades of experience in biotech investing. The most important observation I can make is that there is no place for the efficient market theory in biotechnology, because everything is new and most data is kept confidential. Therefore, the most important validation that investors can get is from the FDA, who gets sees all of the data, including the confidential parts, and is the ultimate arbiter of what is correct. ***We just got that validation from the FDA*** when it told us they accepted our patient selection criteria and path forward to drug approval.

Clinical and statistical experts are telling me that the data is extremely strong and that we should be able to replicate these results in this confirmatory study. If we do so, then we will save lives and, based on other companies in the cancer field, be worth billions.

We have invested over $200 million in our own manufacturing facility built specifically for Multikine, involving significant know-how and trade secrets, and other manufacturing related knowledge and assets. Ultimately, we will likely seek a partnership with a large pharmaceutical company both to sell Multikine worldwide and also to begin studies in other tumors beyond head and neck cancer.

An Invitation To See For Yourself

We invite you to look closely at our data. You now know that the FDA has reviewed it and has accepted that "delicate" newly diagnosed cancer patients may be treated with Multikine in a relatively small confirmatory registration study. You also know from the completed Phase 3 study that the rate of death was cut in half for Multikine-treated vs control in our target group. You know that biotech stocks are volatile, and you know that success in our confirmatory study should lead to the approval of Multikine as the first ever pre-surgical immunotherapy for head and neck cancer. Our path forward is clear—we will give 100% attention to conducting this study as quickly as possible and as perfectly as possible.

For those who want to know more about the science and evidence behind Multikine, as well as the FDA's recognition of the need for such a drug to treat head and neck cancer, I invite you to read on.

Our Foundation: Multikine's Mechanism Of Action

The Biological Reasons For Multikine's Activity

The FDA's acceptance of Multikine's target population could not have happened without presenting hard evidence supporting ***why*** Multikine works. I will provide some technical detail here so you can see for yourself how we achieved this and how well we understand Multikine, which is again one more reason why we think we will be successful.

As an immunotherapy, Multikine relies on the patient's immune system to attack the tumor. As a neoadjuvant (first-line treatment), Multikine operates before the standard of care (SOC) or disease progression has impaired the immune system.[3, 4] As a locally injected treatment, Multikine relies on local lymphatic architecture and immune competence. This biological model suggests that Multikine is most effective in patients who present with the strongest local immune systems, i.e., those with low tumor burden rather than high tumor burden, as was shown in the Multikine Phase 3 study.

[3] Tímár J, Forster-Horvath C, Lukits J, Dome B, Ladanyi A, Remenar E et al. The effect of leukocyte interleukin injection (Multikine) treatment on the peritumoral and intratumoral subpopulation of mononuclear cells and on tumor epithelia: a possible new approach to augmenting sensitivity to radiation therapy and chemotherapy in oral cancer--a multicenter phase I/II clinical Trial. Laryngoscope 2003;113(12):2206-2217. DOI: 10.1097/00005537-200312000-00031.

[4] Tímár J, Ladanyi A, Forster-Horvath C, Lukits J, Dome B, Remenar E et al. Neoadjuvant immunotherapy of oral squamous cell carcinoma modulates intratumoral CD4/CD8 ratio and tumor microenvironment: a multicenter phase II clinical trial. J Clin Oncol 2005;23(15):3421-3432. DOI: 10.1200/JCO.2005.06.005.

OUR FOUNDATION: MULTIKINE'S MECHANISM OF ACTION

Multikine's biological mechanism of action has a strong basis in the scientific literature, as intratumoral and peritumoral immunotherapies with cytokines have been studied extensively.[5, 6, 7, 8, 9, 10, 11, 12, 13] Antitumor activity has been associated with development of an inflammatory response localized to the tumor.[14] This approach has been shown to overcome the tumor's ability to suppress the patient's antitumor immune response.[15] In animals, local administrations of interferons and IL-2 have led to tumor responses.[16]

Certain components of Multikine (e.g., IFN-α, -β and -γ, TNF-α, TNF-β, IL-1, IL-2) have shown antitumor activity in animals and humans.[17] IL-2 is one of the primary components of Multikine, and its activity has been shown in other studies to result in antitumor activity.[18] For example, in one study, injection of IL-2 into the regional lymph nodes of human subjects induced remission of head and neck cancer.[19] In another study, 12 patients were treated with IL-2 before surgery, resulting in marked tumor response.[20] In another trial, IL-2 was administered directly into the tumor area in 20 head and neck cancer patients.[21] Three

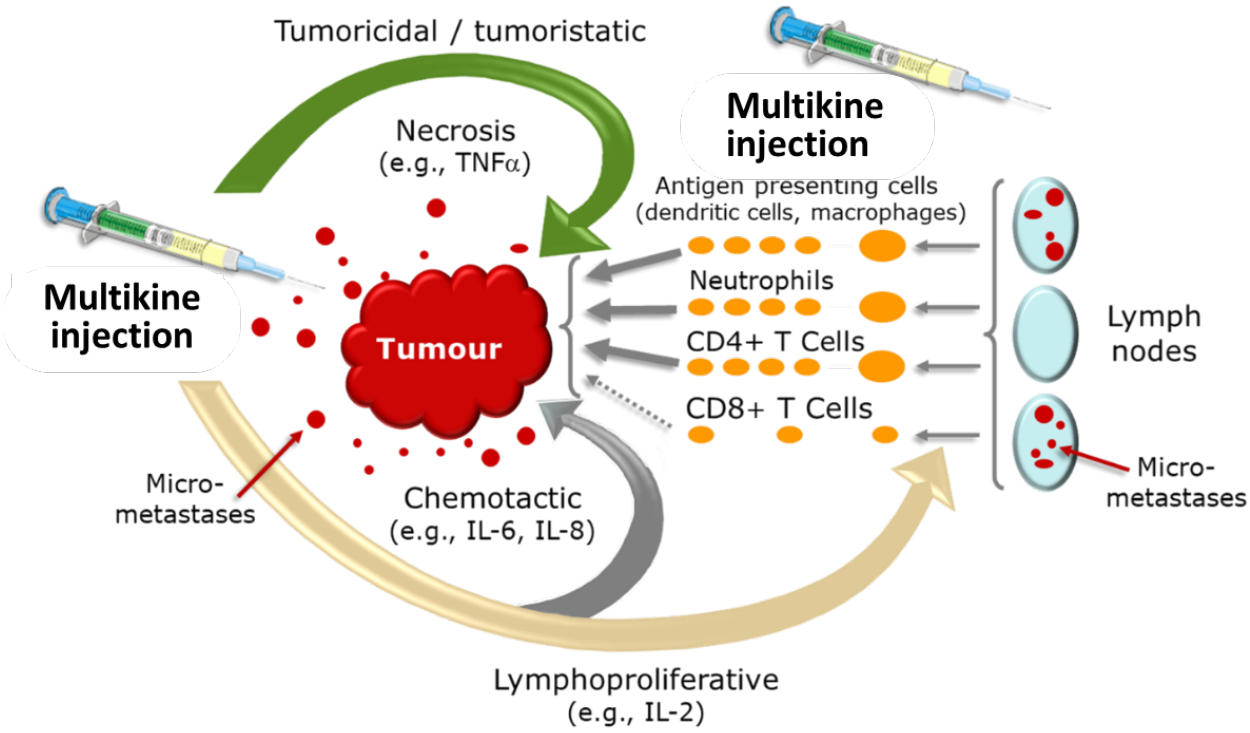
[5] Cortesina G, De Stefani A, Galeazzi E, Cavallo GP, Jemma C, Giovarelli M et al. Interleukin-2 injected around tumor-draining lymph nodes in head and neck cancer. Head Neck 1991;13(2):125-131. DOI: 10.1002/hed.2880130208.
[6] Rivoltini L, Gambacorti-Passerini C, Squadrelli-Saraceno M, Grosso MI, Cantu G, Molinari R et al. In vivo interleukin 2-induced activation of lymphokine-activated killer cells and tumor cytotoxic T-cells in cervical lymph nodes of patients with head and neck tumors. Cancer Res 1990;50(17):5551-5557. (https://www.ncbi.nlm.nih.gov/pubmed/2386961).
[7] Saito T, Kakiuti H, Kuki K, Yokota M, Jinnin T, Kimura T et al. Clinical evaluation of local administration of RIL-2 in head and neck cancer. Nihon Jibiinkoka Gakkai Kaiho 1989;92(8):1265-1270. DOI: 10.3950/jibiinkoka.92.1265.
[8] Saito T, Kawaguti T, Yoda J, Kimura T, and Tabata T. Immunohistology of tumor tissue in local administration of recombinant interleukin-2 in head and neck cancer. Nihon Jibiinkoka Gakkai Kaiho 1989;92(8):1271-1276. DOI: 10.3950/jibiinkoka.92.1271.
[9] Pulley MS, Nagendran V, Edwards JM, and Dumonde DC. Intravenous, intralesional and endolymphatic administration of lymphokines in human cancer. Lymphokine Res 1986;5 Suppl 1:S157-163. (https://www.ncbi.nlm.nih.gov/pubmed/3784610).
[10] Mattijssen V, De Mulder PH, Schornagel JH, Verweij J, Van den Broek P, Galazka A et al. Clinical and immunopathological results of a phase II study of perilymphatically injected recombinant interleukin-2 in locally far advanced, nonpretreated head and neck squamous cell carcinoma. J Immunother (1991) 1991;10(1):63-68. DOI: 10.1097/00002371-199102000-00009.
[11] Edwards L, Whiting D, Rogers D, Luck K, and Smiles KA. The effect of intralesional interferon gamma on basal cell carcinomas. J Am Acad Dermatol 1990;22(3):496-500. DOI: 10.1016/0190-9622(90)70070-x.
[12] Fetell MR, Housepian EM, Oster MW, Cote DN, Sisti MB, Marcus SG et al. Intratumor administration of beta-interferon in recurrent malignant gliomas. A phase I clinical and laboratory study. Cancer 1990;65(1):78-83. DOI: 10.1002/1097-0142(19900101)65:1<78::aid-cncr2820650117>3.0.co;2-5.
[13] Musiani P, De Campora E, Valitutti S, Castellino F, Calearo C, Cortesina G et al. Effect of low doses of interleukin-2 injected perilymphatically and peritumorally in patients with advanced primary head and neck squamous cell carcinoma. J Biol Response Mod 1989;8(6):571-578. (https://www.ncbi.nlm.nih.gov/pubmed/2600601).
[14] Timar 2003; Tímár 2005; Feinmesser R, Hardy B, Sadov R, Shwartz A, Chretien P, and Feinmesser M. Report of a clinical trial in 12 patients with head and neck cancer treated intratumorally and peritumorally with multikine. Arch Otolaryngol Head Neck Surg 2003;129(8):874-881. DOI: 10.1001/archotol.129.8.874.
[15] Gun SY, Lee SWL, Sieow JL, and Wong SC. Targeting immune cells for cancer therapy. Redox Biol 2019;25:101174. DOI: 10.1016/j.redox.2019.101174.
[16] Waldmann TA. Cytokines in Cancer Immunotherapy. Cold Spring Harb Perspect Biol 2018;10(12). DOI: 10.1101/cshperspect.a028472.
[17] Cortesina 1991; Waldman 2018; Fenton 2021.
[18] Pulley 1986.
[19] Cortesina 1991.
[20] Rivoltini 1990.
[21] Saito 1989.

responses were seen, including two complete remissions. In another study with IL-2, four responses were observed in 46 head and neck cancer patients.[22]

Others have shown the rationale and safety for local cytokine therapy like Multikine.[23] In humans, there is evidence for cytokine antitumor activity on cancers in multiple organs, e.g., skin, genitalia, peritoneum, pleural cavity, brain, head and neck, liver, and bladder.[24, 25]

These studies support Multikine's three-part mechanism of action, which is (1) to overcome suppression of the local immune system by the tumor; (2) to enable a local antitumor immune response to occur; and (3) to break down the tumor's tolerances to such an attack. This mechanism of action is summarized graphically in Figure 1 below.

Figure 1 Multikine mechanism of action



More specifically, the components of Multikine produce an antitumor response by recognizing and/or binding to multiple different receptors on the cancer cells, directly affecting/killing cancer cells, and signaling the immune system to produce an antitumor

[22] Saito 1989.
[23] Mattijssen 1991.
[24] Edwards 1990.
[25] Pizza G, Severini G, Menniti D, De Vinci C, and Corrado F. Tumour regression after intralesional injection of interleukin 2 (IL-2) in bladder cancer. Preliminary report. Int J Cancer 1984;34(3):359-367. DOI: 10.1002/ijc.2910340312.

immune response.[26] The combined activity of the different cytokines in Multikine induce a six-fold cascade of events as follows:[27]

(i) tumor necrosis factors (TNF) kill tumor cells, releasing tumor antigens;
(ii) tumor antigens are transported to lymph nodes;
(iii) lymphoproliferative cytokines (e.g., IL 1, IL 2) induce a marked expansion of tumor specific T cells primarily in lymph nodes;
(iv) tumor cells are further killed by increased proportion of CD4+ T cells (vs CD8+), which turns up the antitumor immune response further;
(v) neutrophils recruited from the circulation by Multikine continue to destroy tumor cells;
(vi) cytokines in Multikine and/or from the patient's own immune system induce massive local fibrosis.

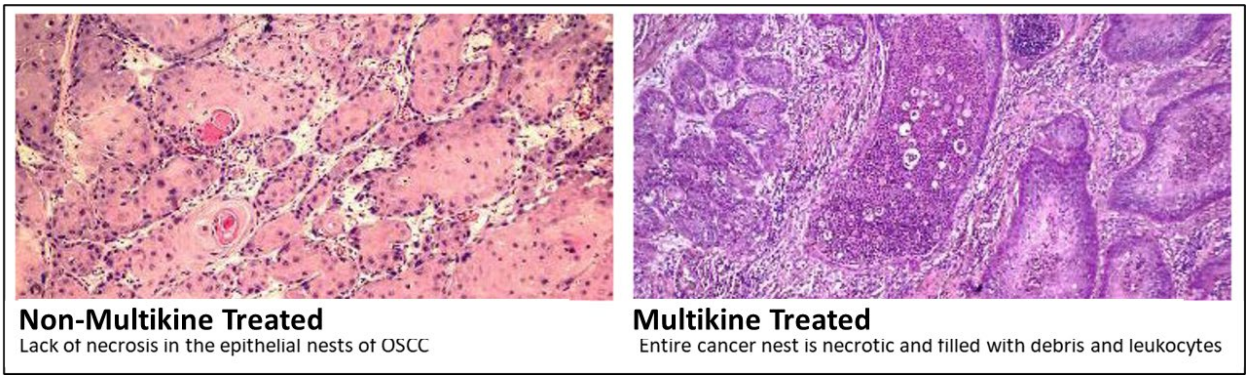
I know this is all extremely technical, but I felt it was important to share just how detailed we have been in terms of understanding Multikine and providing the FDA with hard facts.

Histopathological Evidence Supporting the Mechanism of Action

One thing that I find amazing is that we can actually see Multikine working in the body against the tumor. Such an analysis is called "histopathology," which refers to the study of diseased cells and tissues using a microscope. That is, you can see it with your eyes!

Histopathology analysis from Phases 1 and 2 showed early on that Multikine augments something called "CD4 cells" that infiltrate and attack the tumor. We found by looking through a microscope that Multikine actually increased the CD4 proportions in the tumor and near the tumor.[28] These are shown below in Figure 2 and Figure 3.

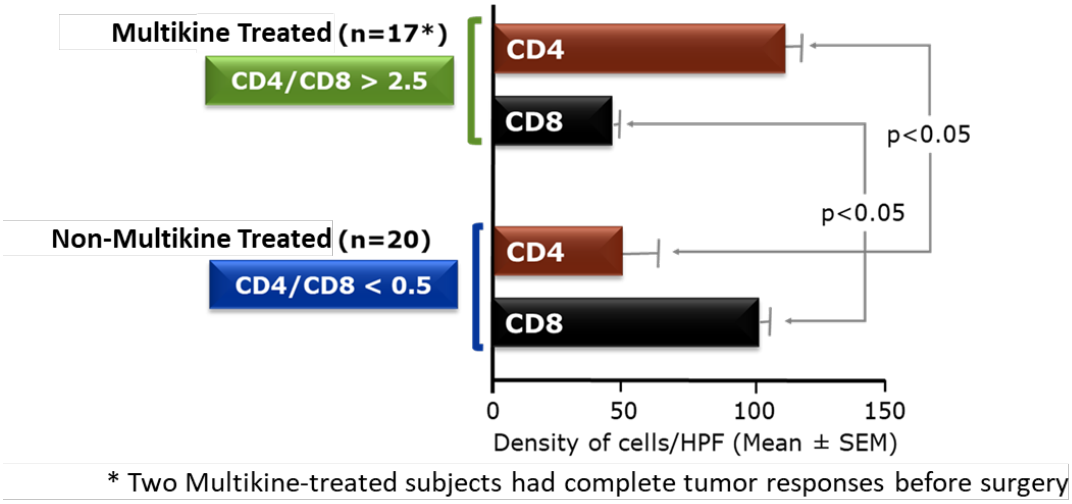
Figure 2 Tumor necrosis histopathology comparison (Phase 2, Tímár 2005)



[26] Tímár 2003; Tímár 2005; Feinmesser 2003.
[27] Tímár 2005.
[28] Tímár 2003; Tímár 2005; Feinmesser 2003.

OUR FOUNDATION: MULTIKINE'S MECHANISM OF ACTION

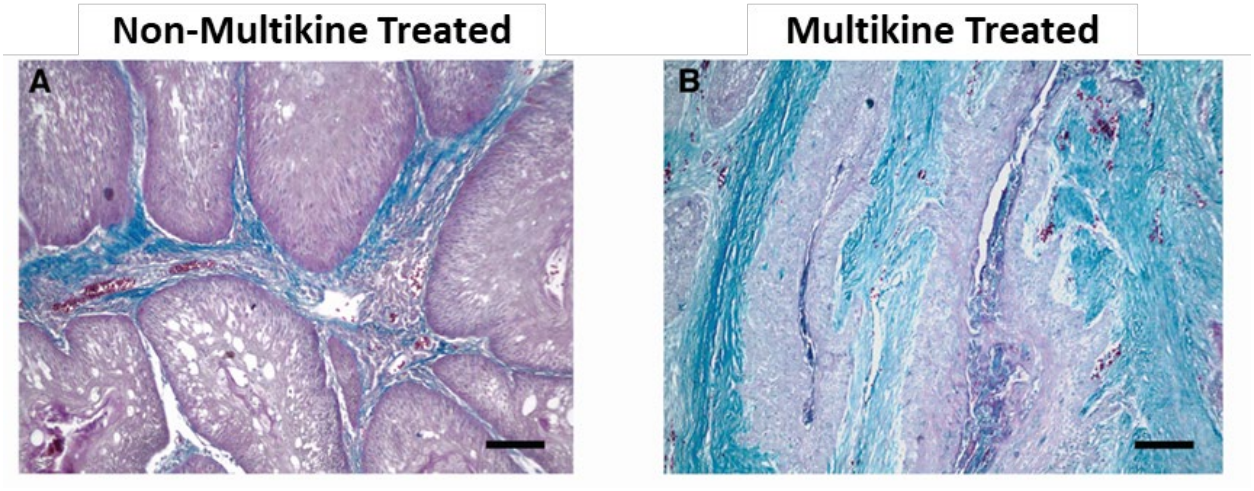
Figure 3 CD4 Increased In Multikine Treated Patients (Phase 2, Tímár 2005)



* Two Multikine-treated subjects had complete tumor responses before surgery

You can see the effect of Multikine clearly under the microscope. One of the clearest examples is from a Phase 2 study of Multikine where we showed the structure of the tumor essentially evaporates away in the Multikine-treated patients, shown in Figure 4 below:

Figure 4 Tumoral structures in Multikine-treated patients vs. control (Tímár 2005)



The same was seen in the histopathology analysis from the completed Phase 3 trial as well.

OUR FOUNDATION: MULTIKINE'S MECHANISM OF ACTION

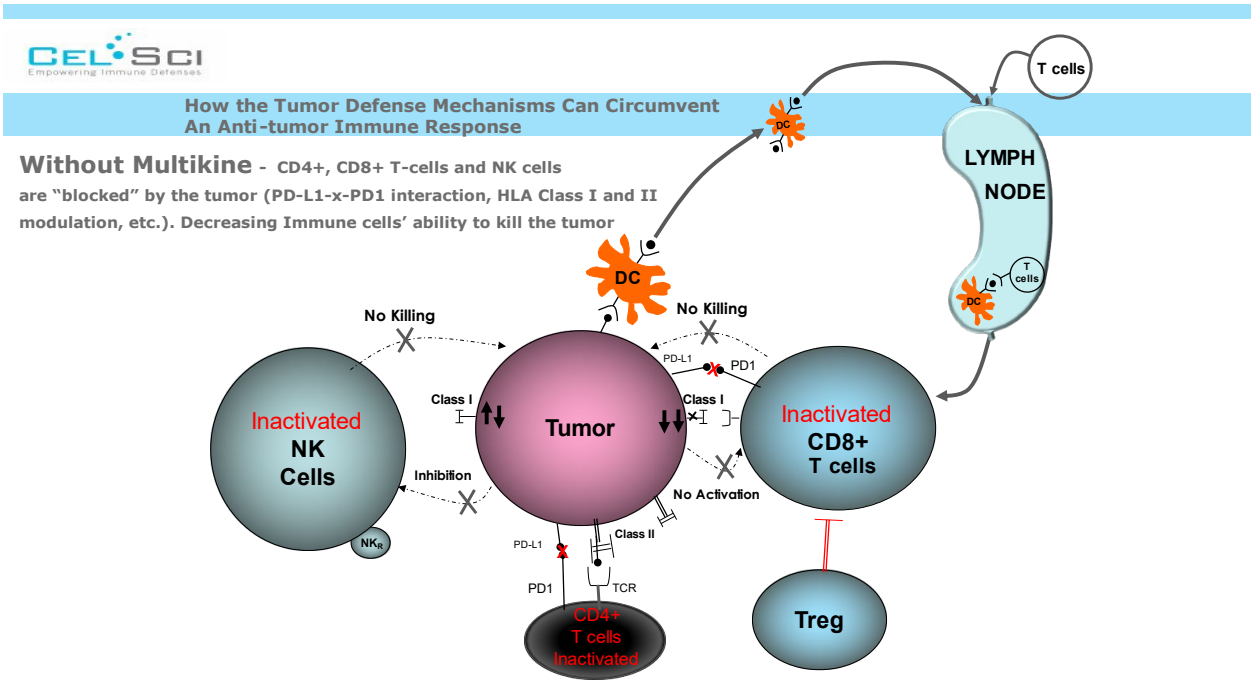
How Does Multikine Bring About Tumor Cell Death?

Multikine is a proprietary (patented and trade secret), well-defined, complex biological product containing a mixture of pro-inflammatory cytokines and small biological molecules that act directly to kill tumor cells and, at the same time, enhance existing antitumor destruction, while bringing about the activation of the patient's antitumor immune response.

Multikine's mechanism of action has been demonstrated in Phase 1 and 2 studies and published (e.g., Timar et al JCO 2005). It was also demonstrated in a randomized Phase 3 study through histopathology and immunohistochemistry gleaned from patients' tumor samples and analysis of tumor microenvironment compared to control arm patients' samples (all performed while blinded to the study).

Without Multikine, immune cells (such as CD8+ T cells, NK cells and CD4+T cells) are blocked by the tumor via various mechanisms including but not limited to: (1) tumor cell modulation of HLA (Human Leukocyte Antigen) expression on the tumor cell surface; (2) interaction of PD-L1 on the tumor with PD1 on immune cells; and (3) downregulation and suppression of cytotoxic CD8+ T cells by myeloid-derived suppressor cells (MDSC) and exosomes which enhance T regulatory cells. Together, these natural mechanisms protect the tumor from the patient's immune system by inactivating antitumor immune cells and diminishing their ability to attack the tumor, as depicted in the diagram below.

Figure 5 Tumor Cell Death Without Multikine

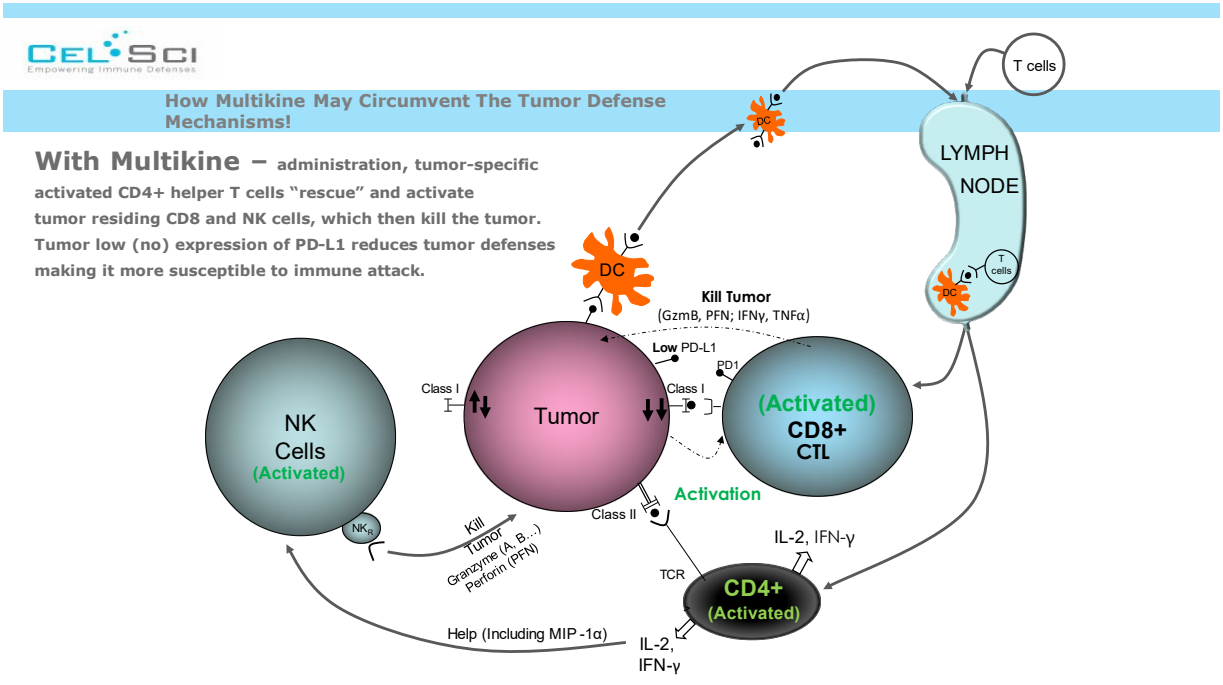


OUR FOUNDATION: MULTIKINE'S MECHANISM OF ACTION

With Multikine, pro-inflammatory cytokines in Multikine (e.g., IFN-γ, TNFα) are able to directly kill tumor cells. This produces tumor antigens that CD1a dendritic cells carry to the local draining lymph nodes where they present these tumor specific antigens and "educate" peripheral T cells (both CD4+ and CD8+ T cells) making them antitumor CD8+ cytotoxic T cells and helper CD4+ T cells. Along with other immune cells (e.g., NK cells), chemotactic cytokines present in Multikine (e.g., RANTES, GM-CSF, MIP-1α, MIP-1β), allow these antitumor specific T cells to hone in on the tumor site and infiltrate into the tumor microenvironment. The antitumor immune activity is sustained via cytokines present in Multikine (e.g., IL-1, IL-2, CSF) as well as cytokines secreted by the now-activated tumor infiltrating immune cells. The antitumor immune cells in the tumor microenvironment interact with and destroy the tumor via the secretion of Granzyme B, Perforin, IFN-γ, TNFα (the latter two are also present in Multikine to further destroy the tumor). Dead and dying tumor cells are then removed by neutrophils summoned from the peripheral circulation via GM-CSF and IL-8, which are also present in Multikine. See Figure 6 below for detail.

The antitumor immune activation is sustained by the continued administration of Multikine, daily, five times per week for three consecutive weeks. Half of the daily dose is injected peritumorally (around the tumor) and the other half is injected perilymphatically (around the adjacent draining lymph node chain). The continued administration of Multikine over the pre-surgical treatment period allows the continued introduction of pro-inflammatory cytokines to the tumor microenvironment and lymphatics in support of the generation of an antitumor immune response and to ensure that the patient's immune system has the time it needs to generate and sustain the antitumor immune response.

Figure 6 Tumor Cell Death With Multikine



The Target Population

A Well Defined Patient Population Based on Robust Phase 3 Data

The confirmatory study will be run with the best performing target population, providing the highest chance of success to get marketing approval. This target population is defined by patients who present with no lymph node involvement of the disease ("N0") determined by PET scan and who also have low PD-L1 tumor expression determined by biopsy. This group represents about 100,000 cases annually worldwide. In the future, we can seek to expand the label to additional indications via further studies.

Low Risk Patients. One of the first things we reported from the Phase 3 study was that Multikine worked best in patients who were deemed "low risk" after surgery, about 40% of the study population. These patients saw a significant 14.1% absolute OS benefit at 5 years and a median OS advantage of 46.5 months—***nearly four years longer than control***. Biologically, it made sense that these patients would benefit most from Multikine, because they tended to have immune systems that were not yet compromised by the disease. "High risk" patients, by contrast, typically had lymph nodes invaded by the tumor, and needed chemotherapy after surgery. Because their lymph nodes were compromised, this made it harder for their immune systems to work, and they needed surgery as soon as possible without waiting an extra three weeks to receive Multikine.

CEL-SCI initially developed criteria for selecting "low-risk" patients at diagnosis—i.e., those having less than two lymph nodes invaded by the tumor (N0 or N1) as determined by PET scan. CEL-SCI published these criteria at the ASCO conference in 2022. However, after discussions with regulators and physicians, CEL-SCI saw that outcomes could be further improved if the N1 patients were excluded, with only N0 patients in the target population.

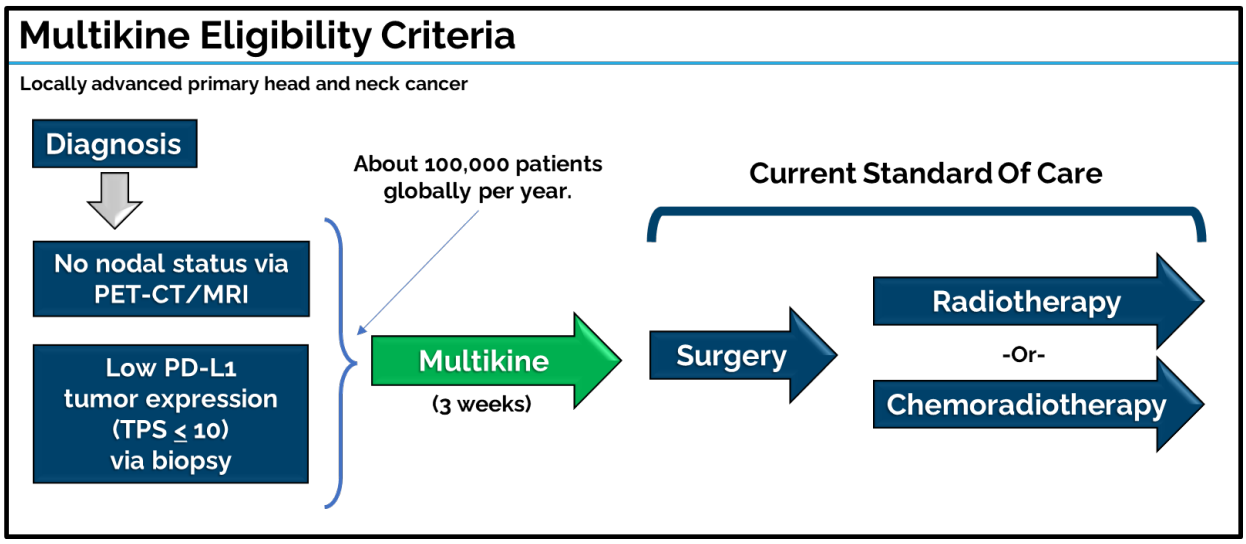
Low PD-L1 Tumor Expression. PD-L1 is a protein receptor on the tumor surface that helps the tumor repel the immune system. It makes sense that low PD-L1 patients would be more likely to respond to Multikine, because their tumors have lower defenses against the patient's immune system. It was not surprising, therefore, when we saw from the Phase 3 data that Multikine was more effective for patients with low PD-L1 tumor expression. These low PD-L1 patients represented about 70% of the study population.

It is important to note that targeting low PD-L1 differentiates Multikine from other immunotherapies. For example, checkpoint inhibitors like Keytruda and Opdivo appear to best serve patients having high PD-L1, because these drugs work by blocking PD-L1 receptors. While none of these drugs are currently approved as a first-line treatment for head and neck cancer before surgery, even if such approvals came in the future, the patients having low PD-L1 (which is the large majority) would still need Multikine.

THE TARGET POPULATION

AN ACCEPTABLE WAY TO DEFINE THE POPULATION *UPON DIAGNOSIS*

Our target population definition was acceptable to FDA. It is shown graphically below:



Multikine's Positive Clinical Data

In order to find our target population acceptable and provide positive feedback on the confirmatory Registration Study for Multikine, the FDA had to determine that Multikine was safe for these patients and that it was ethical to expose more patients to Multikine in the Registration Study. This is a very big achievement for the Company, which was made possible by our positive clinical data:

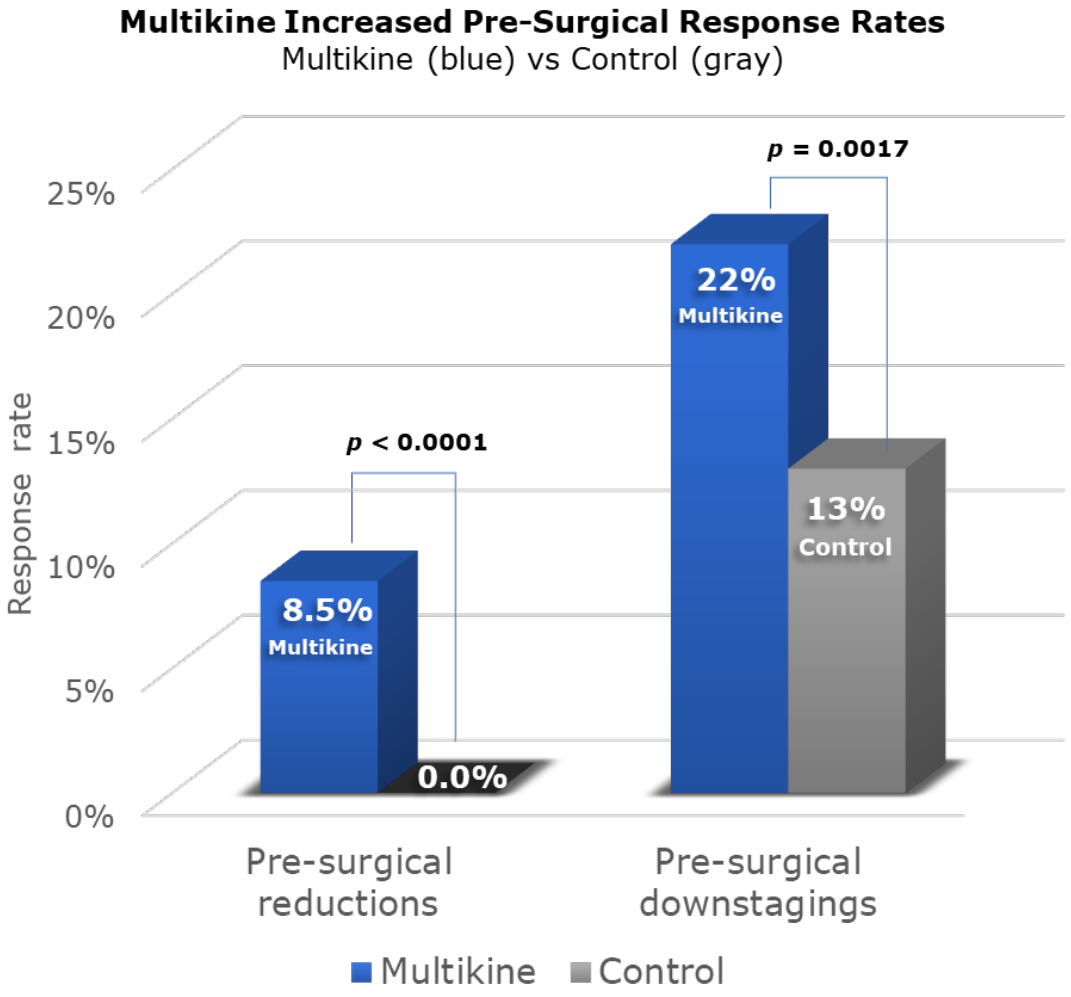
- Multikine causes pre-surgical responses;
- Pre-surgical responses lead to longer life;
- Therefore, Multikine leads to longer life.

MULTIKINE CAUSES "PSRS" AND "PSDS"

A "pre-surgical response" is a significant change in disease before surgery. We saw two kinds of responses in the Phase 3 trial. First, there were pre-surgical reductions (PSR) in the size of the tumor—a reduction of 30% or more qualified as a PSR. Second, there were disease downstages, e.g., the disease improved from Stage IV to Stage III. This is called "pre-surgical downstaging" (PSD).

In the completed Phase 3 trial, PSRs were seen in 8.5% of all Multikine-treated patients compared to ***zero*** in the control (not treated with Multikine). PSDs were seen in 22% of Multikine-treated patients vs 13% in the control, which was a very statistically significant difference. Because the Multikine treatment regimen was the only therapy given to these patients before surgery, Multikine had to be the cause of the higher rates of PSR and PSD.

MULTIKINE'S POSITIVE CLINICAL DATA

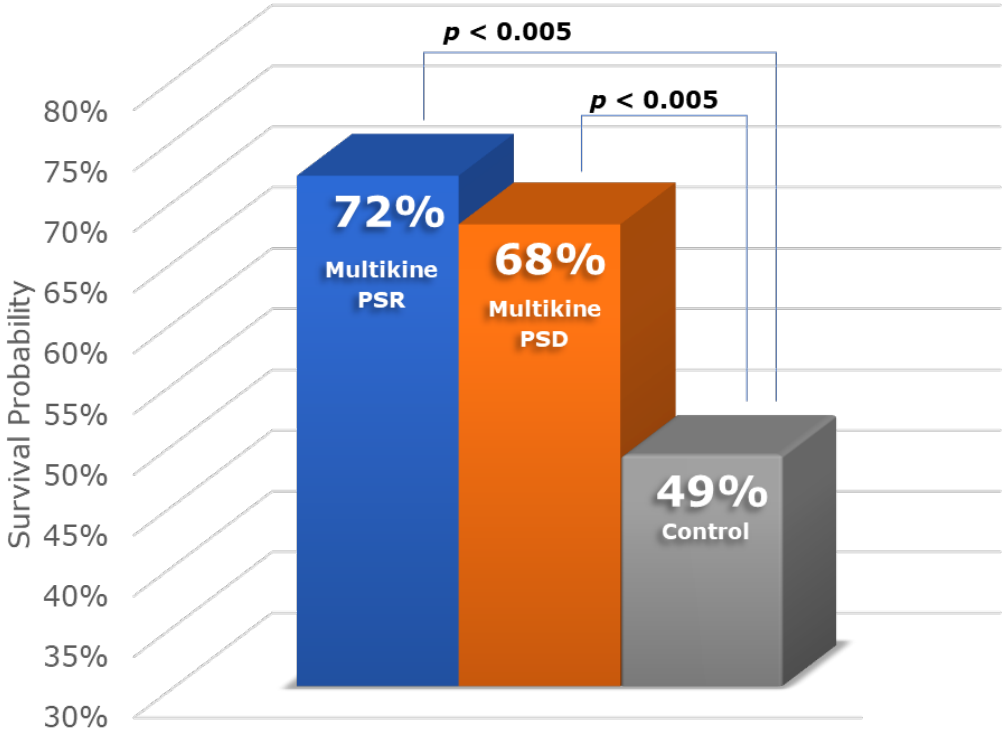


MULTIKINE'S POSITIVE CLINICAL DATA

PSRs and PSDs Lead To Longer Survival

PSR patients had a 72% likelihood to be alive after 5 years, whereas control patients were only about 49% likely to be alive after 5 years. Patients with PSD saw similar improvement: their 5-year chance of survival was about 68%.

Five-Year Overall Survival Higher For PSRs and PSDs
PSRs (blue) and PSDs (orange) vs Control (gray)

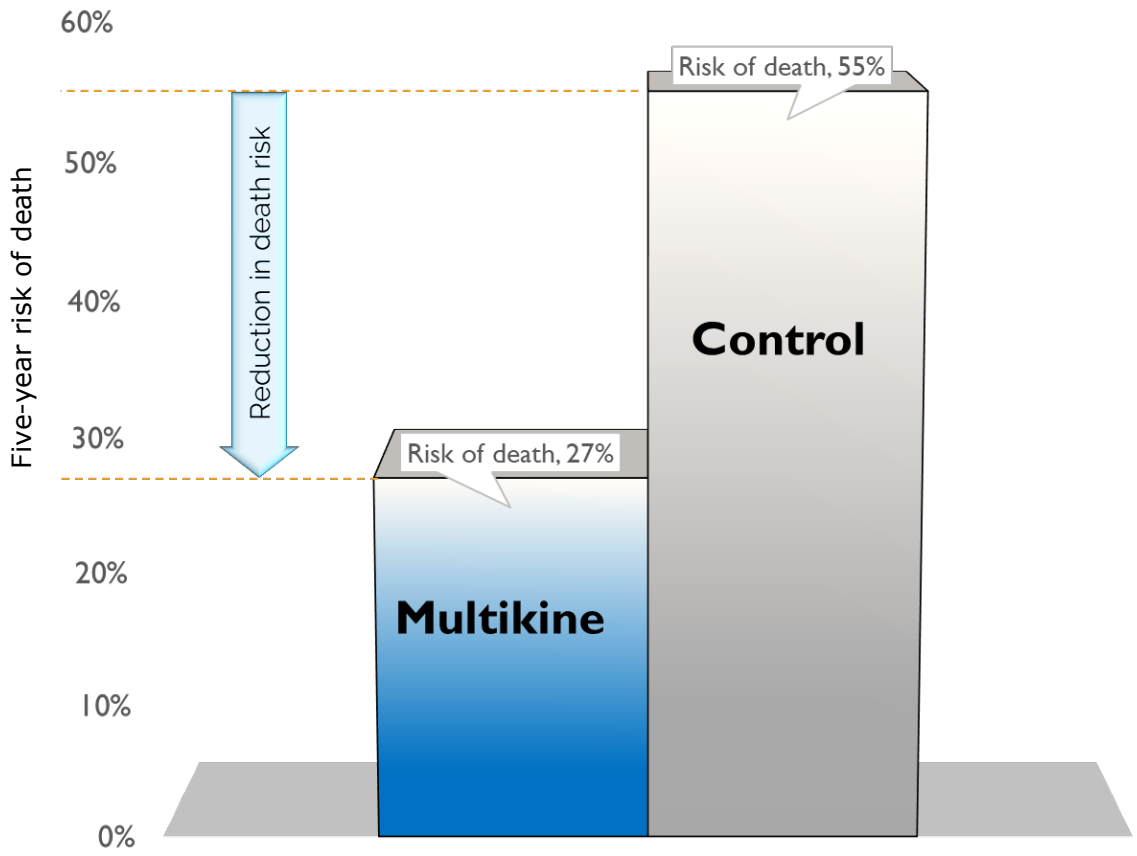


In sum, Multikine's ability to increase the rates of PSR/PSD pre-surgical responses, which extend survival, proves that Multikine helps patients.

Superior Results When The Right Patients Are Selected

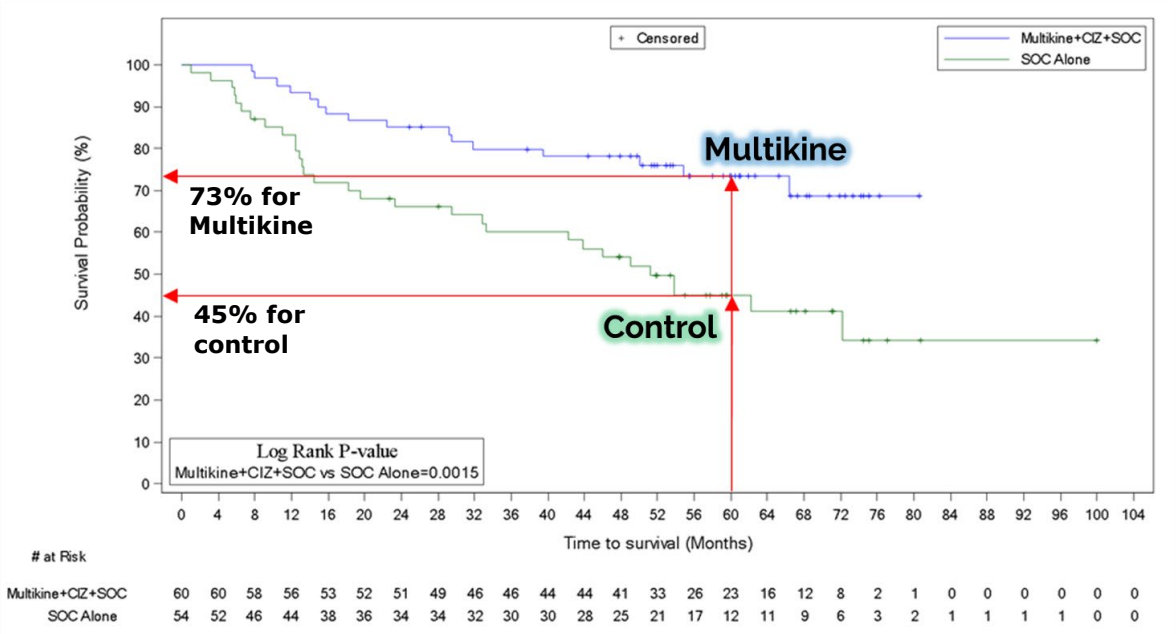
Among patients in the completed Phase 3 study who met the selection criteria, 5-year survival was 73% in the Multikine group versus only 45% in the control group. This means the risk of death fell to 27% in the Multikine group versus 55% in the control, as shown in the graphic below.

MULTIKINE'S POSITIVE CLINICAL DATA



Another way to see the survival benefit of Multikine in the target population is the Kaplan-Meier curve from our ESMO '23 poster, shown below. On the vertical axis is the probability of survival and the horizontal axis is time in months. The blue Multikine line is far above the green control line, meaning the chance of survival is much higher in the Multikine group at every point in time compared to the control (unstratified log rank p=0.0015).

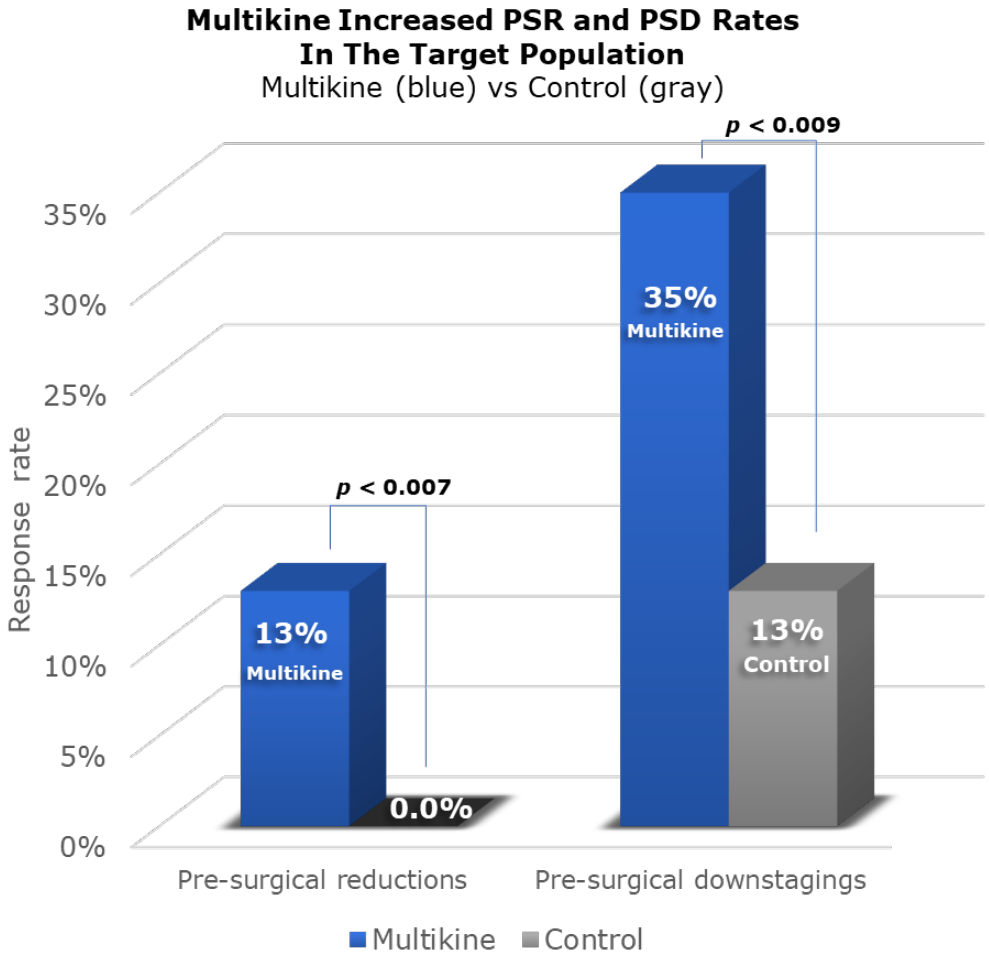
Kaplan-Meier Overall Survival for Multikine target population (n=114) in the Phase 3 study



Another measure of survival benefit is called the "hazard ratio," which compares the chances of dying between two different groups. In the Multikine target population, the hazard ratio was 0.35, which is very low—it means that deaths occurred in the Multikine group about one-third as frequently as in the control group.

These positive survival outcomes in the target population were driven by much higher pre-surgical response rates versus control as shown in the graphic below:

MULTIKINE'S POSITIVE CLINICAL DATA



MULTIKINE'S POSITIVE CLINICAL DATA

In sum, these data support CEL-SCI's confidence that its confirmatory Registration Study is likely to be successful and that Multikine will likely be adopted by the field and become part of the standard of care for head and neck cancer.

Efficacy

- 5-year risk of death cut in half
- Hazard ratio of 0.35
- 28% absolute 5-year survival benefit with p=0.0015
- More than 35% PSR/PSD
- Well-defined target population supported by clinical data and biological mechanism of action

Safety

- No demonstrable safety signals or toxicities across all clinical trials
- Adverse event incidences were not significantly different among treatment and control groups
- No Multikine-related deaths
- Multikine-related adverse events before surgery were local and resolved after surgery

FDA Recognized An Unmet Need For Better Therapies

What drives us forward is the compelling patient need for the PSRs/PSDs from Multikine, which was shown to lead to much better survival. This unmet patient need is paramount to all stakeholders, including patients, regulators, physicians, and CEL-SCI's investors.

Head and neck squamous cell carcinomas (HNSCC) constitute about 4.5% of all new cancers diagnosed annually worldwide.[29] The incidence of HNSCC is on the rise.[30] In the United States, around 71,100 new cases are diagnosed annually (roughly 3% of all malignancies), worldwide about 900,000 annually.

About 90% of oral cancers are primary squamous cell carcinomas arising from the lining of the mouth, the tongue, and the floor of the mouth. Carcinoma of the lip, tongue, and floor of the mouth represent about 65% of oral cavity cancers. Approximately 66% of subjects with HNSCC present with locally advanced disease (Stage III/IVa/IVb) and have poor prognosis.[31, 32, 33] The locally-advanced (LA) patients are targeted by Multikine.

Current standard of care for resectable primary LA HNSCC is surgery followed by either radiotherapy or concurrent chemoradiotherapy depending on risk features after surgery. There are no approved neoadjuvant (first-line) therapies in this indication. There are also no approved immunotherapies in this indication, because these immunotherapies are currently limited to non-resectable or recurrent tumors, versus Multikine's proposed indication for resectable, primary tumors in newly-diagnosed patients.

Primary LA HNSCC has been recognized as ***a "hard-to-treat disease."***[34, 35, 36] Merck stated in July 2022 that "[t]here have been limited advances for patients with locally

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[29] Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, Risk Factors, and Prevention of Head and Neck Squamous Cell Carcinoma. Med Sci (Basel). 2023 Jun 13;11(2):42. doi: 10.3390/medsci11020042. PMID: 37367741; PMCID: PMC10304137.
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[31] Monnerat C, Faivre S, Temam S, Bourhis J, and Raymond E. End points for new agents in induction chemotherapy for locally advanced head and neck cancers. Ann Oncol 2002;13(7):995-1006. DOI: 10.1093/annonc/mdf172.
[32] Glisson BS, Murphy BA, Frenette G, Khuri FR, and Forastiere AA. Phase II Trial of docetaxel and cisplatin combination chemotherapy in patients with squamous cell carcinoma of the head and neck. J Clin Oncol 2002;20(6):1593-1599. DOI: 10.1200/JCO.2002.20.6.1593.
[33] Hitt R, Irigoyen A, Cortes-Funes H, Grau JJ, Garcia-Saenz JA, Cruz-Hernandez JJ et al. Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Ann Oncol 2012;23(4):1016-1022. DOI: 10.1093/annonc/mdr367.
[34] Alsahafi E, Begg K, Amelio I, Raulf N, Lucarelli P, Sauter T et al. Clinical update on head and neck cancer: molecular biology and ongoing challenges. Cell Death Dis 2019;10(8):540. DOI: 10.1038/s41419-019-1769-9.
[35] First Report Manged Care. FDA Approves Opdivo for Head and Neck Cancer Patients. (https://www.hmpgloballearningnetwork.com/site/frmc/article/fda-approves-opdivo-head-and-neck-cancer-patients).
[36] Liu A. ESMO: Bristol Myers' Opdivo-Yervoy, Pfizer-Merck KGaA's Bavencio hit walls in head and neck cancer. Fierce Pharma. (https://www.fiercepharma.com/pharma/bristol-myers-opdivo-yervoy-pfizer-merck-kgaa-s-bavencio-hit-walls-head-and-neck-cancer).

advanced HNSCC, and unfortunately, these results suggest that this disease remains very challenging to treat."[37] Though the SOC has improved over time, the 5-year overall survival remains below 50%, even for patients in the National Comprehensive Cancer Network-defined "low risk" group.[38] Therefore, there remains a high unmet need for improved outcomes in this population. In Alsahafi 2019, the authors discuss efforts to improve outcomes for HNSCC, noting that "the significant problems associated with high toxicities as well as resistance to current treatments, and low quality of life for patients, make these efforts ***particularly crucial***."[39]

For patients in the Multikine target population, no improvements in overall survival outcomes have been shown since methotrexate was approved in the 1960s, despite advances in treatments for other patient populations. For example, the addition of adjuvant chemotherapy (after surgery) to the standard of care in the early-2000s has led to improvements in overall survival for high-risk HNSCC patients. However, patients in the Multikine target population have a lower disease burden and are not likely to be high risk at surgery, and they therefore would not be indicated for adjuvant chemotherapy.

Although immunotherapies like checkpoint inhibitors have become part of the SOC for many types of cancer, including HNSCC, these are indicated only for recurrent, metastatic or non-resectable HNSCC tumors, in other words—late stage disease, whereas Multikine targets treatment-naïve, resectable primary tumors. Checkpoint inhibitors are also most effective on tumors having high PD-L1 tumor expression, whereas the Multikine population is targeted at tumors having low PD-L1 tumor expression (TPS $\leq$ 10). Accordingly, there are still no immunotherapies indicated for the Multikine target population.

"[I]mmunotherapeutic approaches for HNSCC are particularly complicated by the profound immune suppression that is induced by HNSCC, which potentially lessens the effectiveness of immune stimulatory efforts."[40] In other words, head and neck cancer tumors are particularly resistant to immunotherapies, and CEL-SCI notes eight recent immunotherapy

[37] Kansteiner F. Merck's Keytruda posts rare flop in head and neck cancer trial. Fierce Pharma. (https://www.fiercepharma.com/pharma/mercks-megablockbuster-keytruda-flops-head-and-neck-cancer-trial).
[38] Howlader N, Noone A, Krapcho M, Miller D, Brest A, Yu M et al. SEER Cancer Statistics Review, 1975-2017. National Cancer Institute. (https://seer.cancer.gov/csr/1975_2017/).
[39] Alsahafi 2019.
[40] De Costa AM, and Young MR. Immunotherapy for head and neck cancer: advances and deficiencies. Anticancer Drugs 2011;22(7):674-681. DOI: 10.1097/CAD.0b013e328340fd18.

studies for advanced HNSCC that have failed.[41, 42, 43, 44, 45, 46, 47] These studies involved therapies in multiple different settings, but none were for patients in the Multikine target population, which continues to be underserved by the SOC and ongoing clinical research.

Multikine can meet this unmet need by serving patients who are not well-served by the existing standard of care. This is a critically important factor that FDA has acknowledged.

[41] Burtness B, Haddad R, Dinis J, Trigo J, Yokota T, de Souza Viana L et al. Afatinib vs Placebo as Adjuvant Therapy After Chemoradiotherapy in Squamous Cell Carcinoma of the Head and Neck: A Randomized Clinical Trial. JAMA Oncol 2019;5(8):1170-1180. DOI: 10.1001/jamaoncol.2019.1146.
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[45] Taylor N. AstraZeneca's novel checkpoint inhibitor flunks first phase 3, denting partner's share price. Fierce Biotech. (https://www.fiercebiotech.com/biotech/astrazenecas-novel-checkpoint-inhibitor-flunks-first-phase-3-denting-partners-share-price).
[46] *Id.*
[47] *Id.*

Concluding Remarks

As I said before, based on the data and the science, we believe it is only a matter of time before Multikine becomes part of the standard of care for head and neck cancer. Our Phase 3 clinical data has significantly de-risked our prospective confirmatory Registration Study, which has now received positive support from the FDA and which we hope to commence and complete quickly. We are excited to be working all day every day to improve, extend, and save the lives of cancer patients who might be worse off without these efforts. We thank you all for being a part of it.

Very Truly Yours,

Geert R. Kersten

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