Clinical Study Report

A Phase III, Open-label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection (Multikine®) Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity/Soft Palate Versus Standard of Care Only

Short Title: IT-MATTERS Study (NCT01265849)
Test Product: Leukocyte Interleukin, Injection (Multikine)
Indication: Locally advanced primary squamous cell carcinoma of the oral cavity and soft palate

Sponsor/Sponsor Signatory:
CEL-SCI Corporation
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Protocol No.: CS001P3
Development Phase: 3
Study Initiation Date: 01 January 2011
Study Completion Date: 04 December 2020

Responsible Medical Officers:

[redacted]

This study was performed in accordance with Good Clinical Practice, including the archiving of essential documents.

APPROVAL SIGNATURE(S)

A Phase III, Open-label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection (LI, Multikine®) Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity/Soft Palate Versus Standard of Care Only

Short Title: IT-MATTERS Study (NCT01265849)

Protocol No: CS001P3

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Sponsor Signatory:

.....[redacted].....

Sponsor Signatory:

.....[redacted]

Study Medical Monitor (ICON)

.....[redacted]

SYNOPSIS

Name of Company: CEL-SCI Corporation **Name of Finished Product:** LI(MK) **Name of Active Ingredient:** Leukocyte Interleukin (LI), injection	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*

Title of Study: A Phase III, Open-label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection (LI Multikine®) Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity/Soft Palate Versus Standard of Care Only

Short Title: IT-MATTERS Study (NCT01265849 And EudraCT2010-019952-35)

Protocol Number: CS001P3

Study Center(s):
Study CS001P3 was conducted as an international study in which subjects were accrued in over 20 countries on 3 continents, at 78 clinical sites which had at least 1 randomized subject.

Publications (references): ASCO 2022 Abstract #e18070; ASCO 2022 Abstract #6032; ESMO 2022 Abstract #128P; ESMO 2022 Abstract #690P; ECHNO 2023 Abstract #77; ESTRO 2023 Abstract #1231; AHNS 2023 Abstract #129110; ESMO 2023 Abstract #893P; ESMO 2024 Abstract #935P.

Study Period:	**Phase of Development:**
01 January 2011 to 04 December 2020	Phase 3

Objectives:

Primary Objective:

The primary objective was to compare overall survival (OS) in the LI(MK)+Cyclophosphamide, Indomethacin and Zinc as multivitamin (CIZ)+Standard of Care (SOC) regimen *vs* SOC alone regimen for superiority of the former; this included the pre-defined lower-risk and higher-risk groups.

Secondary Objectives:

1. OS: LI(MK)+SOC *vs* SOC
2. Loco-regional control (LRC): LI(MK)+CIZ+SOC *vs* SOC
3. Progression-free survival (PFS): LI(MK)+CIZ+SOC *vs* SOC
4. Objective early response
5. Quality of Life (QOL): LI(MK)+CIZ+SOC *vs* SOC
6. Histopathology (cellular tumor infiltration): LI(MK) injection *vs* SOC (at the time of planned surgery completion)
7. Safety.

Background:

This international, open-label, randomized, pivotal Phase 3 study (Protocol CS001P3) (IT-MATTERS Study) of Multikine (LI[MK]) investigated the effect of LI neoadjuvant immunotherapy, in treatment-naïve locally advanced primary oral squamous cell carcinoma (OSCC) and soft palate, to elucidate the role and effect of LI(MK), a neoadjuvant immunomodulator therapy, on the survival outcome in this unmet medical need population. The study evaluated a 3-week pre-surgery (neoadjuvant) administration of an investigational natural biologic cytokine complex LI(MK) with/without CIZ (one-time low/sub-chemotherapeutic dose of cyclophosphamide given prior to the first dose of LI/MK, and Indomethacin, and Zinc multivitamins (given with LI(MK) to 1-day before surgery) as compared to SOC in in treating locally advanced resectable treatment-naïve

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OSCC (tumor, node and metastasis [TNM] Stage III/IVa) with curative intent. The SOC was as recommended by the National Comprehensive Cancer Network (NCCN) Guidelines based on the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) study results published in the NEJM 2004 (the same SOC recommendation is still in place today). Subjects were accrued in over 20 countries on 3 continents, at 78 clinical sites. The study was designed, submitted, and accepted by the Food and Drug Administration (FDA) and all other regulatory authorities in the participating countries as an open-label study with the SOC alone as the study control. The study also received ethics board (local or central) approvals at all sites (depending on each country's rules) and was conducted in compliance with all ICH Good Clinical Practice (GCP) requirements (International Council for Harmonization of Good Clinical Practice).

Methodology:

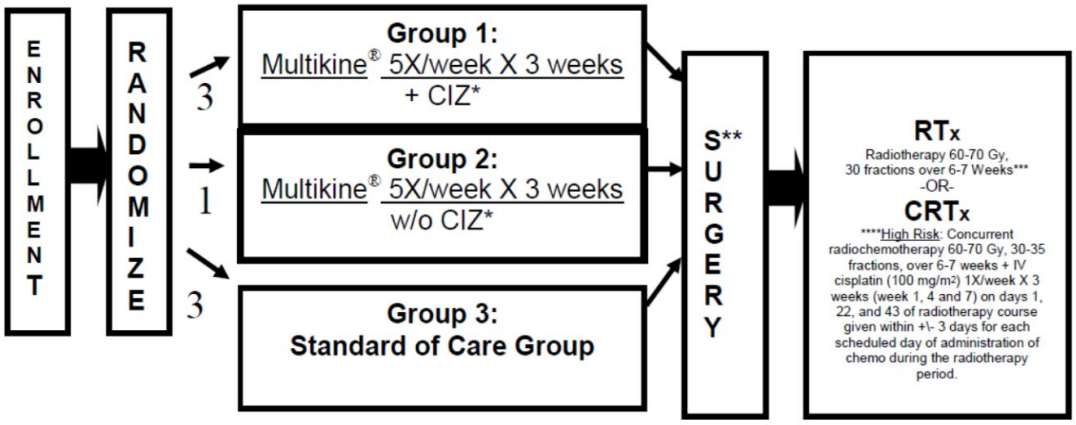
A total of 928 subjects were randomized 3:1:3 to treatment regimens LI(MK) +/- CIZ + SOC or to Control (SOC alone) and treated as described in the below diagram.

The study was designed as an event-driven study and subjects were followed until the study required 298 events (deaths) occurred in the two comparator regimens (LI(MK)+CIZ+SOC and SOC).

Protocol directed structured long-term follow-up visits and assessments were performed every 2 months for the first year, every 3 months for the second year, and every 4 months thereafter for the third year. Subjects were assessed for survival and recurrence of disease until death or until they were lost to follow-up or withdrew consent that did not allow for survival follow-up.

The study was designed in 2006–2010 to follow the NCCN Guidelines for the treatment of locally advanced treatment-naïve OSCC and soft palate carcinoma. The study was initiated in December 2010 and the first subject entered the study in January 2011. The last subject was enrolled in September 2016. Follow-up ended in December 2020. At that time and still today, the determination of risk for recurrence remains a major prognostic factor for these subjects which can only be done following the surgical resection of the tumor and any affected lymph nodes. Therefore, study subjects could not be stratified at entry based on NCCN risk criteria. Moreover, LI(MK) subjects required an additional 3-weeks before surgery than the SOC control group.

Figure S1 – Schematic diagram: Randomization, treatment, and stratification in IT-MATTERS Study



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Abbreviations: CIZ = Cyclophosphamide, Indomethacin, Zinc; CRTx = Concurrent radiochemotherapy; IV = Intravenous; po = Orally; RTx = Radiotherapy; TID = Three times daily; Multikine = LI(MK).

*CIZ: Cyclophosphamide 300 mg/m^2 (× 1, IV, Day -3); Indomethacin 25 mg TID, po (Day 1 to approximately 24 hours prior to surgery) + Zinc (as Multivitamin) po TID daily (from day 1 to approximately 1 day prior to surgery).

** Surgery: complete surgical resection of primary tumor and any positive lymph nodes.

*** Radiotherapy was given per protocol at a total of ≥ 60 Gy to ≤ 70 Gy (in 30 to 35 fractions over a 6 to 7 week period).

**** High-risk subjects were defined as those with: positive surgical margins, 2 or more clinically positive nodes, or extracapsular nodal spread (any or all of the above) and as recommended by the NCCN Guidelines.

NOTE: Per the study design, each risk group had its own control treatment, i.e., lower-risk subjects were to be treated with radiotherapy (RTx) post-surgery (as part of SOC), while higher-risk subjects were to be treated with concurrent radiochemotherapy (CRTx) post-surgery (as part of SOC).

To accommodate the study event goal, the study required an extended enrollment period (5 years) to reach the required number of events. A total of 928 subjects were randomized in the Phase 3 study; this also accounted for intent-to-treat (ITT) exclusions based on pre-defined evaluability criteria. Five subjects randomized to the study could not be included (4 war zone subjects and one subject where the study investigator did not sign the full case report forms (CRF); thus, the ITT population comprised 923 subjects (99.5% of 928 randomized subjects). At FDA's request an Evaluability Review Protocol was constructed in 2017 (nearly one year post the last subject's accrual and treatment) to access all study subjects for compliance with the study procedures and protocols. The evaluability protocol was reviewed and approved by the FDA prior to its implementation. The sponsor was blinded to the implementation and the results of the evaluability protocol. Following execution of the Evaluability Review Protocol, another 200 subjects were declared not to meet the criteria of the evaluability protocol (the remaining 723 were termed the eITT population), which was overcome by focusing on the ITT population (n=923) for analysis, consistent with FDA and ICH guidelines. Results are also presented for the eITT population, consistent with the evaluability protocol which supports the ITT population analysis.

Postoperative therapy was guided by pathologic criteria as described in the protocol; risk assessment followed the NCCN Guideline recommendations. Subjects are considered at higher-risk for recurrence ("Higher-Risk") if pathology demonstrates involved surgical margins or extranodal extension, and these subjects are recommended to receive CRTx. All other subjects are considered lower-risk for recurrence ("Low-Risk") and recommended to receive RTx only post-surgery (See Figure S1, and the protocol for additional details). The study protocol mandated that all study subjects that undergo surgery would receive (at least) radiotherapy post-surgical procedure.

The final decision as to the actual subject-specific Disease-Directed Therapy/Treatment (DDT) regimen was made by the physician on a clinical basis with the best medical interest of each subject and the subject's ability to tolerate the recommended treatment, initiated only after obtaining the subject's informed consent.

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Number of Subjects (Planned and Analyzed):

Of the 928 subjects randomized to the study, 5 cases* were excluded. A total of 923 (99.5%) subjects were included in the ITT population, 723 (77.9%) were in the eITT (evaluable ITT) population, and 511 (55.1%) were in the ePP (evaluable per protocol) population. Risk for recurrence was assessed at surgery (using pathology findings) and was based on NCCN Guidelines. There were 380 lower-risk for recurrence subjects, 467 higher-risk for recurrence subjects, and 76 unclassified risk for recurrence subjects. Overall median follow-up was 55-56 months. The two pre-defined comparator regimens were LI(MK)+CIZ+SOC (n=395) and SOC alone (Control, n=394).

**Four subjects due to 2014 war in Ukraine (Hospital destruction) + one subject (US site) where the Principal Investigator did not sign the completed eCRF*

Test Product, Dose and Mode of Administration:

LI(MK), 400 IU (2 mL) was injected each day of study drug administration, half-dose (1 mL) peri-tumorally and half-dose (1 mL) peri-lymphatically at the vicinity of the jugular lymphatic chain ipsilaterally to the injected (oral cavity or soft palate) tumor site inferior to the tip of the mastoid process in the area of the sternomastoid muscle sequentially during the same visit. Both injections (peri-tumorally and peri-lymphatically) were administered 5 times per week for 3 consecutive weeks.

If scheduled to receive CIZ, subjects also received 300 mg/m^2 cyclophosphamide (IV bolus on Day –3 of the first LI(MK) injection) and 25 mg Indomethacin (po TID) with food, daily from Day 1 of LI(MK) administration to one day prior to surgery). Additionally, a multivitamin supplement containing Zinc (15-40 mg) was given from Day 1 of LI(MK) administration to the day before surgery for immune system/nutritional support.

Reference Product:

All randomized subjects were scheduled to receive SOC. The control group for this study was SOC alone. The SOC included surgery of primary tumor and involved lymph nodes, RTx or concurrent chemoradiotherapy (CRTx) according to the NCCN Guidelines. The protocol required that all subjects who had surgery would have radiotherapy (RTx) following surgical resection of the tumor and any involved lymph nodes. RTx/CRTx were to be administered per the protocol and were modeled after the NCCN Guidelines recommendation (See Figure S1; for additional details see the protocol). Per the study design, lower-risk subjects were to be treated with RTx post-surgery (as part of SOC), while higher-risk subjects were to be treated with CRTx post-surgery (as part of SOC).

Statistical Methods:

The original sample was based on the following assumptions and calculations: The primary comparison was based on 80% power and a 2-sided 5% Type I error to detect a 10% absolute survival advantage (or better) at 3 years (e.g., 55% *vs* 65%); no data existed for the lower-risk or higher-risk groups at that time to perform a prospective sample size calculation. Assuming exponential hazards, this yielded a hazard ratio of 0.721.

This was an event-driven study based on the accrual interval and follow-up to achieve the event goal. For this comparison, the log-rank test required a total of 298 deaths for combined LI(MK)+CIZ+SOC and SOC alone regimens in the eITT population; the timing of the final follow-up was selected to ensure a sufficient number of eITT LI(MK)+CIZ+SOC and SOC alone deaths; deaths in the LI(MK)+SOC regimen were not included in the required 298 deaths count. The study follow-up stopped when exactly 298 eITT deaths were documented in combined LI(MK)+CIZ+SOC and SOC alone; there were 394 ITT deaths which enabled more in-depth analyses.

A 24-month (total) recruitment period and a 30-month follow-up period was originally planned to yield a sample size of 336 subjects in each of the LI(MK)+CIZ+SOC and SOC alone regimens. Under a 3:1:3 randomization (to LI(MK)+CIZ+SOC, LI(MK)+SOC, and SOC alone, respectively), this yielded 112 subjects in the LI(MK)+SOC

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regimen, 336 subjects for the LI(MK)+CIZ+SOC regimen, and 336 subjects for the SOC regimen for a required total estimate of 784 evaluable subjects.

Five pre-defined Time-Critical Intervals (TCIs) were established in the statistical analysis plan (SAP) for efficacy endpoint specific analyses to better understand the effect of LI(MK) at the different stages of treatment and study. Pre-specified hypotheses were defined for OS as primary and PFS and LRC as secondary objectives evaluated from randomization to study exit (TCI E); the hypotheses were constructed as hazard ratio comparisons for LI(MK)+CIZ+SOC *vs* SOC with supporting hypotheses tested for comparing hazard ratios for LI(MK)+SOC *vs* SOC.

Three intervals were pre-defined (in the SAP) for safety analyses; “Pre-surgery”, “During SOC”, and “Post-SOC”. In addition, safety analysis also included for the total interval from study entry to exit (a “fourth interval”). No formal hypotheses were proposed for safety, but the goal was to rule out a 10% higher related treatment-emergent adverse events (TEAE) incidence for both LI(MK) regimens *vs* SOC, alone and in combination, and to rule out a 10% higher related serious adverse event (SAE) incidence for both LI(MK) regimens *vs* SOC, alone and in combination.

Given the different survival outcomes for the two risk groups, the power was retrospectively computed for each risk group using the ITT population. To further protect the Type 1 error, no risk group results were ever examined prior to database lock by the iDMC, the sponsor, or its’ representatives.

Results

Study Subjects:

In total, 99.5% (923/928) of the randomized subjects were included in the ITT population, which was deemed to be the primary analysis population for the clinical study report (CSR).

- Overall, and within the prospectively defined lower-risk and higher-risk groups, the demographics and baseline characteristics were comparable between the treatment regimens.
- All subjects were positive for squamous carcinoma of oral cavity (at entry confirmed by local pathology) with 56.4% having Stage III and 43.6% Stage IVa at entry (disease stage per American Joint Committee on Cancer (AJCC) standards).
- NCCN Guideline definition of a higher-risk for recurrence was applied by the protocol (e.g. positive surgical margin, >2 clinically involved lymph nodes, Level 4 and/or 5 lymph nodes, extracapsular spread, perineural/perivascular invasion):
  - In the ITT population (N = 923), there were 41.2% (380/923) lower-risk subjects and 50.6% (467/923) higher-risk subjects. 8.2% (76/923) subjects could not be classified (unclassified group).
- The extracapsular nodal spread and the positive margin of resection were confined to the higher-risk group; this confirms the original study rationale, and the heterogeneity justifies separate analyses for lower-risk and higher-risk groups which were prospectively defined in the SAP.
- The additional three-week delay of surgery (required for LI(MK) administration) resulted in a lower percentage with lower-risk subjects (2.6% lower for LI(MK)+CIZ+SOC vs SOC alone, 2.3% lower for LI(MK)+SOC vs SOC) which counters the bias that LI(MK) succeeded because of a higher percentage of lower-risk cases:

Risk Group (from surgery)	**LI(MK)+CIZ+SOC (N=395) n (%)**	**LI(MK)+SOC (N=134) n (%)**	**SOC (N=394) n (%)**
Lower-risk (n=380)	158 (40.0%)	54 (40.3%)	168 (42.6%)
Higher-risk (n=467)	200 (50.6%)	69 (51.5%)	198 (50.3%)
Unclassified risk n=76)	37 (9.4%)	11 (8.2%)	28 (7.1%)

- There were no other biases introduced by LI(MK) treatments with respect to surgical stage or subsequent DDT (CRTx, RTx).
- There was good compliance with DDT corresponding to the NCCN Guidelines:
  - Among the 380 lower-risk ITT subjects, 92.6% received RTx and 2.4% received CRTx (representing a site oncology care provider overcall of the NCCN Guidelines recommendation) while the remaining 5.0% did not receive either RTx or CRTx.
  - Among the 467 higher-risk ITT subjects, 9.0% received RTx (representing a site oncology care provider overcall or subject refusal) and 81.2% received CRTx while 9.8% did not receive either RTx or CRTx.
- There was sufficient power to compare LI(MK)+CIZ+SOC vs SOC for the separate ITT lower-risk group (81% power) and higher-risk group (88% power). Overall follow-up time was comparable between all study randomization groups (55-56 months) among those (n=461) reported as last alive.

Efficacy Results

Primary Efficacy:

- For the overall ITT (n=923) and eITT (n=723) populations, there was no effect on OS in favor of LI(MK)+CIZ+SOC versus SOC alone; the primary efficacy endpoint for the primary objective was not met

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at any timepoint measured; there was no evidence of a 10% absolute survival advantage for the subjects on LI(MK)+CIZ+SOC (TCI E):

- Overall: Median (95% CI) OS for ITT was 46.3 months (95% CI: [39.3-55.0]) for LI(MK)+CIZ+SOC as compared to 52.9 months (95% CI: [46.5-66.6]) for SOC alone; the log-rank p-value did not reach significance for the comparison of these groups overall (p = 0.4051). Median (95% CI) time to death for eITT was 51.9 months 95% CI: [42.2-64.2]) for LI(MK)+CIZ+SOC as compared to 52.9 months (95% CI: [46.6-69.4]) for SOC alone; neither the stratified or unstratified log-rank p-values reached significance for the comparison of these two treatment regimens.

- For the lower-risk ITT (n=380) and eITT (n=317) populations, there were significant OS advantages in favor of LI(MK)+CIZ+SOC *vs* SOC alone (TCI E):
  - For the lower-risk ITT population the median (95% CI) time to OS was 101.7 months (64.1 - NR – i.e., not reached) for LI(MK)+CIZ+SOC as compared to 55.2 (48.0 - NR) for SOC alone, which represents a 46.5-month median OS advantage in favor of the LI(MK)+CIZ+SOC (unstratified log-rank p = 0.0478; 0.68 hazard ratio, Wald p=0.0236). The Kaplan Meier estimate to be alive at 36 months (percent survival rate) for the lower-risk group was 72.4% (95% CI: 64.4 - 78.9) for LI(MK)+CIZ+SOC as compared to 67.5% (95% CI: 59.7 - 74.1) for SOC alone. The Kaplan Meier estimate to be alive at 60 months was 62.7% (95% CI: 54.0 - 70.2) for LI(MK)+CIZ+SOC as compared to 48.6% (95% CI: 40.4-56.4) for SOC alone which represents an absolute advantage of 14.1% to the LI(MK)+CIZ-treated *vs* SOC alone at 60 months.
  - The hazard ratio of 0.68 equates to a >12 months OS prolongation for LI(MK)+CIZ+SOC treated vs SOC alone control.
  - To our knowledge, this is the first advance in OS in the treatment of resectable, treatment-naïve, locally advanced primary (lower-risk for recurrence) squamous cell carcinoma of head and neck (SCCHN) (oral cavity/soft palate) resulting from a 3-week neoadjuvant treatment in many decades.

AJCC Stage Migration From Screening/Entry to Surgery (Pre-surgery Downstaging [PSD]):

- The LI(MK)+CIZ+SOC regimen saw a notable 5.2% increase in PSD vs SOC control (25.6% vs 20.4%) in the overall ITT.
- In the lower-risk group, the PSD distribution shift for the LI(MK)+CIZ+SOC regimen vs SOC control was significant (p=0.0210) with 12% more downstage reporting vs SOC alone control (38.9% vs 26.9%).
- PSD was strongly associated with OS benefit:
  - Significant increase in PSD (per AJCC) vs SOC control;
  - LI(MK)+CIZ+SOC PSD was associated with >25% absolute 5-year OS benefit (p<0.01).
  - LI(MK)+CIZ+SOC (*n*=347), PSD *vs* no-PSD hazard ratio was 0.405 (95% CIs [0.272, 0.602], Wald p<0.0001).
  - PSD rates were notably higher in the overall ITT but favored the NCCN lower-risk for recurrence subgroup *vs* the higher-risk for recurrence (HR) subgroup, showing a significant advantage, due to the relatively advanced disease of HR subjects, unable to exploit LI(MK)'s mechanism of action that relies on an intact local immune system to attack the tumor.
  - Long-term OS results were driven by PSD (both associated with the administration of the investigational treatment); PSD utilization avoid having to resort to risk group analysis.

Joint TN Score Shift From Screening/Entry to Surgery (in Support of AJCC Stage Migration):

- All members of the lower-risk group had a more favorable joint TN score distribution at screening than the higher-risk group; subjects with lesser disease burden at screening/entry are the ideal candidates for the proposed indication for use.
- There was no evidence to suggest that objective early responders (to LI[MK] treatment) had a joint TN score advantage at screening/baseline vs non-responders.
- LI(MK) treatment delivered as evidenced by a general 6-7% advantage (including all subjects) in percent's improved stage at surgery vs entry favoring the LI(MK) treatments vs SOC; this analysis was based on all LI(MK) subjects. There were no SOC responders so it is not possible to compare SOC vs LI(MK) responders with respect to the screening/entry distribution.
- The joint TN score distribution difference was highly significant for lower-risk vs higher-risk (two-sided chi square $p<0.0001$); the joint TN score was more favorable at screening/entry for the lower-risk group. In addition, lower-risk and higher-risk subjects should be able to be identified at baseline by the oncology care provider with the current (e.g., positron emission tomography (PET)-computerized tomography (CT)/magnetic resonance imaging (MRI)) imaging tools available and routinely used in this disease.
- The joint TN Stage distributions at screening/entry for lower-risk *vs* higher-risk demonstrated highly significant overall differences between lower-risk and higher-risk subjects.
- Taken together, this justifies and enables the search for lower-risk subjects at screening/entry as the population intended for LI(MK) neoadjuvant treatment.

Objective Early Response (OER; also Referred to as Pre-surgery Response [PSR]):

- In the ITT population (n=923), the two LI(MK) regimens (LI(MK)+CIZ+SOC and LI(MK)+SOC; N=529) had 45 subjects (8.5%) with complete (CR) or partial (PR) tumor responses as determined by Response Evaluation Criteria in Solid Tumors (RECIST 1.0) for the time from randomization to surgery, with surgery/pathology confirmation
  - LI(MK)+CIZ+SOC: Five CRs were confirmed by pathology within one week after completion of treatment at surgery (from the resected surgical specimens). An additional 27 PRs were observed.
  - LI(MK)+SOC: A total of 13 PRs were observed (and no CRs).
  - SOC: No PR or CR were detected (or reported), consistent with no spontaneous tumor regressions reported for locally advanced oral cavity and soft palate SCCHN in the scientific literature.
- OERs were observed in the ITT lower-risk group (n=34, including 5 CRs and 29 PRs), the higher-risk group (n=10), and in the unclassified group (n=1); the 11 responses (10 higher-risk, 1 missing risk classification) were all partial responses.
  - The response rate was 16% (34/212) in the ITT lower-risk population and was 15.2% (24/158) among the ITT lower-risk LI(MK)+CIZ+SOC subjects, which confirms early responses observed in the published LI(MK)-treated Phase 2 studies and which was the motivation for this pivotal study.
  - The response rate in the ITT higher-risk population was 3.7% (10/269) among ITT LI(MK) treated subjects and was 3.5% (7/200) among ITT LI(MK)+CIZ+SOC treated subjects.

Objective Early Response Impact:

- OER was highly associated with OS benefit. Proportional hazard analyses were performed to estimate the underlying hazard ratios and statistical significance for achieving an early response. For the 212 ITT lower-risk-of-recurrence LI(MK)-treated subjects, objective early responders achieved a significantly higher response rate (two-sided Fisher Exact p-value $p<0.0001$). For the 158 ITT lower-risk-of-recurrence subjects in the LI(MK)+CIZ+SOC treatment regimen, objective early responders achieved a 0.246 hazard ratio (95% CI: [0.077, 0.787]).
- Regarding the death rate, there was a consistent >65% relative reduction in subsequent death rate for responders within the LI(MK) treatment groups combined (two-sided Fisher Exact p-value < 0.0001), for the lower-risk LI(MK)-treated group (two-sided Fisher Exact p-value = 0.0067) and for

the lower-risk LI(MK)+CIZ+SOC (two-sided Fisher Exact p-value = 0.0101).

- With ~80% of OER in LI(MK)-treated subjects reaching 5-year OS, OER may be considered as prognostic/predictive for long-term survival in the ITT LI(MK)+CIZ+SOC treatment regimen. At the pre-specified 36-month follow-up, OERs had an absolute OS advantage of more than 25% versus ITT SOC (control), with non-overlapping 95% confidence intervals. This absolute OS advantage persisted at Month 48 and Month 60. Median OS time was not reached for the OERs compared to 55.2 months in the control (SOC alone). Thus, LI(MK)-treated subjects with OER confirmed at surgery live much longer than subjects treated with SOC alone.

Selection Process of Lower Tumor Burden Subjects (by exclusion of subjects with NCCN Adverse features and higher disease burden determined at screening/entry):

In order to administer the LI(MK) treatment to the ideal population (in future studies), the assignment of risk requires prospective identification based on data known only at the time of screening/entry. PET/CT-MRI (PET-imaging was not readily available or in routine practice during study CS001P3) is instrumental to help identify the NCCN defined adverse features, so LI(MK) can be reserved for those subjects with a minimum of adverse features and the LI(MK) therapy can be administered before surgery.

The following selection criteria are used to remove subjects with higher disease burden at entry as follows:

Step 1: Exclude those subjects with N1-2 provisional to leave only subjects with N0

Step 2: From the remaining N0 subjects, exclude those who exhibit extra capsular nodal spread (as determined from clinical and PET-imaging or best practice for determining extracapsular nodal spread at entry)

The remaining subjects are proposed to be the "lower-risk" group (those not excluded). The 2-step approach was required as a significant number of subjects were reported with extracapsular nodal spread although they were staged with N0 (in the CS001P3 Study). With increased usage of PET-CT/MRI, improved higher-risk case exclusion is expected in SCCHN (oral cavity/soft palate).

The following highlights were identified:

- Among the lower-risk cases, 62.4% (237/380) met the selection criteria (>50% target) from entry data
- Among all cases meeting the selection criteria exclusion criteria, 62.6% (365/583) are in the higher-risk category
- Among the higher-risk cases, 78.2% (365/467) were properly excluded (i.e., met selection exclusion criteria – from data at entry)

The 2-step selection strategy provided near perfect (99.9%) ITT population coverage and excluded 78.2% of the higher-risk group.

The selection criteria performance was assessed by comparing the ITT OS for LI(MK)+CIZ+SOC *vs* SOC alone for the lower-risk group (n=206 after excluding 32 LI(MK)+SOC subjects). The survival advantage comes from the lower-risk population with a significant OS advantage (hazard ration=0.514; 2-sided log-rank p=0.0058) for the indicated population LI(MK)+CIZ+SOC *vs* SOC only by the 2-step selection criteria. Thus, the selection criteria identify a group where LI(MK)+CIZ+SOC has a significant advantage *vs* SOC alone.

The higher-risk subjects included in the algorithm had a 1.024 hazard ratio (excluding LI(MK)+SOC) and a 1.027 hazard ratio (including all three treatment regimens); thus, the overall 1.33 hazard ratio for the higher-risk group (seen in the CS001P3 Study) has been mitigated; this analysis was based on 102 higher-risk subjects who were not excluded. The HR included (i.e., not excluded by the selection criteria) have a disease burden that is on the 'lower spectrum' of the disease continuum with fewer adverse features (reduced tumor burden), relative to the excluded HR subjects, and thus had a more favorable Kaplan Meier survival lifetables.

Higher-risk Case Management Moving Forward:

- Long-term OS results were driven by OER/PSD:
  - The higher-risk LI(MK)+CIZ+SOC regimen saw a significant 15.1% absolute five-year OS disadvantage *vs* higher-risk SOC control (hazard ratio=1.33 [95%CI 1.02, 1.73, Wald p=0.0321],

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unstratified log-rank test p=0.0456), despite the absence of excess adverse event (AE)/SAE incidence in LI(MK)-treated subjects vs SOC control.

– Selection criteria were determined to help minimize higher-risk disadvantage by prospectively excluding subjects who present with nodal involvement (>N0) and/or extracapsular spread (ECS). Thus, the higher-risk disadvantage can be mitigated prospectively in future studies.

The remaining higher-risk subjects (after exclusions) had 5-year OS estimates: 43.1% for LI(MK)+CIZ+SOC *vs* 49.2% for SOC alone from the corresponding Kaplan Meier lifetable (two-sided p= 0.9403). The two-sided p-value was 0.5155 according to the pre-specified proportional hazard model when controlling for tumor location, stage, and geographic region. Thus, the selection criteria were able to achieve LI(MK)+CIZ+SOC parity *vs* SOC alone after exclusion; the remaining higher-risk subjects had comparable survival for LI(MK)+CIZ+SOC *vs* SOC alone; in future studies, higher-risk subjects will be excluded by PET-CT/MRI.

Specifically, prospective recruitment of subjects with N0 at entry [with no ECS, as determined with the use of PET-imaging] could diffuse the negative impact seen in the higher-risk group, whose disease severity does not allow for the additional time to surgery required for the administration of LI(MK), while identifying a population with lower tumor burden who are the ideal candidates to benefit from LI(MK). Thus, in future studies the low disease burden (lower-risk) subjects can be prospectively identified with currently recommended imaging methods (PET-CT/MRI).

Secondary Efficacy:

- There was no effect on PFS or LRC in favor of LI(MK)+CIZ+SOC or LI(MK)+SOC *vs* SOC in the ITT population.
- For the ITT lower-risk group, PFS results supported OS efficacy outcome (TCI E). For the ITT population the hazard ratio was 0.76 (95% CI: 0.55, 1.04, p = 0.0896) for LI(MK)+CIZ+SOC *vs* SOC; this supports PFS non-inferiority:
  - In the lower-risk ITT group, the median (95% CI) time to progression or death was 66.4 months (905%CI [47.5-101.7]) for LI(MK)+CIZ+SOC as compared to 51.2 months (905%CI [42.5 – 72.2]) for SOC; the 15.2-month median prolongation was considered clinically significant.
- In the lower-risk ITT population, the hazard ratio was 0.84 (95% CI: 0.55, 1.28, p=0.4082) for LRC Failure favoring LI(MK)+CIZ+SOC *vs* SOC; the median (95% CI) time to LRC Failure was not reached (NR months) for LI(MK)+CIZ+SOC and SOC alone.
- Additional time to event analyses performed for the lower-risk reflecting concurrent RTx DDT following surgery comparing LI(MK)+CIZ+SOC versus SOC alone supported OS efficacy observed previously in the primary analysis for the LI(MK)+CIZ+SOC:
  - the median (95% CI) time to death was 101.7 months (64.2 - 101.7) in the LI(MK)+CIZ+SOC compared to 56.9 months (48.6- NR) for SOC alone
  - OS ITT lower-risk: DDT RTx: LI(MK)+CIZ+SOC favorable (p=0.0787)
- The following table summarizes lower-risk efficacy for LI(MK)+CIZ+SOC *vs* SOC for each of OS, PFS, and LRC; the OS advantage (0.68 hazard ratio) extends to PFS (0.76 hazard ratio) and LRC (0.84 hazard ratio) in the ITT lower-risk population:

Summary: ITT Lower-risk- Study Entry to Exit: Ns, Failures, Hazard Ratios, P-values, Medians

	Treatment Comparison	OS (380; 166d)	PFS (380; 188p)	LRC (380; 104f)
	Failures (Group '1', '2', '3')*	(58, 24, 84)	(70, 27, 91)	(41, 16, 47)
ULR P-value	LI(MK)+CIZ+SOC *vs* SOC	0.0478	0.1797	0.6142
SLR P-value	LI(MK)+CIZ+SOC *vs* SOC	0.0364	0.1471	0.6221
Hazards Ratio	LI(MK)+CIZ+SOC *vs* SO	0.68 (0.48- 0.95)	0.76 (0.54 – 1.04)	0.84 (0.55 – 1.28)
	LI(MK)+SOC *vs* SOC	0.82 (0.52 – 1.29)	0.84 (0.54 – 1.30)	0.93 (0.53 – 1.65)
Cox PH P-value	LI(MK)+CIZ+SOC *vs* SOC	0.0236	0.0896	0.4082
	LI(MK)+SOC *vs* SOC	0.3859	0.4376	0.8131
Median (months)	LI(MK)+CIZ+SOC	101.7 months	66.4 months	Not reached
	LI(MK)+SOC	68.2 months	68.2 months	Not reached
	SOC	55.2 months	51.2 months	Not reached
Cox model included treatment (SOC referent), tumor stage, tumor location, and geographic location				

Abbreviations: d = deaths; p = progressions; f = failures; LRC = local regional control; OS = overall survival; PFS = progression-free survival; SLR = stratified log-rank; ULR = unstratified log-rank.

*Group '1' = LI(MK)+CIZ+SOC; Group '2' = LI(MK)+SOC; Group '3' = SOC alone

Histopathology:

- The histopathology findings confirm the advantage for LI(MK)+CIZ+SOC *vs* SOC as displayed below for the 3-way interactions modeling (using all 453 subjects with samples analyzed) and then for two-way interactions modeling (using all 210 lower-risk subjects). There were a total of 279 possible tests for each data set; under a one-sided 2.5% null hypothesis, 7 (279 x 0.025) significant findings would be expected by chance alone.
    - Using the 3-way interactions modeling, there were a total of 66 significant findings with 61 (26 OS, 17 PFS, and 18 LRC) favoring LI(MK+CIZ+SOC *vs* SOC (exclusively for lower-risk interactions) and only 5 (1 OS, 2 PFS, 2 LRC) favoring SOC *vs* LI(MK)+CIZ+SOC (exclusively for higher-risk interactions); there were never any significant SOC advantages coupled with lower-risk interactions. The excess (61 *vs* 5) was highly significant ($p<0.0001$) favoring LI(MK)+CIZ+SOC; this significance held for OS, PFS, and LRC considered individually (all $p<0.0001$).
    - Results were confirmed using the 2-way interactions modeling with all 54 (21 OS, 16 PFS, and 17 LRC) favoring LI(MK)+CIZ+SOC *vs* SOC; the excess (54 *vs* 0) was highly significant ($p<0.0001$); this significance held for OS, PFS, and LRC considered individually (all $p<0.0001$). The chi square test also was significant for the expected number of significant tests for the Overall Group (21.9% *vs* 2.5%; $p<0.0001$) and for the lower-risk group (19.4% *vs* 2.5%; $p<0.0001$) relative to 2.5% chance; significance was also seen separately for OS, PFS, and LRC for both the Overall Group and the lower-risk group (all conditional binomial $p<0.0001$).

Histopathology Results: LI(MK)+CIZ+SOC *vs* SOC Proportion Statistically Significant, 1-sided $p \leq 0.025$

Endpoint	Overall Group (n=453) Favoring Group 1**	Lower-risk Group (n=210)* Favoring Group 1	Overall Group (n=453) Favoring SOC
OS	26/93	21/93	1/93
PFS	17/93	16/93	2/93

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LRC Failure	18/93	17/93	2/93
Totals	61/279 (21.9%>>2.5%)	54/279 (19.4%>>2.5%)	5/279 (1.9% <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

Lower-risk subjects with low TPDL-1 expression (defined as Tumor Proportional Score [TPS] < 10, comprised 70% of the lower-risk subgroup) had a high likelihood of achieving survival benefit when initially treated with LI(MK)+CIZ+SOC *vs* SOC alone. The Kaplan Meier lifetable for the low TPDL1 (TPS <10) subgroup demonstrated a significant log-rank test (2-sided p=0.034) favoring LI(MK)+CIZ+SOC *vs* SOC alone. This result supports the 3-way and 2-way analyses having more favorable 0.6 and 0.55 hazard ratios, respectively, as compared to the overall 0.68 hazard ratio for the lower-risk group. Furthermore, immunohistochemistry marker analyses shows the benefit of LI neoadjuvant administration in improving OS, when considering subject's selection criteria for treatment having biomarkers (N0 no ECS and low tumor PDL1 expression). In addition, improved OS was observed in the LI+CIZ+SOC treated vs SOC group in subjects with low tumor cell PD-L1 expression (TPS <10), in both the ITT and in ITT lower-risk (LR) cohorts. Evaluating TPS low cases, a significantly better prognosis was demonstrated for LI-treated subjects, with an absolute survival advantage of 20% at month 60 favoring LI+CIZ+SOC vs SOC alone (60% vs 40% alive, respectively). Considering the further addition of all selection parameters (i.e., LR/ low disease burden, N0, no ECS and TPS low) markedly improved the survival likelihood of the LI(MK)+CIZ+SOC treated subjects, produced a significant test (p=0.0027) favoring LI(MK)+CIZ+SOC vs SOC alone (control), and a 0.27 (95% CI: [0.12, 0.64], Wald p=0.0027) (see Table S1).

Table S1: Hazard ratios in the ITT lower-risk and Histopathology lower-risk cohort, association of tPD-L1 TPS <10 with improved OS in both ITT LI-treated and Histopathology lower-risk LI-treated groups

Population	Model covariates	Hazard ratio [95% CI]
ITT lower-risk (n=380)	LI(MK) + CIZ + SOC vs SOC*	0.68 [0.48, 0.95; Wald p=0.0236]
HP lower-risk (n=210)†	LI(MK) + CIZ + SOC vs SOC*	0.64 [0.41, 1.01; Wald p=0.0569]
HP lower-risk (n=210)	LI(MK) + CIZ + SOC vs SOC; tPD-L1: TPS 10-<20 and TPS >20 vs TPS <10)	0.55 [0.32–0.96; Wald p=0.0355]
HP overall tPD-L1 (TPS <10) and algorithm entry selected criteria (N0, no ECS) (n=114)‡	LI(MK) + CIZ + SOC vs SOC*	0.34 [0.18-0.65; Wald p=0.0012]

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HP lower-risk tPD-L1 (TPS <10) and algorithm entry selected criteria (N0, no ECS) (n=79)	LI(MK) + CIZ + SOC vs SOC*	0.27 [0.12-0.61; Wald p=0.0027]

*Model included terms for tumor stage, tumor location, and geographic region

† ESTRO 2023 Abstract #1231, ‡ ESMO 2024 Abstract #935P (Appendix 16.1.12)

Abbreviations: CI = confidence interval; CIZ = Cyclophosphamide, Indomethacin, Zinc; ECS = extracapsular spread; HP = histopathology; ITT = intent-to-treat; LI = Leukocyte Interleukin, Injection; OS = overall survival; SOC = standard of care; TPS = Tumor Proportional Score; tPD-L1 = Tumor PD-L1.

Safety:

AEs were categorized based on three separate time intervals of interest and then one overall (including those with no TEAE start date). The three intervals of interest for the timing of the AEs were:

Pre-surgery AEs (start date of AE was on or after the date of informed consent signature [for all randomized subjects] until the date of surgery);

During the SOC AEs (start date of AE was on or after the date of surgery and end date of AE was on or before 60 days post the last date of RTx/CRTx);

Post-SOC AEs (start date of AE was after 60 days post the last date of RTx/CRTx).

In addition, **Post-randomization** includes all TEAEs with start dates reported pre-surgery, during SOC (DDT) and post SOC (after DDT completion) as well as those TEAEs with a missing start date up to the end of the study.

Pre-surgery Interval

LI(MK)+CIZ+SOC

In 383 subjects receiving LI(MK)+CIZ+SOC, 39.2% (150/383) of subjects reported at least one TEAE pre-surgery, of which 17.0% (65/383) reported a TEAE that was considered treatment-related. A total of 2.3% (9/383) of subjects reported at least one TEAE with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTC) Grade 3 or 4.

A total of 0.5% (2/383) of subjects reported at least one TEAE that led to study drug discontinuation.

A total of 0.8% (3/383) of subjects reported at least one serious TEAE of which 0.3% (1/383) of subjects reported a serious TEAE that was considered treatment-related.

None of the subjects in the LI(MK)+CIZ+SOC treatment regimen had a TEAE leading to death.

Three subjects in the LI(MK)+CIZ+SOC treatment regimen had a TEAE leading to death but these were all due to disease progression.

LI(MK)+SOC

In 129 subjects receiving LI(MK)+SOC, 46.5% (60/129) of subjects reported at least one TEAE pre-surgery, of which 19.4% (25/129) reported a TEAE that was considered treatment-related. A total of 1.6% (2/129) of subjects reported at least one TEAE with CTC Grade 3 or 4. None of 0% (0/129) subjects reported at least one TEAE that led to discontinuation. A total of 0.8% (1/129) of subjects reported at least one serious TEAE of which 0.8% (1/129) subjects reported a serious TEAE that was considered treatment-related.

None of the subjects in this treatment regimen had a TEAE leading to death.

One subjects in this treatment regimen had a TEAE leading to death, but it was due to disease progression.

TEAEs in the LI(MK)+SOC treatment regimen were similar in incidence to that observed in the LI(MK)+CIZ+SOC treatment regimen. However, as expected in the pre-surgery time-frame, SOC alone (which did not receive any treatment during this time-frame) overall had fewer subjects (12.3% [45/367]) reported to have had TEAEs compared to subjects receiving the investigational treatment.

SOC

Among 367 subjects, none of the subjects in the SOC alone regimen had TEAEs pre-surgery that were considered treatment related. A total of 0.5% (2/367) of subjects reported at least one TEAE with CTC Grade 3 or 4. None of the subjects in the SOC treatment regimen reported a TEAE that led to discontinuation. A total of 0.5% (2/367) of subjects reported at least one serious TEAE; none were treatment related. None of the subjects in the SOC alone treatment regimen had a TEAE leading to death. It should be noted that subjects in the SOC alone regimen as the control group never received study investigational treatment (i.e., no LI(MK)).

During SOC Interval

LI(MK)+CIZ+SOC

In 383 subjects receiving LI(MK)+CIZ+SOC, 82.5% (316/383) of subjects reported at least one TEAE, of which 81.5% (312/383) of subjects reported a TEAE that was considered treatment-related (including all treatments that includes DDT and subsequent therapies besides LI(MK)). A total of 27.2% (104/383) of subjects reported at least one TEAE with CTC Grade 3 or 4. A total of 7.8% (30/383) of subjects reported at least one TEAE that led to

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discontinuation. A total of 10.7% (41/383) of subjects reported at least one serious TEAE of which 5.7% (22/383) of subjects reported a serious TEAE that was considered treatment-related. A total of 1.6% (6/383) of subjects in this treatment regimen had a TEAE leading to death.

LI(MK)+SOC

In 129 subjects receiving LI(MK)+SOC, 86.0% (111/129) of subjects reported at least one TEAE, of which 82.9% (107/129) of subjects reported a TEAE that was considered treatment-related (including all treatments that includes DDT and subsequent therapies besides LI(MK)). A total of 34.1% (44/129) of subjects reported at least one TEAE with CTC Grade 3 or 4. A total of 7.0% (9/129) of subjects reported at least one TEAE which led to discontinuation. A total of 10.1% (13/129) of subjects reported at least one serious TEAE of which 8.5% (11/129) subjects reported a serious TEAE that was considered treatment-related. A total of 0.8% (1/129) of subjects in this treatment regimen had a TEAE leading to death.

The proportion of subjects reported a TEAE in the LI(MK)+SOC was similar to that observed in the LI(MK)+CIZ+SOC treatment regimen.

SOC

Among 367 subjects, a total of 87.2% (320/367) of subjects in the SOC alone regimen had TEAEs that were considered treatment related. A total of 28.6% (105/367) of subjects reported at least one TEAE with CTC Grade 3 or 4. A total of 11.7% (43/367) of subjects in the SOC treatment regimen reported a TEAE that led to discontinuation, which was higher than percentage of subjects discontinuing due to an AE in the LI(MK)+CIZ+SOC treatment regimen (7.8%). For SOC alone, 10.1% (37/367) of subjects reported at least one serious TEAE of which 7.1% (26/367) of subjects had at least one serious TEAE that was considered treatment related. The numbers were comparable to that observed in the LI(MK)+CIZ+SOC treatment regimen. A total of 1.6% (6/367) of subjects in the SOC alone treatment regimen had a TEAE leading to death.

Post-SOC Interval

LI(MK)+CIZ+SOC

In 383 subjects receiving LI(MK)+CIZ+SOC, 42.3% (162/383) of subjects reported at least one TEAE post-SOC, of which 25.3% (97/383) of subjects reported a TEAE that was considered treatment related. A total of 13.1% (50/383) of subjects reported at least one TEAE with CTC Grade 3 or 4. None of the subjects reported at least any TEAE that led to discontinuation. A total of 12.0% (46/383) of subjects reported at least one serious TEAE of which 2.9% (11/383) of subjects reported a serious TEAE that was considered treatment related. A total of 4.7% (18/383) of subjects in this treatment regimen had a TEAE leading to death.

LI(MK)+SOC

In 129 subjects receiving LI(MK)+SOC, 42.6% (55/129) of subjects reported at least one TEAE post-SOC, of which 27.1% (35/129) of subjects reported a TEAE that was considered treatment related. A total of 12.4% (16/129) of subjects reported at least one TEAE with CTC Grade 3 or 4. None of the subjects reported at least any TEAE which led to discontinuation. A total of 12.4% (16/129) of subjects reported at least one serious TEAE of which 1.6% (2/129) of subjects reported a serious TEAE that was considered treatment related. A total of 1.6% (2/129) of subjects in this treatment regimen had a TEAE leading to death.

SOC

The total proportion of subjects reporting at least one TEAE in subjects receiving SOC only treatment regimen was 40.9% (150/367) and was similar to that observed in the LI(MK)+CIZ+SOC treatment regimen.

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Among 367 subjects, a total of 24.3% (89/367) of subjects in the SOC alone regimen had TEAEs that were considered treatment related. A total of 10.4% (38/367) of subjects reported at least one TEAE with CTC Grade 3 or 4. A total of 9.3% (34/367) of subjects reported at least one serious TEAE of which 2.2% (8/367) of subjects reported a serious TEAE that was considered treatment related. A total of 4.1% (15/367) of subjects in this treatment regimen had a TEAE leading to death.

Post-randomization Interval

LI(MK)+CIZ+SOC

In 383 subjects receiving LI(MK)+CIZ+SOC, 93.0% (356/383) of subjects reported at least one TEAE, of which 86.7% (332/383) of subjects reported a TEAE that was considered treatment related (including all treatments which includes DDT and subsequent therapies besides LI(MK)). A total of 37.6% (144/383) of subjects reported at least one TEAE with CTC Grade 3 or 4. A total of 8.6% (33/383) of subjects reported at least one TEAE which led to discontinuation. A total of 25.3% (97/383) of subjects reported at least one serious TEAE of which 10.2% (39/383) of subjects reported a serious TEAE that was considered treatment related. A total of 8.6% (33/383) of subjects in this treatment regimen had a TEAE leading to death; no subjects died from a TEAE starting pre-surgery. The most frequently reported TEAEs leading to death (excluding deaths, recurrences, and progressions) in the LI(MK)+CIZ+SOC regimen were pneumonia (1.8% [7/383], cardio-respiratory arrest (0.8% [3/383], and completed suicide (0.8% [3/383].

LI(MK)+SOC

In 129 subjects receiving LI(MK)+SOC, 97.7% (126/129) of subjects reported at least one TEAE, of which 89.1% (115/129) of subjects reported a TEAE that was considered treatment related (including all treatments which includes DDT and subsequent therapies besides LI(MK). A total of 41.9% (54/129) subjects reported at least one TEAE with CTC Grade 3 or 4. A total of 7.8% (10/129) of subjects reported at least one TEAE which led to discontinuation. A total of 24.8% (32/129) of subjects reported at least one serious TEAE of which 13.2% (17/129) of subjects reported a serious TEAE that was considered treatment related. A total of 5.4% (7/129) of subjects in this treatment regimen had a TEAE leading to death; no subjects died from a TEAE starting pre-surgery. The most frequently reported TEAEs leading to death (excluding deaths, recurrences, and progressions) in the LI(MK)+SOC regimen were cardiopulmonary failure (1.6% [2/129]), myocardial infarction (0.8% [1/129]), cardiac arrest (0.8% [1/129]), sudden death (0.8% [1/129]), lower respiratory tract infection (0.8% [1/129]), and lymphorrhea (0.8% [1/129]).

SOC

In 367 subjects receiving SOC, the total number of subjects reporting at least one TEAE was 97.5% (358/367) and was similar to that observed in the LI(MK)+CIZ+SOC treatment regimen. A total of 93.2% (342/367) of subjects in the SOC alone regimen had TEAEs that were considered treatment related. A total of 37.1% (136/367) of subjects reported at least one TEAE with CTC Grade 3 or 4. A total of 12.3% (45/367) of subjects in the SOC treatment regimen reported a TEAE that led to discontinuation, which was higher than percentage of subjects discontinuing due to a TEAE in the LI(MK)+CIZ+SOC treatment regimen (8.6%). In the SOC alone regimen, 21.5% (79/367) of subjects reported at least one serious TEAE of which 11.7% (43/367) of subjects had at least one serious TEAE that was considered treatment related. Both numbers were similar in incidence to that observed in the LI(MK)+CIZ+SOC treatment regimen. A total of 7.6% (28/367) of subjects in the SOC alone treatment regimen had a TEAE leading to death, no subjects died from a TEAE starting pre-surgery. The most frequently reported TEAEs leading to death (excluding deaths, recurrences, and progressions) in the SOC alone regimen

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were cardiac arrest (0.8% [3/367]), general physical health deterioration (0.8% [3/367]), sudden death (0.8% [3/367]), and pulmonary embolism (0.8% [3/367]).

Safety Summary:

- There were no significant safety signals identified in this study.
- There was no difference in AEs and time-adjusted AEs, thus no dose-limiting signal emerged.
- No signal of significantly increased SAEs presented.
- Local site of injection reactions and AEs due to the injection of LI(MK) during randomization to pre-surgery interval were observed in the LI(MK) arms of the study, none persisted post-surgery.
- The SOC alone regimen did not receive LI(MK) or other injections (at the same time interval) thus, SOC had no reported injection site AEs.
- When adjusted for the time interval duration, the proportion of subjects with any TEAEs were 41.0% for LI(MK) arms versus 31.8% for SOC alone (randomization to surgery), while during the same period the adjusted proportion of subjects with any SAEs were 0.8% and 1.6%, respectively, suggesting no excess safety concerns.
- LI(MK) was administered as planned to >95% of all LI(MK) subjects, with 90% receiving the complete series of injections.
- LI(MK)-related pre-surgery TEAEs were all local; the study iDMC concurred that there were no LI(MK)-related systemic TEAEs.
- LI(MK)-related SAEs (5 cases reported by investigators) included edema, bleeding, osteoradionecrosis, atrial fibrillation, and delirium.
- LI(MK) TEAEs leading to LI(MK) discontinuation (2 cases) were attributed to another edema and to pyrexia.
- No deaths were directly attributed to LI(MK) administration, and none resulted from TEAEs with initiation date at pre-surgery; all 5 deaths reported were related to progressive disease.
- LI(MK) pre-surgery TEAEs all resolved after surgery; no LI(MK) TEAEs persisted after surgery.
- LI(MK) did not delay surgery or interfere with subsequent DDT administration.
- In the lower-risk subjects, lower incidence of CTC Grade ≥3 TEAEs and SAEs were reported as compared to higher-risk subjects. There was increased Grade 3+ AE incidence resulting from CRTx administered to the majority (81.1%) of subjects in the higher-risk group.
- The LI(MK)-treatment regimen was safe and well-tolerated, as the incidence of TEAEs observed was comparable with that imparted by the SOC alone regimen.

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Overall Conclusions:

While the overall population did not reach significance for OS in this study, the major finding of the study was a significant OS advantage for LI(MK)+CIZ+SOC vs SOC for the lower-risk group (n=380) in contrast to a significant survival disadvantage for the higher-risk group (n=467). Additional analyses demonstrated that computed AJCC downstaging (from entry TN staging determined just prior to and confirmed at surgery) and PSR were both reasonably likely biomarkers which can serve as markers for predicting OS. Selection criteria were identified as N0 (by use of PET-CT/MRI imaging to ensure no extra capsular spread) at entry for the future selection of OSCC/soft palate subjects which represents the population most likely to benefit from LI(MK) neoadjuvant administration.

The IT-MATTERS Study conclusions:

- One 3-week cycle of LI(MK) produces a 14% absolute improvement in OS over lower-risk control (SOC only) and a 15% response rate for the lower-risk group.
- Overall, this improvement transfers into a 46.5-month median OS advantage in favor of the LI(MK)+CIZ+SOC lower-risk group over lower-risk control.
- The survival benefit correlates with pathologic response to LI(MK) treatment.
- The lower-risk significant OS advantage (0.68 hazard ratio) is supported by PFS (0.76 hazard ratio) and LRC (0.84 hazard ratio).
- The survival benefit is further confirmed by improved pathology at surgery for the treatment regimens.
- The median time to objective response was 3-5 weeks. Objective responses were not RECIST confirmed (as in systemic therapy studies in the recurrent/metastatic setting) because of the timing of resection (at median of 35 days from randomization) but were instead confirmed by pathology at surgery.
- All 5 CRs were observed in the LI(MK)+CIZ+SOC lower-risk group.
- LI(MK)-treatment was easy to administer and well-tolerated, did not interfere with the ability to perform surgery or to administer subsequent DDT. The LI(MK)-treatment regimen was safe and well-tolerated, as the incidence of TEAEs observed was comparable with that imparted by the SOC alone regimen.

The outcomes of the IT-MATTERS Study for lower-risk population represents the *first* advance in OS in the treatment of resectable locally advanced primary OSCC and soft palate (SCCHN) in many decades.

Date of Report: 16 Jan 2025