Leukocyte Interleukin, Injection (LI) Immunotherapy

Neoadjuvant Immunotherapy for Head and Neck Cancer: Low Tumor PD-L1 Expression - *IT-MATTERS – RCT*

By: Eyal Talor*, Philip Lavin, Jozsef Timar, Dusan Markovic, John Cipriano

Conflict of Interest Statement

***Dr. Talor (PhD)**

- CSO, CEL-SCI Corporation, inventor and developer of Leukocyte Interleukin, injection (Immunotherapy)

Dr. Lavin (PhD)

- Independent Biostatistician consultant to CEL-SCI – Principal/Founder Lavin Consulting LLC

Prof. Dr. Timar (MD, PhD, DSc)

- Academic Pathologist (Pathology KOL consultant to CEL-SCI) – Phase 3 Study, Director Central Pathology Laboratory, Semmelweis University

Dr. Markovic (MD)

- Vice President Global Medical Affairs, Ergomed Group (Phase 3 Study CRO's Head Physician)

John Cipriano (MSc, RPh)

- Senior Vice President Regulatory Affairs, CEL-SCI Corporation

LI-Multikine Immunotherapy: What, When, How, Who, & Why

Natural	LI-Multikine is a mixture of cytokines and other small molecules with immune-cells boosting capacity, that naturally occur in our bodies
First-line (neoadjuvant)	LI-Multikine is given ***right after diagnosis***, before surgery, when the immune system is not yet affected by surgery, radiation, chemotherapy, or disease progression
Immune System Activation	LI-Multikine ***activates the immune system*** (cellular components) to recognize and attack the tumor, as well as directly killing the tumor cells
Target population	The target population is locally advanced primary head and neck cancer patients which present with no lymph node involvement and with low PD-L1 tumor expression (about 145,000 p.a. globally)
RCT Phase 3 results in the target population	LI-Multikine ***reduced the risk of death by 50% at five years*** versus the control. No systemic toxicities or LI-Multikine-related deaths in 529 LI-Multikine-treated subjects

What is LI-Multikine?

- LI-Multikine is a cGPM Manufactured investigational immunotherapy - a mixture of pro-inflammatory (and other) cytokines.
- A combination of proteins derived from the stimulation of allogeneic normal blood-donor PBMCs, in short-term culture.
- LI-Multikine is available off-the-shelf (2-yr shelf-life at -20 degrees centigrade).
- LI-Multikine (a biologic) containing cytokines for cancer treatment - has a proven physiologically mediated mechanism of action*.
- Resulting in an effective and less toxic cancer therapy

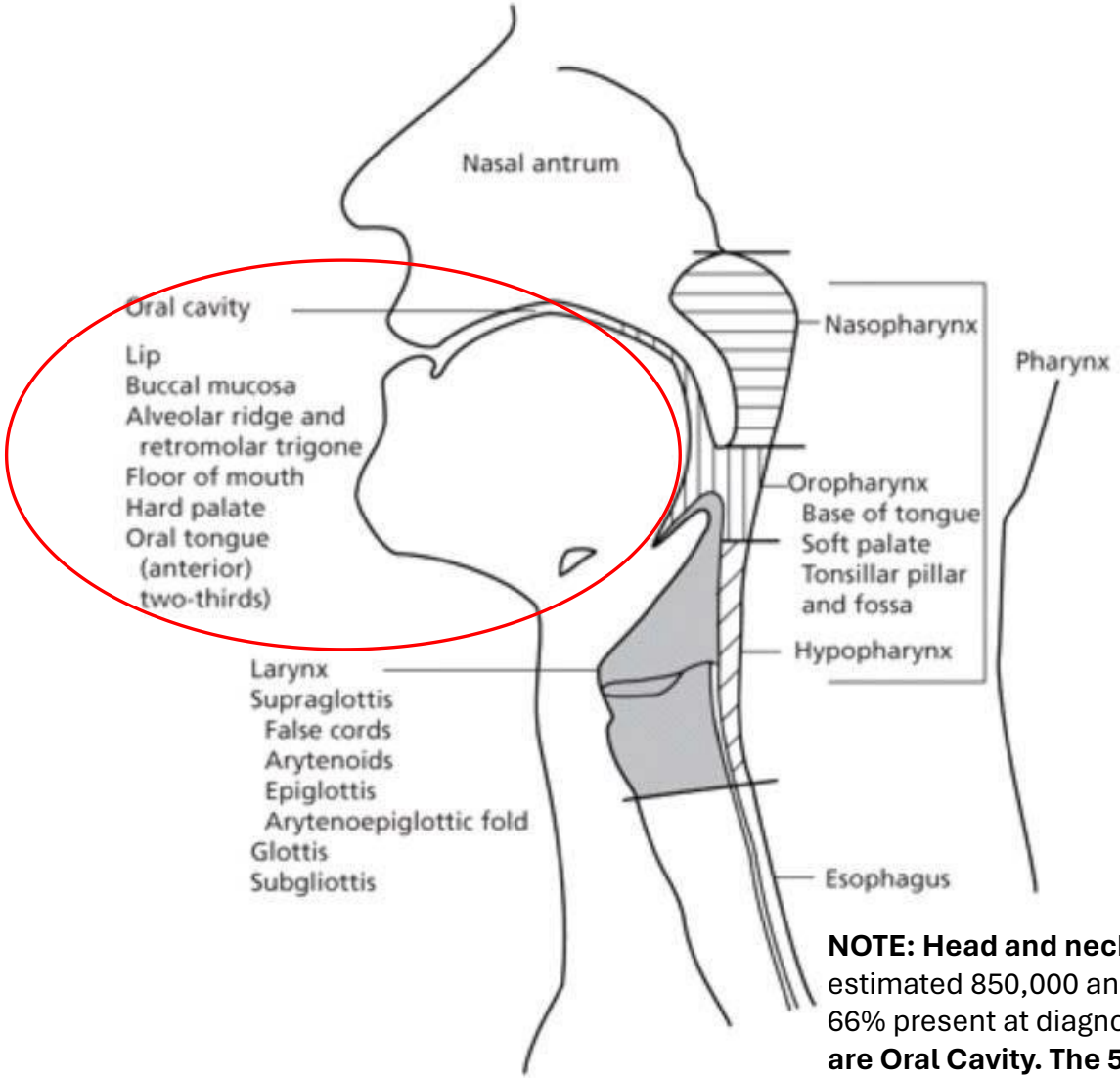
  Key features:

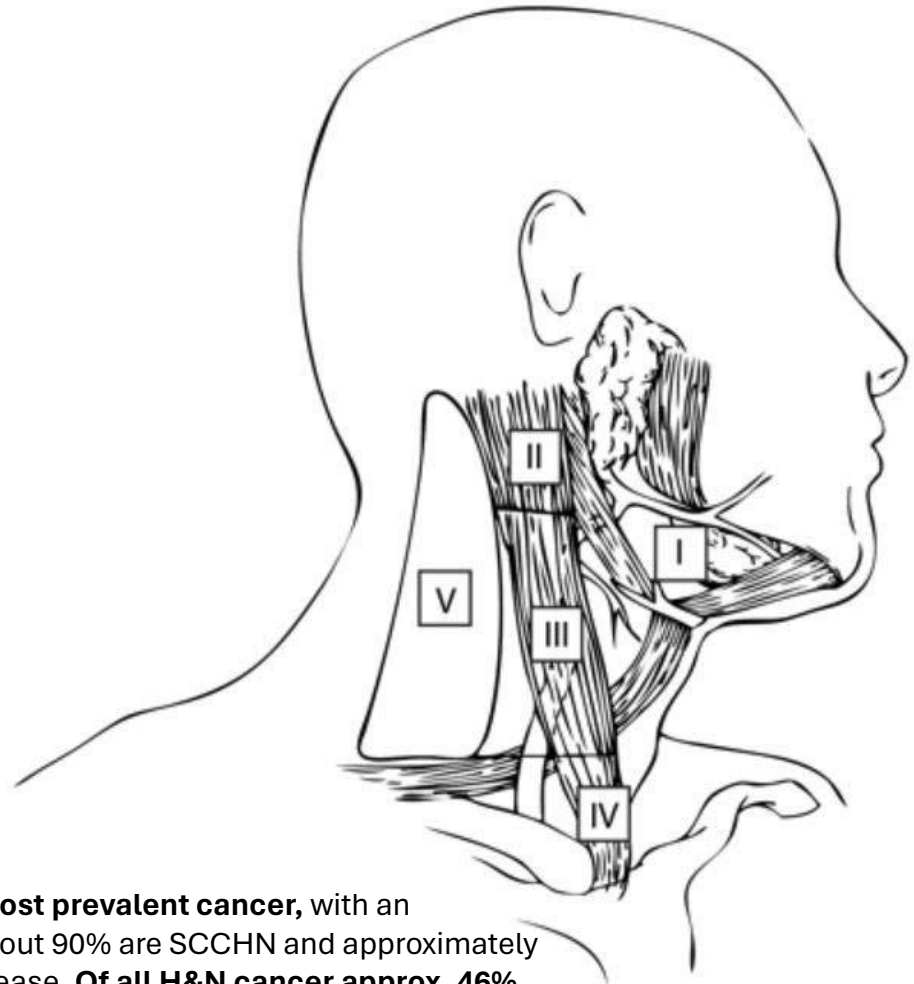
  - LI-Multikine is delivered locally, not systemically, in low dose to avoid toxicity seen in other cytokine treatments.
  - LI-Multikine is administered as a neoadjuvant while the immune system is still intact (Prior to the First Standard of Care therapy).

Major Cytokine(s) and other Cellular Products in Multikine	
IL-1 α	IL-6
IL-1β	IL-8
IL-2	TNF-β
IL-3	G-CSF
TNF-α	RANTES
IFN-γ	MIP-1α
GM-CSF	MIP-1β

*Published: Timar et al., JCO, 2005;
Results of the RCT Phase 3 presented at: ASCO 2022, ESMO 2022 and 2023, ECHNO 2023, ESTRO 2023, and AHNS 2023

Cartoon Adapted from: NCCN Guidelines – Standard of Care

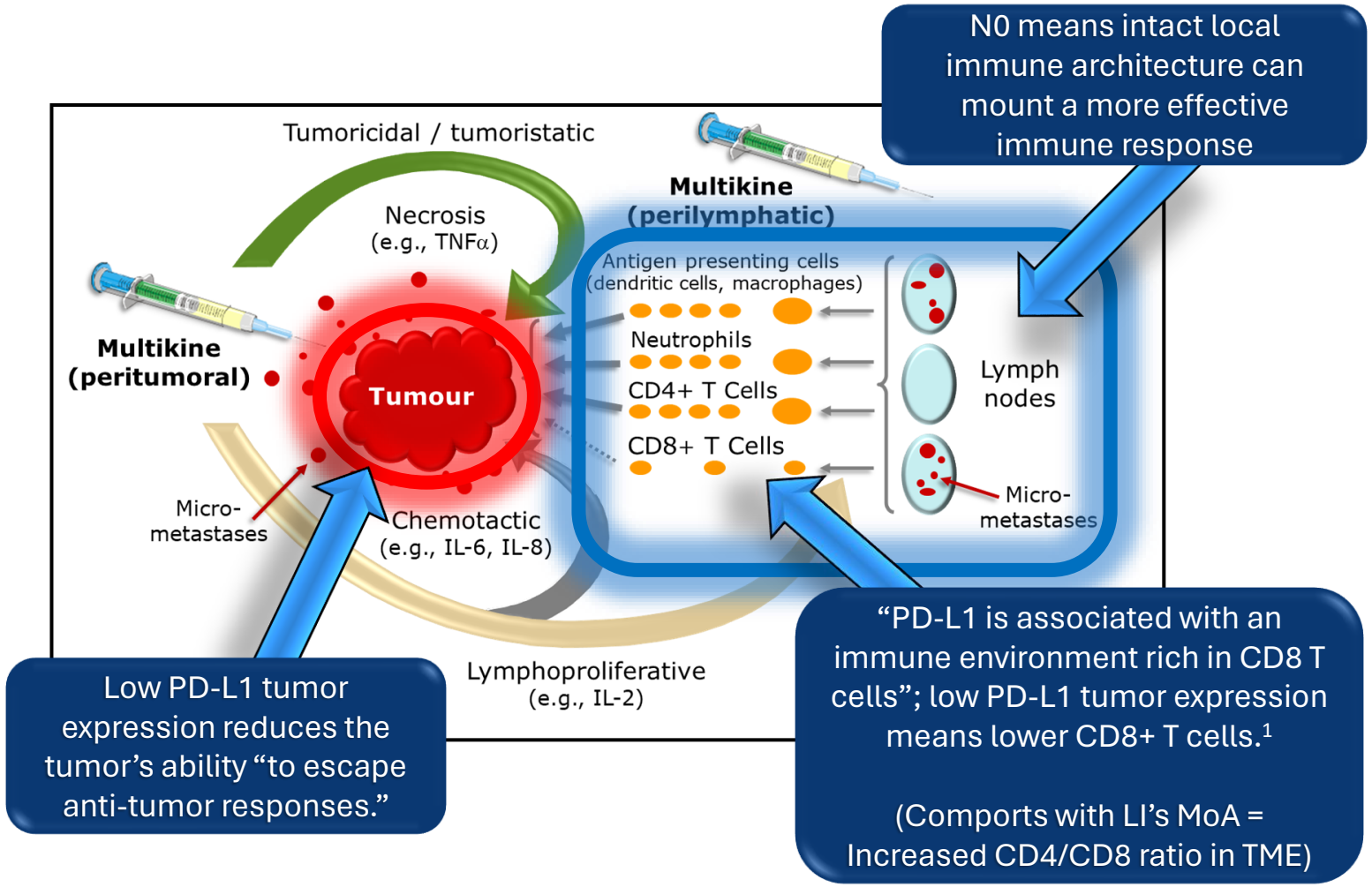




NOTE: Head and neck cancer world's 6th most prevalent cancer, with an estimated 850,000 annual cases globally; about 90% are SCCHN and approximately 66% present at diagnosis with Advanced Disease. **Of all H&N cancer approx. 46% are Oral Cavity. The 5-yr Overall Survival of locally advanced disease patients is <50% when treated with SOC - a clear unmet medical need.**

LI-Multikine Mechanism of Action

- LI-Multikine activated immune cells potentially may:
  - Recognize and present to immune cells or bind to multiple (different) antigens (or receptors) on the cancer cells.
  - Signal the immune system to produce an anti-tumor immune response.
  - Directly affect/kill tumor cells.
- The various cytokines present in the LI-Multikine e.g., TNF, IL-2, IFN, along with other cytokines, are responsible for this potential activity.
- Clinical and histopathology data demonstrates augmentation of the type of cells that infiltrate and attack the tumor changing the tumor microenvironment (e.g., ratio of CD4/CD8 cells from CD-8 cells to predominantly CD-4 cells).
- These CD-4 cells have the potential to bring about local anti-tumor immune response



1. Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res*. 2020;10(3):727-742. Published 2020 Mar 1. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7136921/).

RCT LI-Multikine Phase 3 Trial Design

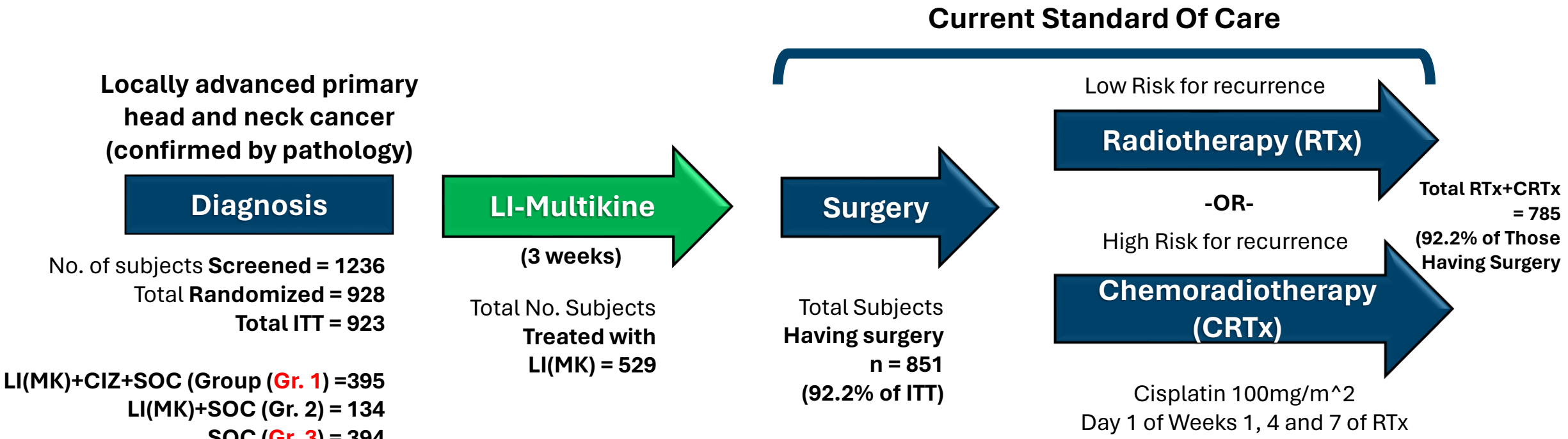
Schematic: Randomization and Treatment of Enrolled Patients with Disease Stage III and IVa

Note: The **overall survival comparison is made between groups 1 and 3**. The primary purpose of the smaller Group 2 is to gain additional information on the mechanism of action and toxicity of Multikine. CIZ is added to decrease tumor suppressor mechanisms and thereby is thought to increase Multikine's effectiveness.

* CIZ: Cyclophosphamide 300 mg/m^2 (x1,IV, day -3); Indomethacin 25mg tid, po (day 1 to 24 hrs prior to surgery) + 15 - 45mg Zinc (as Multivitamin) i.d., p.o.
** Surgery: complete surgical resection of primary tumor and any positive lymph nodes.
*** High risk patients are per NCCN Guidelines

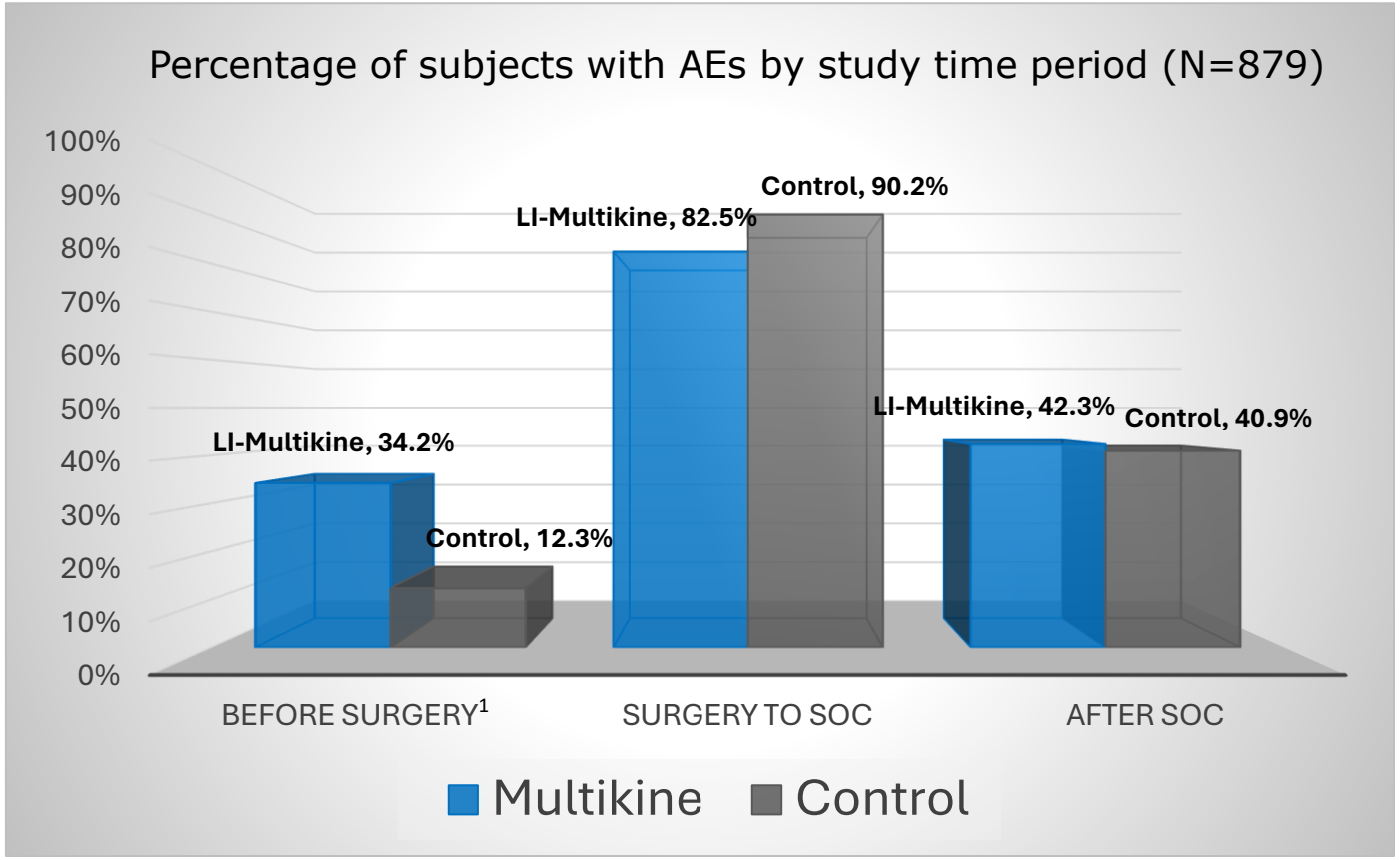
RCT - Phase 3 Locally Advanced OSCC and Soft Palate (ITT=923): LI-Multikine Treatment Timing and Regimen

LI-Multikine administered prior to the current Standard of Care, delivered locally via injections around the tumor and adjacent lymph nodes for three consecutive weeks, 5 days per week before surgery:



“First – Do No Harm” - LI-Multikine Demonstrated Excellent Safety Profile

- No LI-Multikine-related deaths.
- Only two withdrawls due to LI-Multikine (pyrexia, oedema) both known and listed in the IB
- LI-Multikine-related adverse events before surgery were local and resolved after surgery.
- Adverse event rates in the LI-Multikine and control groups were not significantly different.



1. The post-randomization/pre-surgery interval is not adjusted for SOC (median 12 days) vs LI(MK) (median 35 days), thus requiring a 2.92 multiplier to adjust (resulting in a TEAE rate of 35.7%). All other intervals did not have time differences, thus not requiring adjustment.

Target Population for LI-Multikine: Clearly Defined And Well-Understood

- Locally Advanced primary head and neck patients who present with:
  - **No lymph node involvement (N0)** (via PET-CT/MRI)
  - **Low PD-L1 tumor expression** (via biopsy)

- Physicians routinely assess these features at baseline as part of standard practice.
- This population represents about 145,000 patients globally per year.

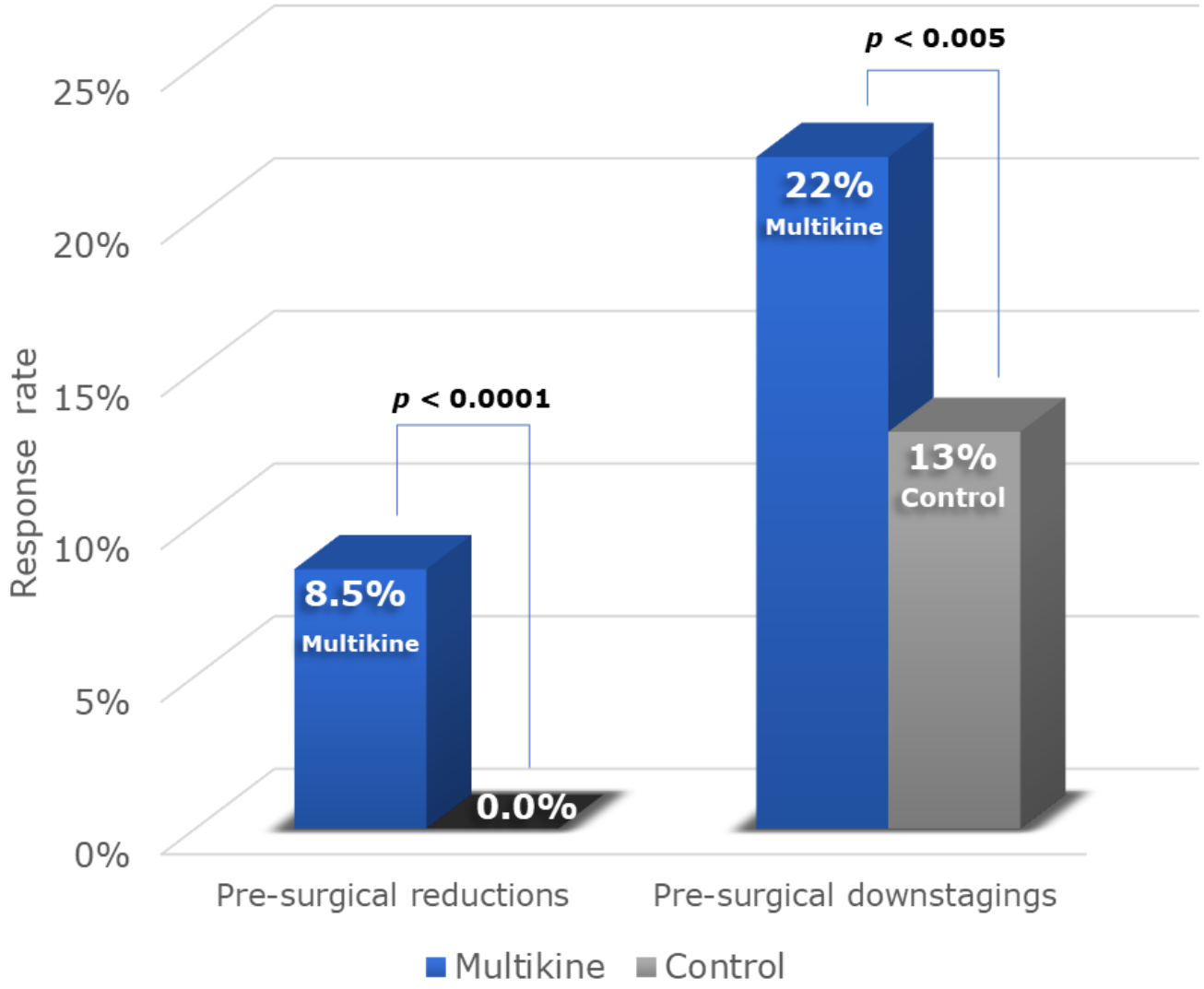
Pre-Surgical Responses In The Phase 3 Trial

- **A pre-surgical response is a significant change in disease *before surgery*.**
  - These emerged just a few weeks after treatment onset.

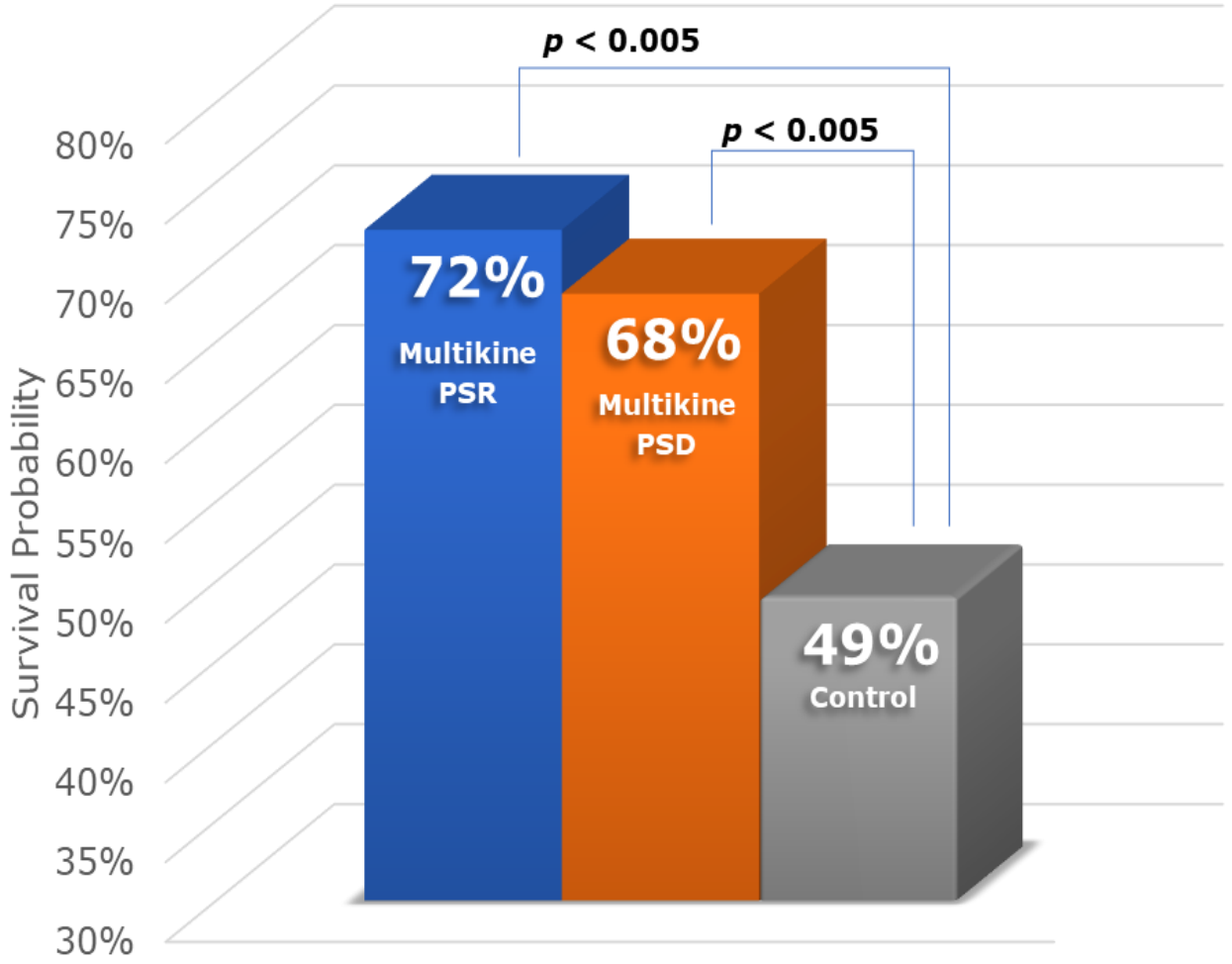
- **We saw two kinds of responses in the Phase 3 trial:**
  - ***"Tumor reductions"*** - There were "reductions" in the size of the tumor - a reduction of 30% or more qualified as a "pre-surgical reduction (PSR)" (per RECIST – confirmed by Pathology at surgery)
  - ***"Disease downstages"***- There were disease "downstages," e.g., the disease improved from Stage IV to Stage III (per AJCC). Referred to as: "pre-surgical downstaging (PSD)"

Pre-surgical responders saw improved 5-year survival - Advantage for LI-treated vs Control

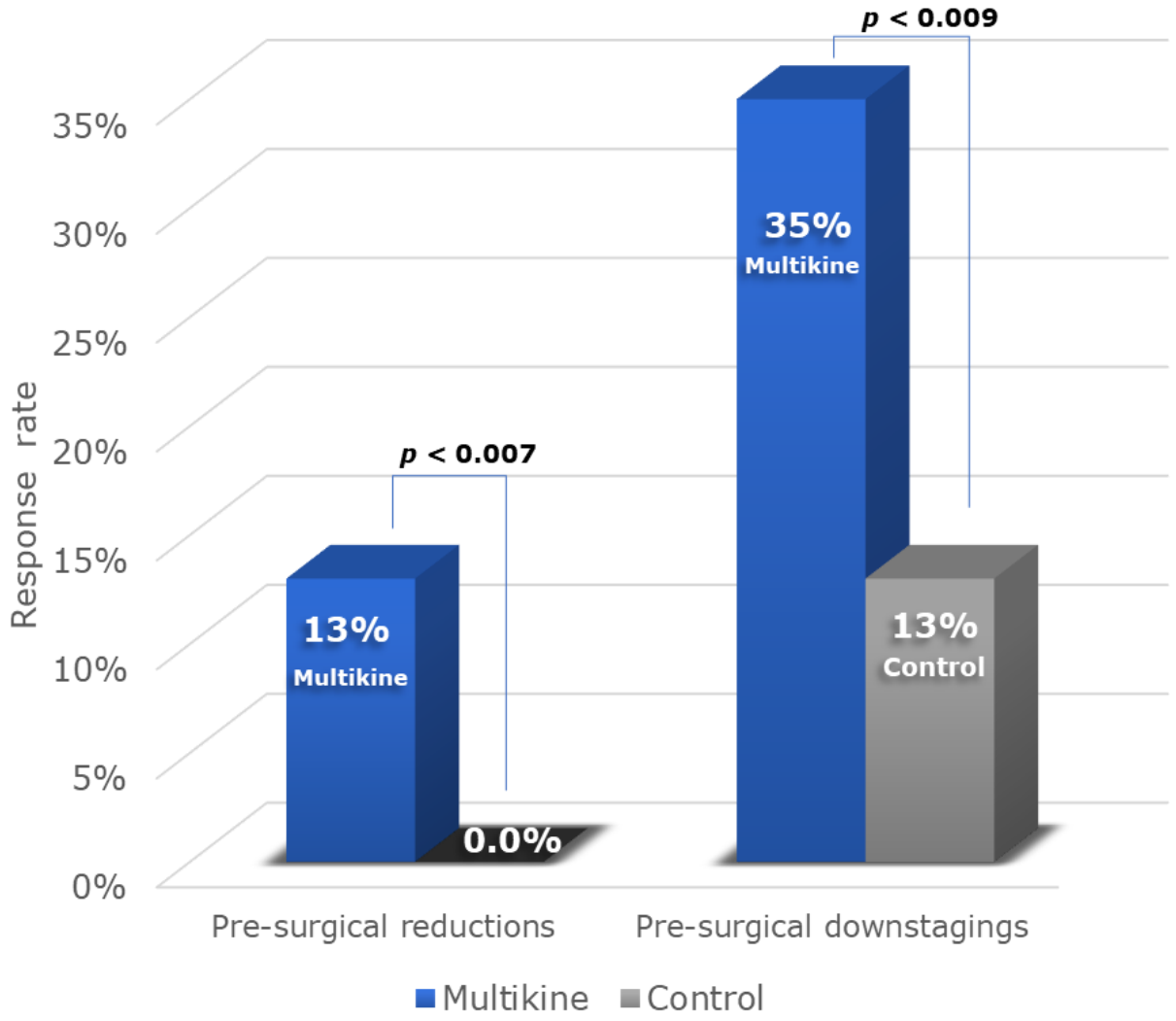
Significant Increase In PSRs/PSDs Across The Phase 3 Study ITT Population (n=923)



PSRs/PSDs Resulted In Significantly Improved Survival Across The Phase 3 Study ITT Population (n=923)



Higher PSR/PSD Rates In The Target Population (N0 [no ECS], tPD-L1 TPS <10) (n=114)



Cellular Biomarkers and Ranges Pre-defined for Pathology Immunohistochemistry

Prospectively Defined Biomarkers (2 [L/H] or 3 levels [L/M/H])

1. p16: 10% positivity threshold
2. HLA: L<45, H>90
3. B2M: L<40, H>80
4. MR1: L<50, H>100
5. TPDL1: L<1, H>50
6. CD4: L<600, H>1200
7. CD8: L<400, H>800
8. CD3: L<1000, H>2000
9. FOXP3: L<250, H>500
10. CD20: L<250, H>500
11. CD68: L<50, H>100
12. CD163: L<60, H>120
13. CD1a: L<15, H>30
14. CD208: L<2, H>8
15. MPOX: L<30, H>60
16. PD1: L<10, H>20
17. CTLA4: L<9, H>18
18. PDL1: L<10, H>20
19. CD25: L<40, H>80
20. NK p46: L<2, H>8

Pathology IHC : Clearly Defined And Well-Understood

Immunohistochemistry (IHC) DAB reaction, Positive cells are brown, All IHC photos same magnification; Bar = 200 µm

(Top row LI-Multikine treated; Bottom row Control)

Figure 1. LI(MK) Treated: High CD4 T cell density in tumor stroma

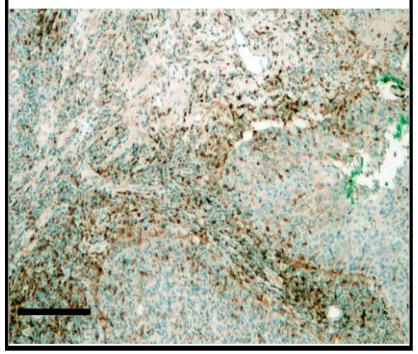


Figure 2. LI(MK) Treated: High CD8 T cell density in the tumor stroma

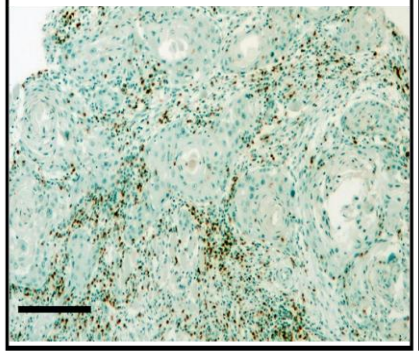


Figure 3. LI(MK) Treated: High CD68 macrophage cell density in the tumor stroma

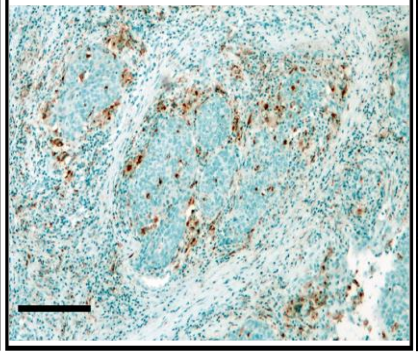


Figure 4. LI(MK) Treated: Low CD1a dendritic cell density in the tumor stroma

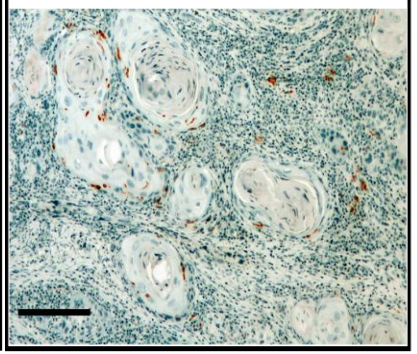


Figure 5. LI(MK) Treated: Low tumor cell PDL1 expression/negativity.

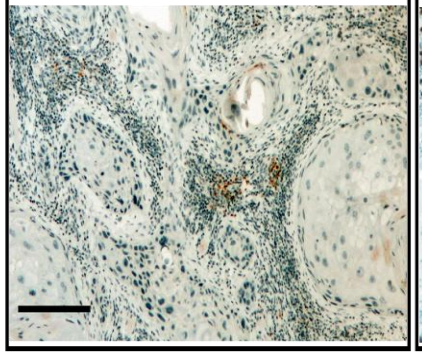


Figure 6. LI(MK) Treated: High CD20 B cell density in the tumor stroma

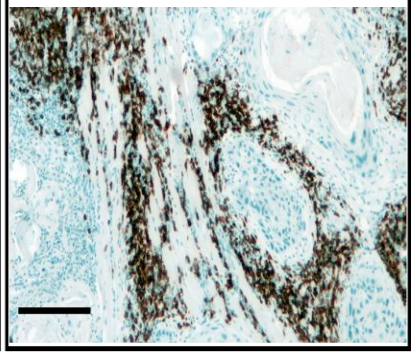


Figure 1a. SOC only (control): Low CD4 T cell density in tumor stroma

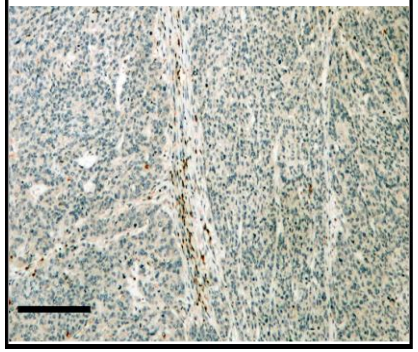


Figure 2a. SOC only (control): Low CD8 T cell density in the tumor stroma

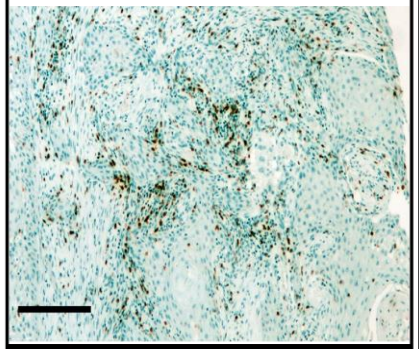


Figure 3a. SOC only (control): Low CD68 macrophage cell density in the tumor stroma

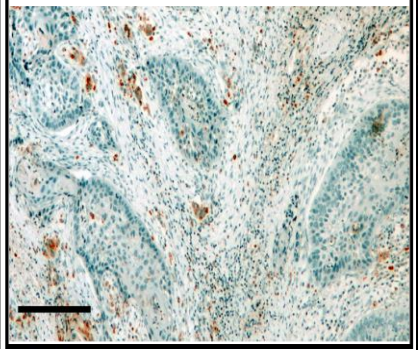


Figure 4a. SOC only (control): High CD1a dendritic cell density in the tumor stroma

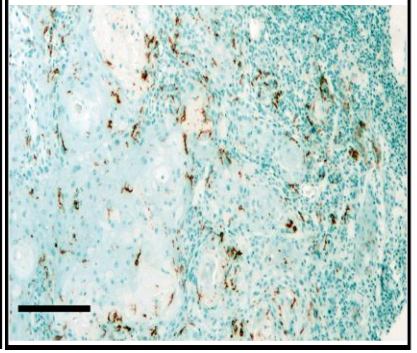


Figure 5a. SOC only (control): High tumor cell PDL1 expression

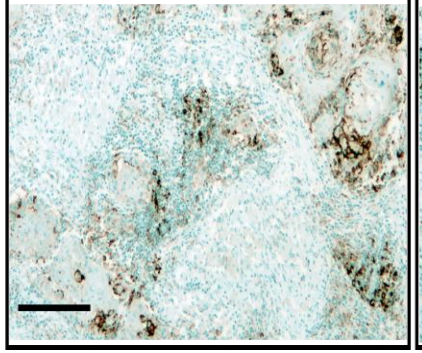
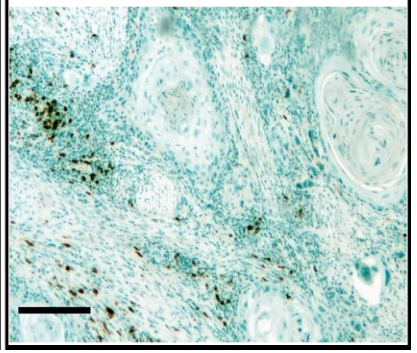


Figure 6a. SOC only (control): Low CD20 B cell density in the tumor stroma



*3,3'-diaminobenzidine (DAB)

Prospectively Defined Ratios and Combinations of Cellular Biomarkers

Two ratios were constructed with L, M, and H thresholds (based on above definitions of H & L, M was neither H nor L) as follows:

1. CD8/FOXP3 ratio: 1 and 2
2. CD4/CD8 ratio: 1 and 2

Fourteen combinations were constructed as follows:

1. CD3+ and CD25+ All Positive
2. CD3+, CD8+, and CD25+ All Positive
3. CD3+, CD4+, and CD25+ All Positive
4. CD3+, CD4+, CD8+, and CD25+ All Positive
5. CD1a+ and TMR1+ All Positive
6. CD1a+ and NK p46+ All Positive
7. CD1a+ and CD163+ All Positive
8. CD3+, CD4+, CD25+, and NK p46+ All Positive
9. CD3+, CD4+, CD25+, and CD163+ All Positive
10. CD3+, CD4+, CD25+, CD1a+, and TMR1+ All Positive
11. CD3+, CD4+, CD25+, CD1a+, TMR1+, and CD163+ All Positive
12. CD3+, CD4+, CD25+, CD1a+, TMR1+, and NK p46+ All Positive
13. CD3+, CD4+, CD25+, CD1a+, TMR1+, CD163+, NK p46+ All Positive
14. CD3+, CD4+, CD25+, CD1a+, CD163+, and NK p46+ All Positive

Immunohistopathology Supports MoA of LI-Multikine

Significant Outcomes All Favoring LI (MK) + CIZ + SOC vs SOC

	Histopathology Results: Proportion Statistically Significant, 1-sided p≤0.025		
Endpoint	Overall Group (n=453) Favoring Group 1**	Lower-risk Group (n=210)* Favoring Group 1	Overall Group (n=453) Favoring SOC (Group 3)
OS	26/93	21/93	1/93
PFS	17/93	16/93	2/93
LRC	18/93	17/93	2/93
Totals	61/279 (21.9%>>2.5%)	54/279 (19.4%>>2.5%)	5/279 (1.8% <2.5%)

*There were no significant tests (0/279) favoring SOC alone in the lower-risk group
** Group '1' = LI(MK)+CIZ+SOC
Note: <2.5% = by chance alone

Overall Survival In The LI-Multikine Target Population (LA OC + Soft Plate SCC, N0 [no ECS], tPD-L1 TPS <10)

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

5-year survival

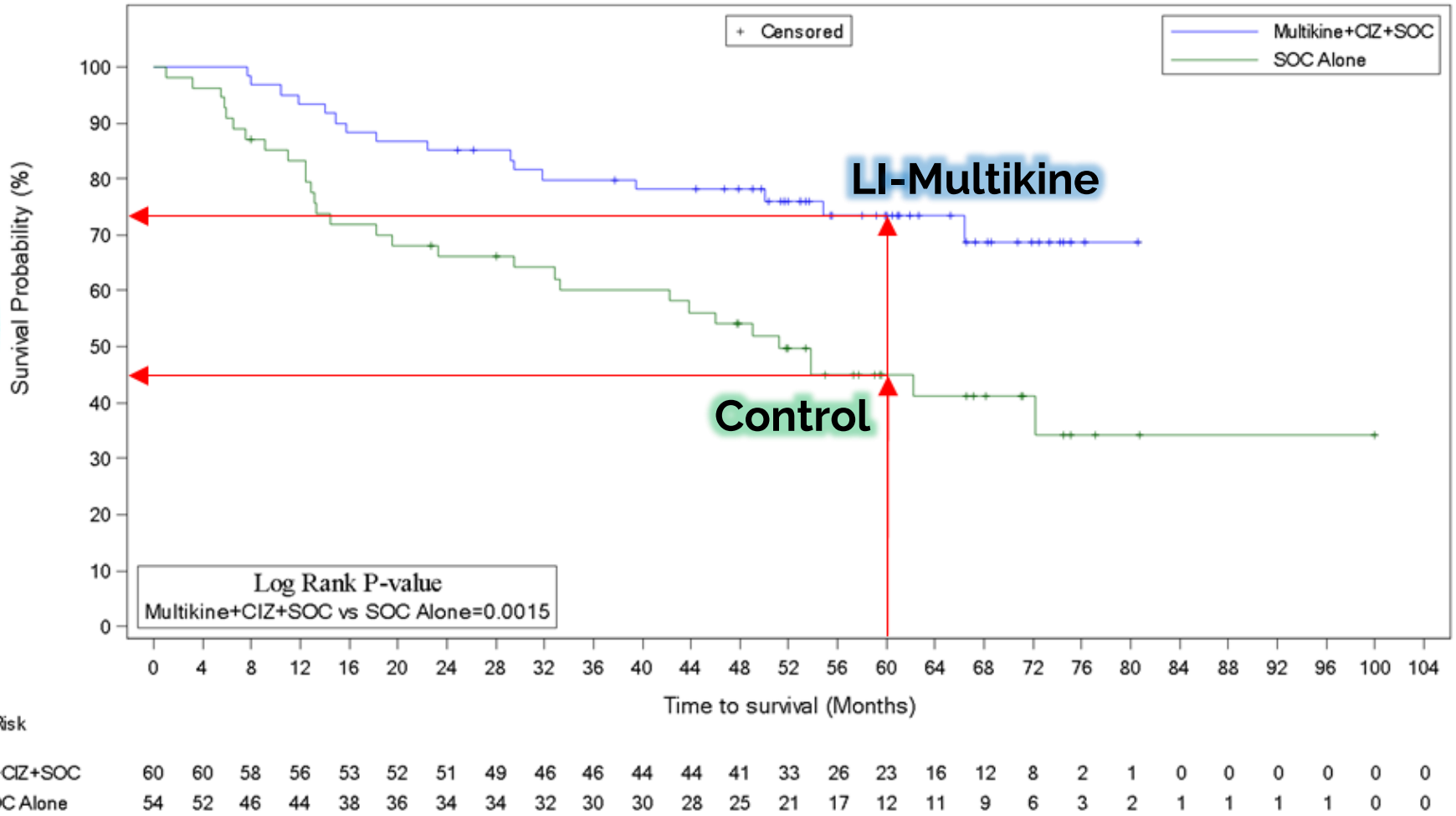
73%

vs

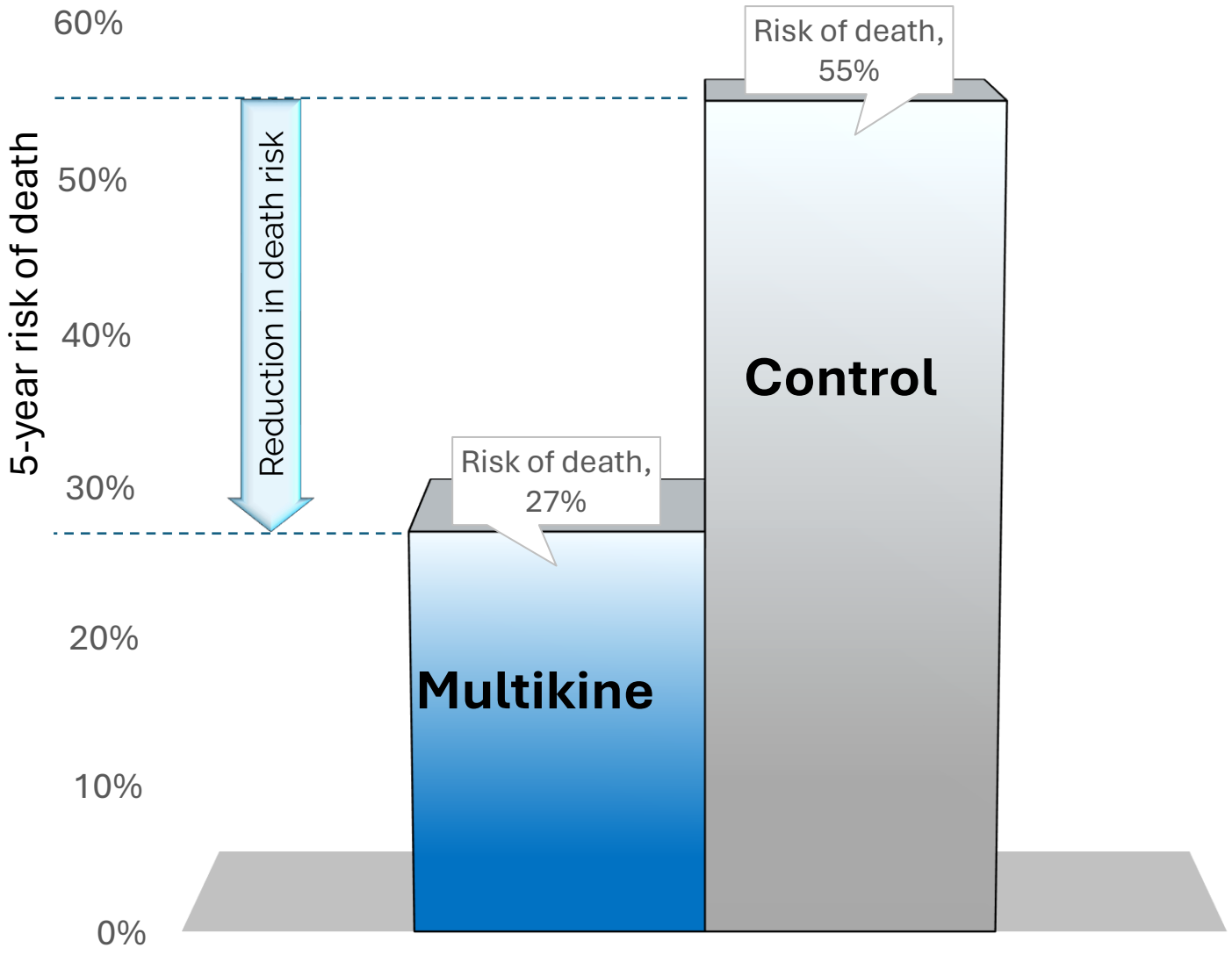
45%

Log Rank p=0.0015

HR 0.35 (95% CI 018, 0.66; Wald p=0.0015)



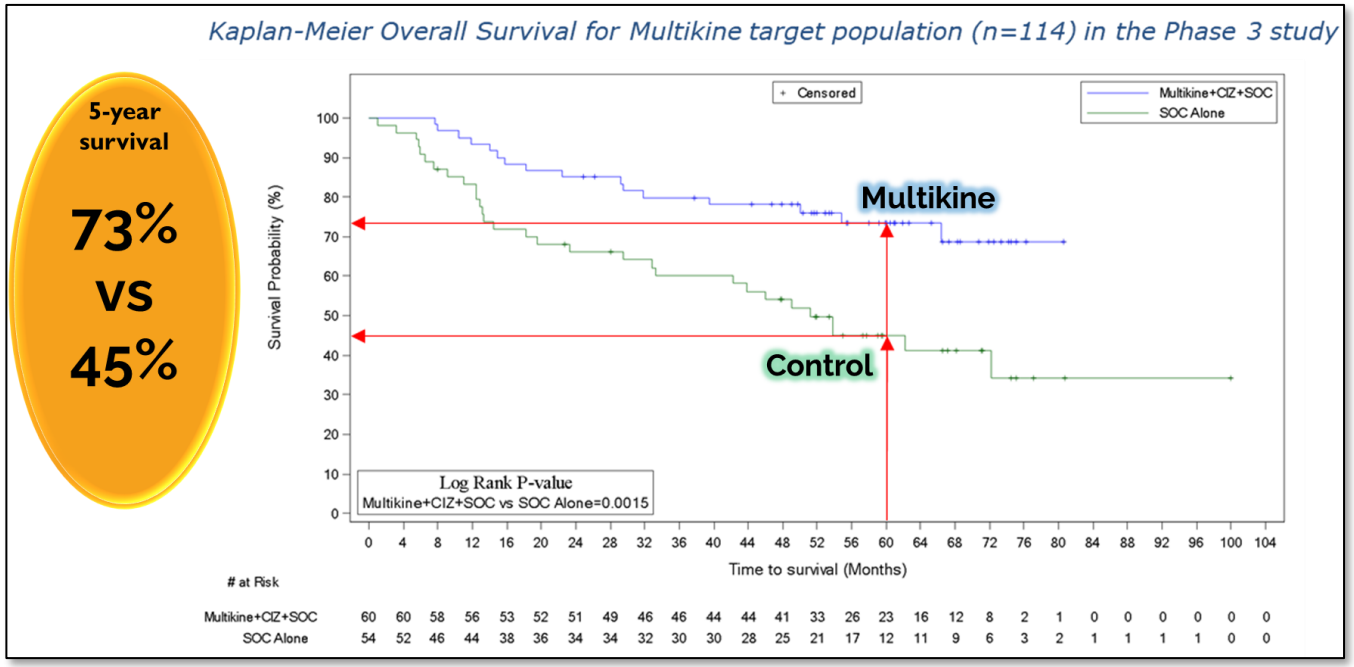
LI-Multikine Treatment *Cut The Risk Of Death At 5-years In Half* In The Target Population



In Summary

Oral Cavity + Soft Palate (N0, tPD-L1 TPS <10) (n=114)

- ✓ 73% overall survival (OS) for LI-Multikine vs 45% in the control, at 5 years
- ✓ 28% increase in 5-year absolute overall survival (OS), Log Rank p = 0.0015
- ✓ 5-year risk of death Reduced by ½ 55% (Control) to 27% (LI-Multikine)
- ✓ Hazard ratio = 0.35 (95% CIs [0.18, 0.66]; Wald p=0.0015)
- ✓ LI-Multikine Tx Tumor reduction rate >13%
- ✓ LI-Multikine Tx Tumor downstaging rate >35%
- ✓ No safety signals or toxicities vs standard of care



Oral Cavity only (N0, tPD-L1 TPS <10) *(n=99)*

- 27% absolute increase in overall survival (OS) 73% for LI-Multikine vs 46% (OS) for control, Log Rank p=0.0055
- Hazard ratio = 0.36 (95% CI [0.18, 0.73]; Wald p=0.0044)

Thank You

The Study Sponsor and authors wish to thank:

- The patient volunteers and their families
- The dedicated Investigators and staff (in 23 countries on three continents)
- The CROs who helped conduct and monitor the study
- The international independent DSMB for safety oversight
- The Central Laboratories and many other Study collaborators