# Shareholder Letter From The CEO

October 25, 2023

# DEAR SHAREHOLDERS

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# Dear Shareholders

This shareholder letter will be longer and much more detailed than prior letters. My goal is to show you the clinical data supporting Multikine's survival benefits, explain how we identified the target population of head and neck cancer patients who should receive Multikine, and describe our efforts with the world's leading regulatory bodies to bring Multikine to market as quickly as possible.

Why are we confident that Multikine should be approved as soon as possible? First, we can clearly identify patients who should get Multikine. Second, Multikine definitely benefits patients by causing pre-surgical responses. Third, the Multikine survival benefit in the target population is outstanding. Fourth, as a statistical matter, another trial is more than 95% likely to be successful and therefore should not be necessary for approval. Fifth, there are regulatory pathways specifically designed for our situation where the target population is selected from the larger Phase 3 study population. We believe that we meet these factors with strong evidentiary support and are eager to move forward.

## A Well-Defined Target Population

Last week at the European Society for Medical Oncology (ESMO) conference—the most important annual European cancer conference—we presented new data on Multikine's efficacy that is far superior to the results we presented last year. We accomplished this by focusing our target population on patients mostly to have pre-surgical responses to Multikine. We identified these patients based on the clinical data, cellular analysis, and advice from regulators and top consultants, including two of the most respected head and neck immuno-oncologists in the world. ***This is a huge achievement***, because it means Multikine patients can be identified *upon diagnosis* with tests that physicians routinely use in cancer screenings. In addition, we can now meet a critical regulatory requirement: the writing of an approval label for Multikine.

## Multikine Undeniably Helps Patients, Period.

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 you have a pre-surgical response, then your survival is greatly improved. Therefore, ***we know that Multikine improves survival for those with pre-surgical responses***. I will show you the data that proves this to be true.

# DEAR SHAREHOLDERS

## THE CLINICAL DATA IS OUTSTANDING

By way of summary, Phase 3 patients in the finalized target population saw the following:

- ✓ ***risk of death cut in half at five years*** versus the 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 downstages (p<0.01); and
- ✓ low PD-L1 tumor expression (vs high PD-L1 where Keytruda and Opdivo work best).

## CEL-SCI HAS ALL THE INGREDIENTS FOR APPROVAL

We can identify *at diagnosis* the patients most likely to have pre-surgical responses to Multikine. The survival statistics in this target population are so good that it is hard to imagine how they could be challenged or ignored. Multikine's safety profile is very favorable compared to other oncology agents. And, we have a manufacturing plant that can make an estimated $2 billion worth of Multikine annually.

CEL-SCI is ready—and we believe patients and doctors are, too. A new drug for our targeted disease (previously-untreated locally advanced primary resectable squamous cell carcinoma of the head and neck) has not been approved by FDA in decades. The current standard of care provides only a 50-50 chance of living past five years. Large companies have tried and failed to improve this figure. Patients desperately need better treatments.

We now have the ingredients for delivering results to investors as well. While the biotech stock market always has its ups and downs, and has been dismal lately, ***the clinical data will stand firm and drive the final success for CEL-SCI.*** We have presented our new data to regulators in Europe and the UK. Canada and the United States (FDA) have not yet seen these data, and we plan to present to them in the next quarter.

CEL-SCI plans to seek approval for immediate patient access to Multikine ***without waiting on the results of a new trial wherever possible***. There are regulatory pathways specifically designed for such approvals that CEL-SCI is pursuing worldwide. These pathways are called "conditional approvals" (or, in the U.S., accelerated approval) which means you can be approved first while a confirmatory study is ongoing and before that study is completed. Our situation—where we have selected a portion of the Phase 3 study for our target population—is precisely why these regulatory pathways were adopted by regulatory bodies, so that patients do not need to wait many years before gaining access to promising drugs that have already been shown to provide clinical benefit.

# Multikine Leads To Longer Life

Multikine's positive clinical outcomes come from the following pathway, which has been definitively proven in our Phase 3 trial:

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

Imagine you are diagnosed with advanced head and neck cancer and you fit the target population. Your doctor immediately puts you on the three-week Multikine regimen. After this, your doctor may say: "your tumor has significantly shrunk" or "you went from Stage III cancer to Stage II." Not everyone gets these responses, but more than 1 out of 3 Multikine-treated patients in the target population of the Phase 3 trial did. For these patients, the five-year risk of death was cut in half. ***That is the power of Multikine.***

## MULTIKINE CAUSES "PSRS" AND "PSDS"

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

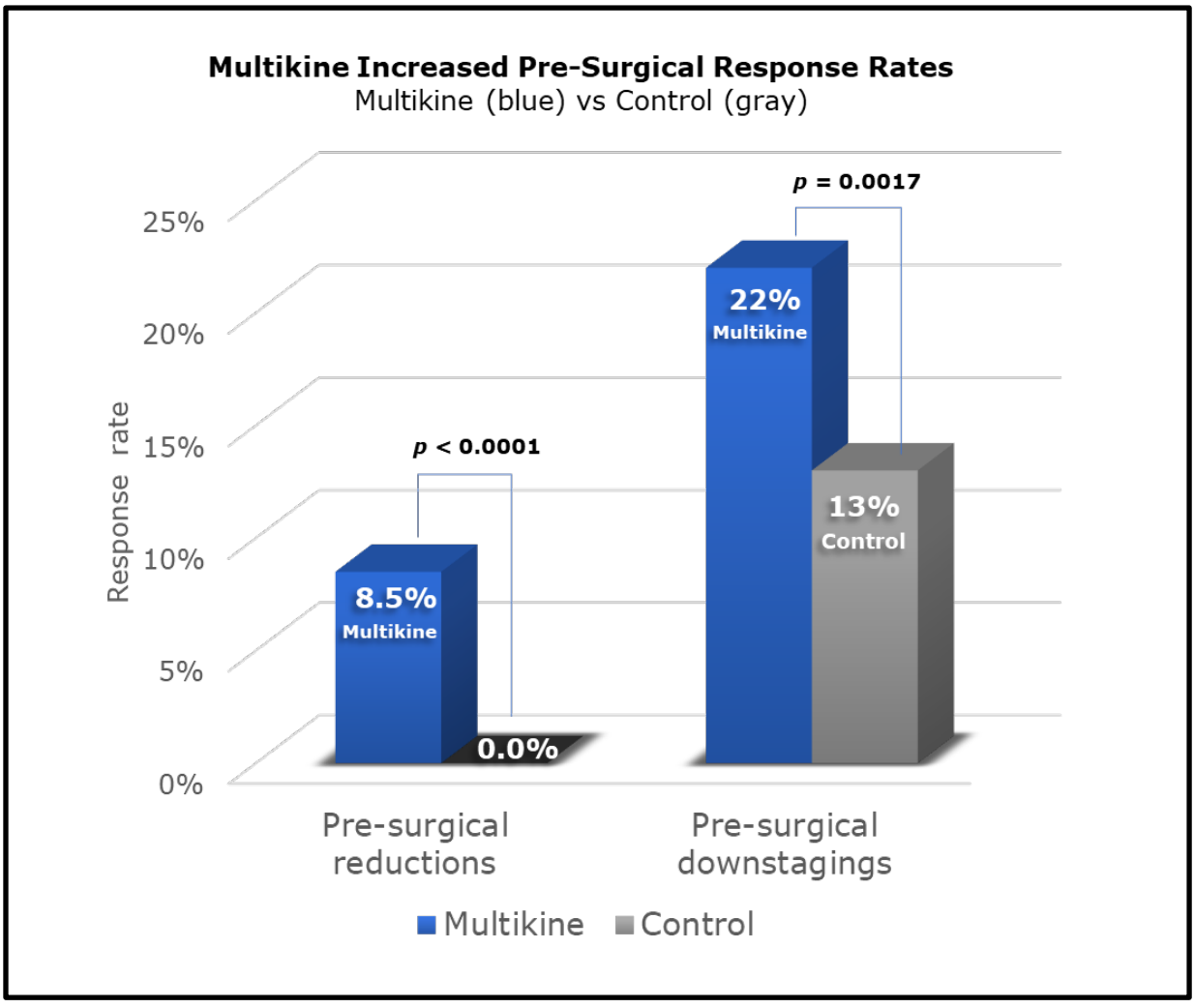
Our 2022 ESMO cancer conference presentation reported on PSR, and our new 2023 ESMO presentation reported on PSD.

Across the whole Phase 3 trial, PSRs were seen in 8.5% of Multikine patients compared to ***zero*** in the control. PSDs were seen in 22% of Multikine patients vs 13% in the control. Because Multikine 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 LEADS TO LONGER LIFE

These data are presented visually below. The taller blue columns show PSR and PSD rates in all 529 Multikine-treated patients in the Phase 3 trial, and the gray columns show PSR and PSD rates for all 394 control patients. The p-values above the columns show comparisons between Multikine and control. A p-value tells how likely it is that the results are due to the treatment, rather than random chance. The smaller the p-value, the more confident one can be that Multikine was the cause of the difference. A p-value of 0.05 or less means there is at least a 95% chance that the results of a study were caused by the drug rather than by random chance. Thus, a p=0.05 or less is generally accepted as "statistically significant."

***With Multikine, the low p-values show that there is more than a 99.8% chance that the increases in PSR/PSD in the Phase 3 study were caused by Multikine.***




We note that these results are from ***the entire Phase 3 study population***, not from a subgroup, which means we did not "data mine" to show these benefits. These data show definitively and without a reasonable doubt that Multikine caused these PSRs/PSDs.

# MULTIKINE LEADS TO LONGER LIFE

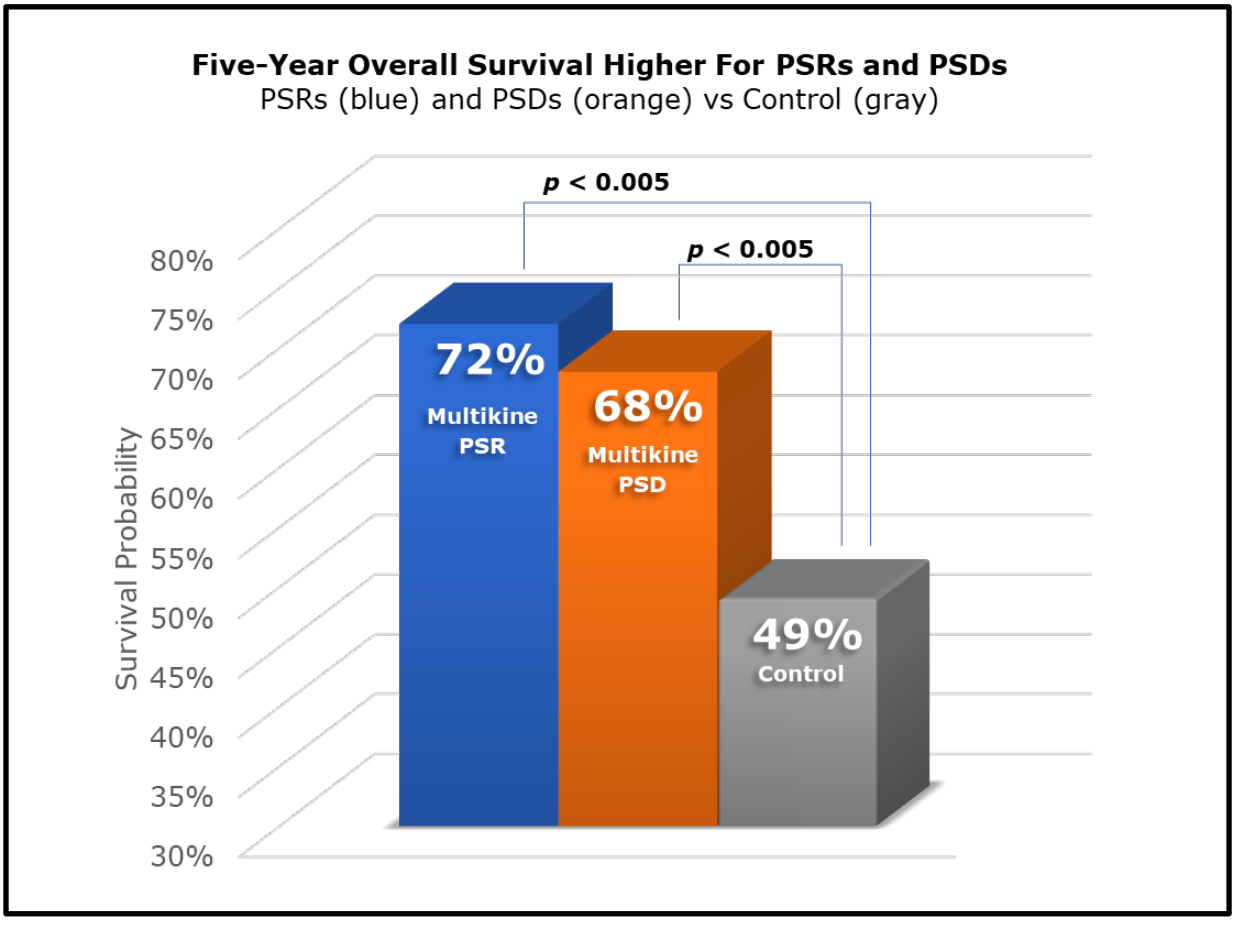
## PSRs and PSDs Lead To Longer Life

It was not enough for us to prove that Multikine lead to PSRs and PSDs. We also had to prove that PSRs and PSDs lead to improved survival. And we did so successfully.

PSR patients were 72% likely to be alive after five years, whereas control patients were only about 49% likely to be alive after five years. Patients with PSD saw similar improvement: their five-year chance of survival was about 68%. Therefore, patients who had PSR or PSD from Multikine lived a lot longer than those without Multikine.

I note that these results are from the entire Phase 3 study population, not from a subgroup. ***The p-values of less than 0.005 means there was at least a 99.5% chance that these results are due to Multikine rather than random chance.***

The likelihood of living at least five years is shown in the graphic below for patients with PSR (blue), patients with PSD (orange) and patients who did not receive Multikine (gray).




In sum, Multikine's ability to cause PSR/PSD, which extend survival, proves once and for all that Multikine helps patients.

# Finalizing Our Target Population

Having proved the causal link between Multikine and survival benefit, Multikine is poised for success. But recall our announcement in 2021 that the Phase 3 study's primary endpoint of 10% survival benefit was not met. You may wonder: How then can we be so sure that Multikine actually benefits patients? The answer is simply this: while Multikine clearly helped patients with PSR/PSD, there were simply not enough PSR/PSD in the Phase 3 study population to yield a 10% survival benefit for the whole population. In other words, the benefits from PSR/PSD were too diluted when averaged with the other patients in the study.

None of this changes the fact that Multikine caused PSR/PSD and that these PSR/PSD led to a higher chance of living five years or longer—we simply had to define a target population who would have a larger number of PSR/PSD. To do so, we analyzed Multikine's biological mechanism of action, talked to regulators and physicians who knew best, and were guided by the Phase 3 data, ***including patient-specific data down at the cellular level***.

All this of course took time, but we have succeeded and are ready to move forward.

### 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 5-year survival benefit vs control. It made sense biologically 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 no lymph nodes invaded by the tumor (N0) or only one lymph node invaded by the tumor (N1) as well as no extracapsular spread 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 improved if the N1 patients were excluded, and only the N0 patients were included in the target population.

### Low PD-L1 Tumor Expression

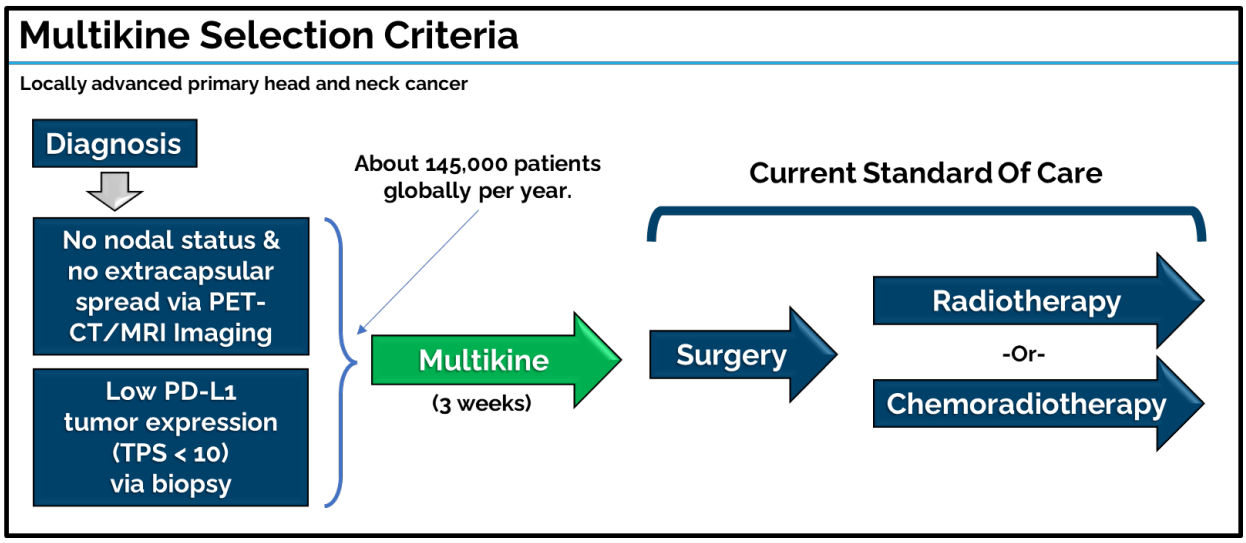
We also saw from the Phase 3 data that Multikine was more effective for patients with low PD-L1 tumor expression than for patients with high PD-L1 expression. (This analysis was pre-specified in the statistical analysis plan, so we didn't hunt for it.) PD-L1 is a protein receptor on the tumor surface 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. Low PD-L1 patients represented about 70% of the study population.

# FINALIZING OUR TARGET POPULATION

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 before surgery, even if such approvals came in the future, the large majority of patients in this group having low PD-L1 would still be expected to need Multikine.

## Defining The Population Upon Diagnosis

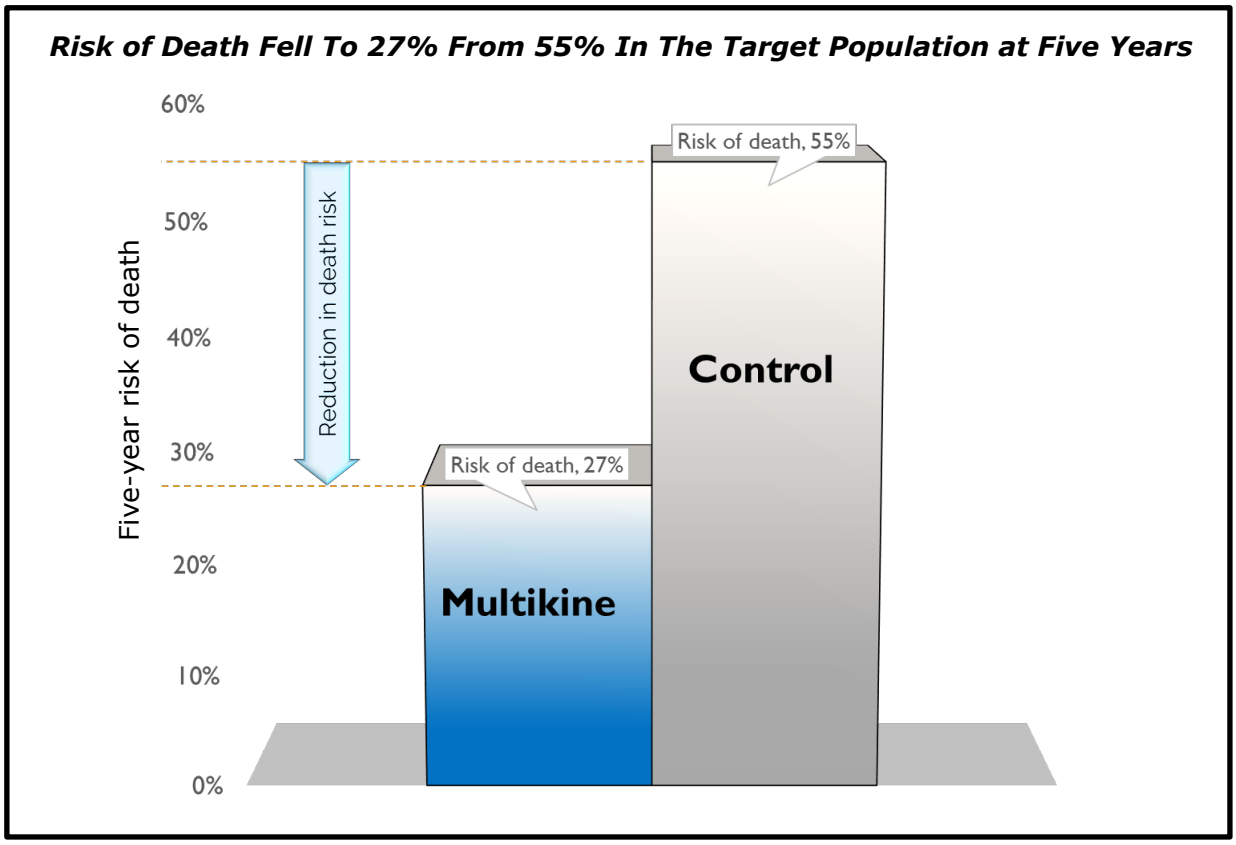
Our target population is now directed to patients who present at diagnosis with N0 nodal involvement and no extracapsular spread and also with low PD-L1 tumor expression (defined as tumor proportions score (TPS) < 10). These patients can be readily identified upon diagnosis with tests that physicians routinely use in cancer screening, a crucial achievement towards Multikine becoming available for use. For instance, a PET scan should be used to determine the N0 nodal status and no extracapsular spread, and a screening biopsy should be used to determine the low PD-L1 expression. Doctors already routinely screen head and neck cancer patients using PET scans and biopsy. This is another reason why we are so excited about where we are now—no new tests, no new costs.



# Superior Results In The Target Population

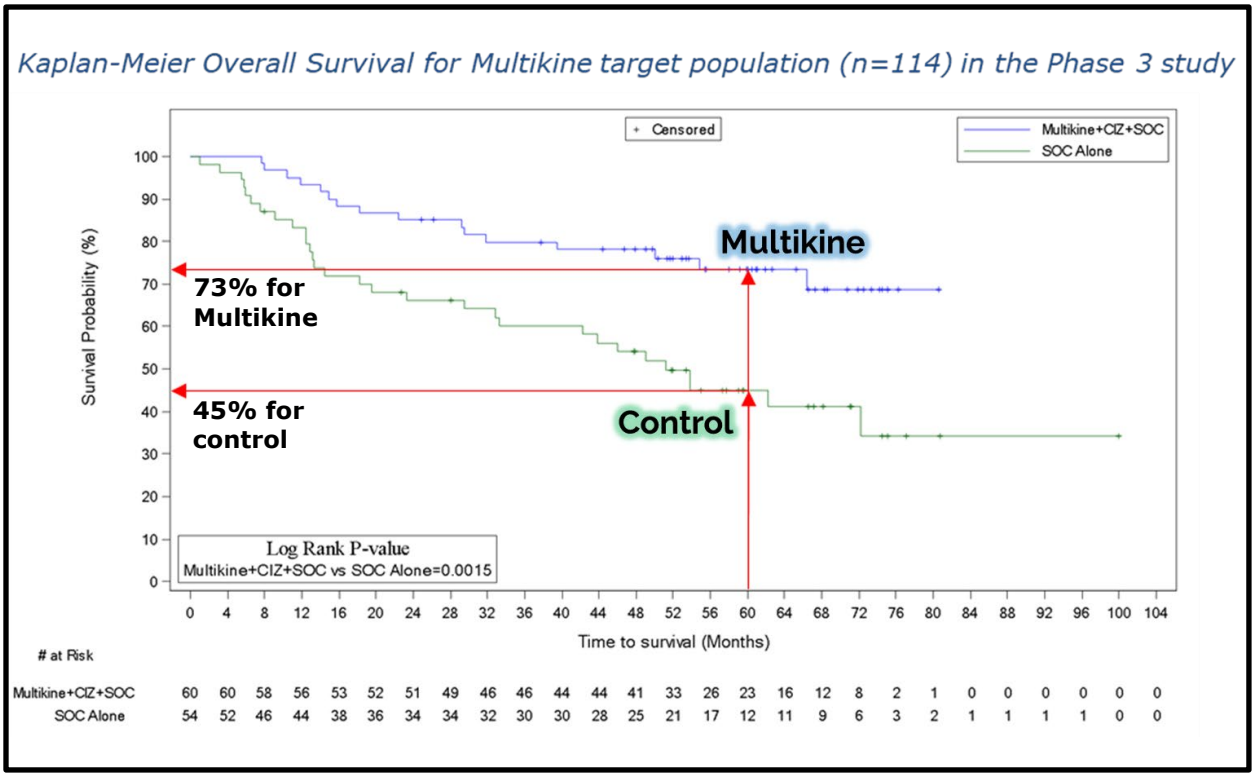
Our results show that Multikine ***cut the risk of death in half at five years*** versus the control in the finalized target population. Survival increased from 45% in the control group to 73% in the Multikine group at five years. This means the risk of death fell to 27% in the Multikine group from 55% in the control, shown below.

***Risk of Death Fell To 27% From 55% In The Target Population at Five Years***



# SUPERIOR RESULTS IN THE TARGET POPULATION

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. These results had a low p-value of 0.0015, which is very significant as a statistical matter.




Our physician consultants tell us that the early separation of these two survival curves (e.g., at 12 months) further confirms that these effects are real.

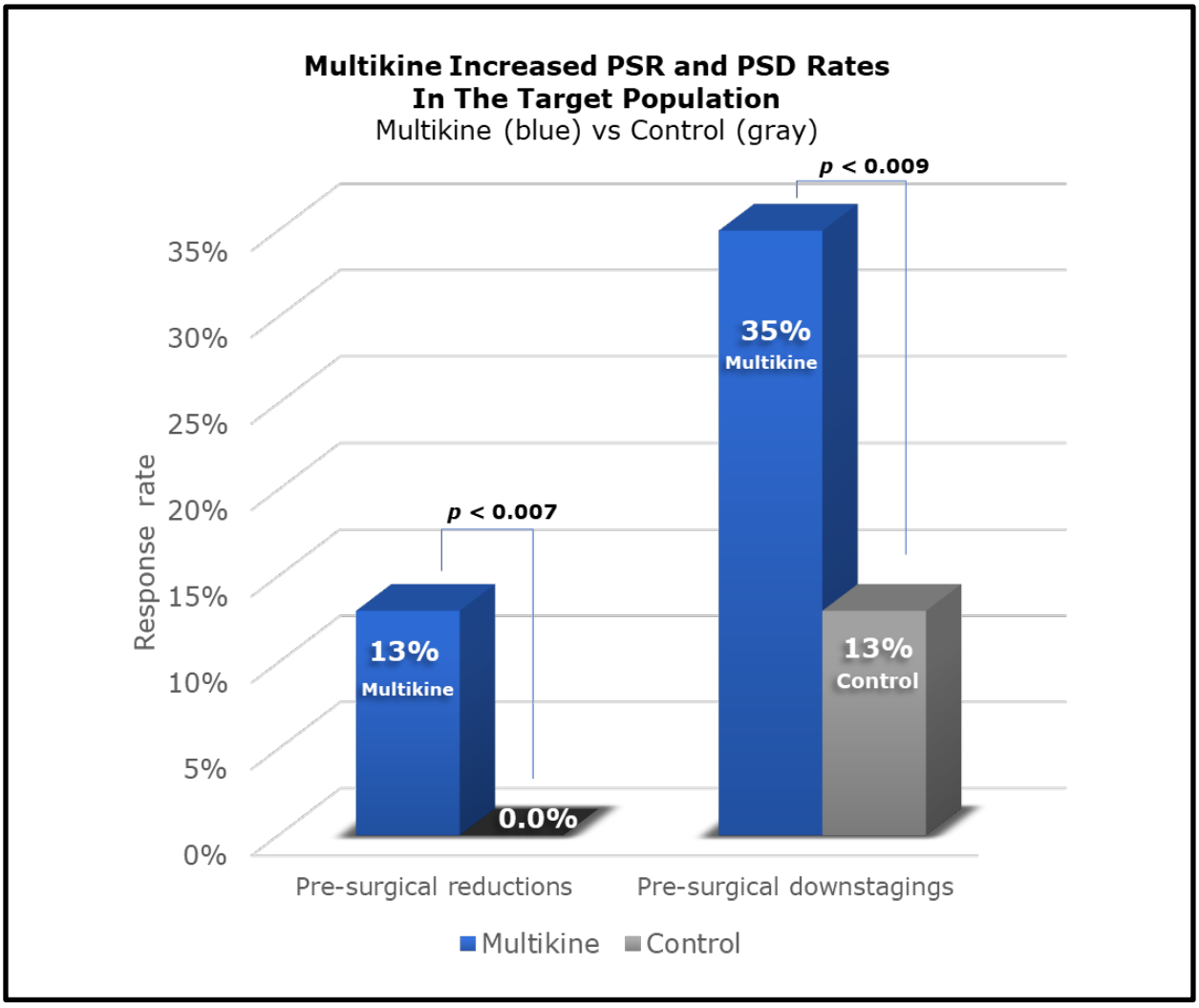
Another measure of survival benefit is called the “hazard ratio,” which compares the chances of dying between two different groups. In cancer trials, a hazard ratio helps to see if a new treatment is better or worse than the standard one. If the hazard ratio is 1, it means both groups have the same risk. If the hazard ratio is more than 1, it means the treatment group has a higher risk than the control, which is bad. If it is less than 1, it means the treatment group has a lower risk than control, which is good. Here, in the new Multikine target population, the hazard ratio was 0.35, which means that deaths occurred in the Multikine group about one-third as frequently as in the control group.

It is also extremely important to note that the hazard ratio’s “95% confidence interval” remained far below 1.0. A confidence interval is a range of values within which one reasonably expects the true or actual hazard ratio to be. In the case of Multikine, statistically speaking, there is a 95% chance that the hazard ratio would fall between 0.18

# SUPERIOR RESULTS IN THE TARGET POPULATION

and 0.66 if Multikine were tested in the target population in another study. A hazard ratio of 0.66 as the "so called worst case scenario" is still below (better) than the hazard ratio required for most drug approvals. This is why we believe Multikine is approvable without waiting for the results of another study, which is statistically >95% likely to succeed.

These positive survival outcomes—increased overall survival, reduced risk of death, widely separated Kaplan-Meier curves with early separation, low hazard ratio, low p-values, low confidence intervals—were driven by high PSR/PSD rates in the target population, as shown in the graphic below:




All of these data together support CEL-SCI's confidence that it can request approval in the new target population without waiting until the completion of another clinical trial.

# Our Pathway To Approval: Patient Need

Our regulatory strategy going forward is to seek immediate approval of Multikine wherever possible. ***We believe that Multikine should be approved based on the data generated to date, using a conditional approval pathway with a follow-on confirmatory study since the survival benefit is high and statistics are so strong***. This view is based on advice from the regulators and consultants I mentioned above, and the conditional approval regulatory pathways are specifically designed for our situation.

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

## A Compelling Patient Need For Multikine's PSRs and PSDs

When the Phase 3 trial was designed, there was no evidentiary basis for excluding either of the low-risk or high-risk patient groups before surgery. Therefore, the study had to include a large percentage of high-risk patients with immune systems already compromised by disease. These subjects generally did not respond to Multikine. CEL-SCI has narrowed its target population as compared to the overall Phase 3 study population to focus on patients most likely to have PSR/PSD and to exclude the rest.

***We acknowledge that efficacy in the target population has not been tested prospectively, but the data generated to date already present a compelling patient need in the target population that justifies immediate access to Multikine***. This is why the conditional approval pathways were created in the first place. We believe that patients should not have to wait many more years before gaining access to the benefits of Multikine PSRs/PSDs and increased survival, particularly given Multikine's safety profile and data that mechanistically and empirically supports the target population definition.

The benefit-risk balance strongly favors immediate patient access to Multikine:

**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

# OUR PATHWAY TO APPROVAL: PATIENT NEED

## Unmet Need For Improved Survival

An "unmet need" is a factor for approval considered by all major regulatory bodies worldwide. In the Multikine target population, there is also a tremendous unmet need for improved survival. The current standard of care provides only about a 50/50 chance of surviving five years, whereas Multikine could increase that survival rate to over 70% based on the Phase 3 data. Chemotherapy has improved outcomes for some head and neck patients, but chemotherapy is only indicated for high-risk patients, who are not likely to fall within the Multikine target population. Currently available immunotherapies are given after surgery or where surgery is not indicated, in contrast to Multikine, which is given before surgery to patients with resectable tumors. Available checkpoint inhibitors work best on tumors with high PD-L1 expression, whereas Multikine works best in tumors with low PD-L1 expression. Therefore, Multikine's target population is underserved, and will continue to be underserved, by current therapies, but Multikine can meet the need for improved survival.

## Our Regulatory Plan Going Forward

The major regulatory bodies we are working with all have conditional approval pathways designed for situations where the target population has not been fully tested prospectively and there is strong data supporting clinical benefit for patients. The reason is that regulators understand that in many cases patients should not have to wait for additional data before being offered the chance to benefit from a new drug. Every situation is different and depends on the specific facts. We believe our data already clearly shows benefit and that patients should get that benefit as soon as possible.

We had meetings with the FDA and Health Canada earlier this year, but they have not yet seen these new data, and we are excited to provide it to them in the coming months. In Canada, we plan to ask for conditional approval under their Notice of Compliance with Conditions (NOC/C) pathway, as they had suggested. This permits approval of drugs based on safety and "promising" efficacy data while a post-market confirmatory study is ongoing. The approval can be given ***before*** the post-market study. In the U.S., the FDA has an accelerated approval pathway that is similar, but a new law in December 2022 requires enrollment in the confirmatory study to be underway before approval will be given in the U.S. Therefore, we plan to start this confirmatory trial as soon as possible in the new year and will then seek accelerated approval using data from that study as well.

Our first priority, however, is seeking approval in Europe and the UK, as there are more than twice as many patients in the target population overseas than in North America. In Europe, we have submitted requests for Scientific Advice and are hopeful for meetings by the end of January 2024. It is possible we could know before the end of January 2024 how our data is perceived by European regulators. In the UK, we have requested a meeting and are awaiting their response. Once a meeting date has been set, we will be able to discuss the data and gain advice on the path forward. It is possible that we may be advised at that time to proceed with formal application papers. If that occurs, it would be very good news for the Company indeed. We are hopeful for a meeting in December 2023.

# Advice From True Experts

In addition to the consultants from University of California San Diego and Yale Medical School that we mentioned in our October 23 press release, we are excited to announce that one of Europe's leading head and neck oncologists, Dr. Mehmet Sen, MD, FRCR, has joined our consulting team. Dr. Sen has been treating head and neck cancer patients for more than 30 years, and he continues to do so today. He is a Consultant Clinical Oncologist & Honorary Senior Lecturer at the St. James Institute of Oncology in Leeds, UK, where he had been their Clinical Lead from 2010-2020. In addition to his clinical work, Dr. Sen is a Council Member of the British Association of Head and Neck Oncologists (BAHNO) and a Member and former Chair of the European Society for Radiotherapy and Oncology (EORTC) Head and Neck Cancer Group. He is a co-author on more than 100 peer-reviewed publications on head and neck cancer and is a regular reviewer of submitted abstracts and articles for scientific meetings and journals on head and neck cancer. Dr. Sen has been a teacher and lecturer, including teaching for the European Society for Therapeutic Radiology and Oncology (ESTRO) on "Evidence Based Oncology and Methodology of Clinical Trials." He is the radiotherapy UK representative on the scientific program committee of ESTRO and for the biannual meetings for the International Congress on Innovative Approaches in Head & Neck Oncology (ICHNO). Dr. Sen is also a Principal Investigator and trial management group member for six ongoing prospective clinical trials in head and neck cancer. Needless to say, we are extremely excited to have Dr. Sen's advice and wise consult.

## Our Value Proposition For Investors

We believe our company is significantly undervalued. The benefits for patients demonstrated by Multikine in the Phase 3 trial—PSRs and PSDs that lead to longer life—are undeniable. The remaining question was whether we could define a population that captures enough of these responders to result in a survival benefit overall. We have achieved this and we are now strongly hopeful for approval based on these data.

Let me leave you with the following thoughts. Many successful cancer drugs have been purchased by big pharmaceutical companies for multiple billions of dollars. All of these companies had to de-risk their data and regulatory path before those sales occurred. We are in the process of doing just that. We think that we will also end up partnering Multikine with a big company, in part because Multikine needs to be developed for many other cancers as well. Therefore, we expect that the path for bringing Multikine to market and the path towards partnering with a big company are one and the same.

Some of you may remember that in 2018 our stock went as low as $0.82 and few gave us a chance for a comeback. Then in 2021 our stock hit $41. The stock price of any clinical-stage biotech company is obviously not a true reflection of the underlying business, partly because so much of the information is unavailable to the market and also because much of the price fluctuation is driven by short term speculation. What stands solid in this storm is the clinical data, and I continue to believe that survival data in a cancer drug is a big deal that will lead to drug approval. Once you know that a cancer drug works to extend life, you have eliminated the biggest risk. The next biggest risk is that you cannot define the patient population for an approval label, but we have eliminated that risk as well. We believe our success is only a matter of time now.

# Parting Words For Now

The future for CEL-SCI is bright. We have finally achieved what we have worked on for so long—proof that Multikine works and a way to identify the patients who need it. We have world-class advice and are actively engaged with regulators worldwide.

In our view, based on the data and the science, it is only a matter of time before Multikine becomes part of the standard of care for head and neck cancer. We are excited to be working all day every day to try to improve, extend, and even save the lives of cancer patients who might be worse off without these efforts. We are grateful that you're a part of this project, and I look forward to the next letter.

Very Truly Yours,

Geert R. Kersten

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