ECHNO 2023 Abstract #77: Leukocyte Interleukin Injection (LI) immunotherapy followed by radiotherapy extends overall survival (OS) in treatment naïve locally advanced primary squamous cell carcinoma of the head & neck: the IT-MATTERS Study.

Eyal Talor(1); Philip Lavin(2); Dusan Markovic(3); John Cipriano(1); Jozsef Timar(4); Igor Bondarenko(5); Srboljub Stosic(6); Aliaksandr Zhukavets(7); Chih-Yen Chien(8); Magdalena Bankowska-Wozniak(9); Mihály Kisely(10); James E. Young(11); Christopher L. Oliver(12); Sheng-Po Hao(13)

(1) CEL-SCI Corporation (2) Boston Biostatistics Research Foundation (3) Ergomed plc (4) Semmelweis University Budapest (5) Dnipro State Medical University, Dnipro (6) Military Medical Academy, Clinic Maxillofacial Surgery, Belgrade (7) N.N. Aleksandrov National Scientific and Practical Center for Oncology and Medical Radiology of Belarus, Minsk (8) Chang Gung Medical Foundation- Kaohsiung Branch Chang Gung Memorial Hospital, Niaosong (9) Centrum Onkologii im. Prof. F. Lukaszczyka, Bydgoszcz (10) Markusovszky Lajos Teaching Hospital,Department of Oto-Rhino-Laryngology and Head –Neck Surgery, Szombathey (11) McMaster University; St-Joseph's Health Care, Hamilton (12) Colorado Head and Neck Specialists, Denver (13) Shin Kong Wu Ho-Su Memorial Hospital, Taipei

ABSTRACT

Background: The 3-week pre-surgery peri-tumoral/peri-lymphatic administration of an investigational pro-inflammatory cytokine complex biologic (LI(MK)) with CIZ (single low dose cyclophosphamide IV-bolus, 300 mg/m^2), indomethacin (po 25mg tid) and Zinc as multivitamins (po 15-45mg Zinc) + Standard of Care (SOC) to oral and soft-palate SCCHN subjects, resulted in early response (CRs/PRs) prior to surgery [RECIST] (confirmed at surgery by pathology) and significantly prolonged OS in the NCCN-defined Lower risk for recurrence (LR) intent to treat (ITT) population vs SOC alone. We present response, efficacy, and safety outcomes for all LR subsequently treated with radiotherapy only (RTx). These data are from the pivotal study IT-MATTERS Clinicaltrials.gov NCT01265849. No safety issues were noted for LI(MK) in this or previous phase 2 studies.

Methods: Subjects (923 ITT; 352 LR received RTx) meeting protocol entry criteria (including AJCC Stage III/IVa OSCC, soft-palate SCCHN, treatment naïve) were randomized 3:1:3 to treatment arms LI(MK)+/-CIZ)+SOC or to Control (SOC alone). LI(MK) treated were administered 200IU peritumorally (1/2 daily dose) and the same (other 1/2) dose peri-lymphatically daily for 3-weeks before surgery. All LR study subjects were to receive RTx (per NCCN Guidelines) while high risk subjects were to receive CRTx post-surgery. Follow-up was comparable (56-57 months median per treatment group).

Results: Pre-surgery responders (PSR; CR/PR) in ITT LR LI(MK) RTx treated (+/- CIZ) groups were 16.5% (32/194) vs 0% (0/158) for SOC. Early response lowered death rates from 48.7% (77/158) for LR RTx SOC (non-responders) in contrast to 15.6% (5/32) for LI(MK) LR RTx responders (two-sided Fisher Exact p=0.0007) to 43.8% (71/152) for LI(MK) LR RTx non-responders (carryover evidence). Proportional hazard ITT LR RTx treated HR was 0.70 (95% CI: [0.49 - 1.00]) favoring LI(MK)+CIZ+SOC vs SOC (two-sided p=0.047 controlling for tumor stage, tumor location and geographic region). The absolute OS advantage in ITT LR RTx LI(MK)+CIZ+SOC vs SOC was 2.8%/8.3%/15.6%, at 36/48/60 months (M), representing 72.3% vs 69.5% (36 M); 67.6% vs 59.3% (48 M), and 65.3% vs 49.7% (60 M) with a 33.5 M median OS advantage (101.7 M [LI(MK)+CIZ+SOC] vs 68.2 M [SOC]; 49.1% prolongation). The corresponding PFS advantage was 8.4% (60 M) for LI(MK)+CIZ+SOC vs SOC; the HR was 0.81 (95% CI: [0.58 - 1.13]) in support of multi-dimensional efficacy. Percent treatment emergent adverse event incidences (TEAEs System Organ Class) were comparable among all treated groups pre-surgery and post-surgery. No excess adverse events were reported for LI(MK) RTx treatment vs SOC RTx treatment.

Conclusions: LI(MK) immunotherapy enabled favorable efficacy outcomes (OS and PFS) including response prior to surgery and subsequent RTx. There were no excess safety issues or TEAEs. ITT LR RTx LI(MK)+CIZ+SOC absolute OS advantage over SOC alone increased over time; the 0.70 HR corresponds to a 43% prolongation of median survival in a population without any new therapy options in decades.

STUDY DESIGN:

Previously untreated advanced primary SCCHN patients (oral cavity including anterior tongue (only), floor of mouth, buccal mucosa (cheek), and soft palate) were consented, and consenting study subjects were enrolled following having met Inclusion/Exclusion criteria (see Clinicaltrials.gov NCT01265849). They were then randomized 3:1:3 to one of the following treatments:

Group 1 – LI(MK)+CIZ+SOC; n=395
Group 2 – LI(MK)+SOC; n=134
Group 3 – SOC alone (Control); n=394

Groups 1 and 3 were equally sized and functioned as the main comparator arms of the study. Group 2 had approximately 1/3 the number of patients in either group 1 or 3 and was included to assess the need for CIZ and the toxicity of LI(MK) alone (i.e., without CIZ).

Primary study objective was to assess OS superiority of LI(MK)+CIZ+SOC over SOC alone (Control).

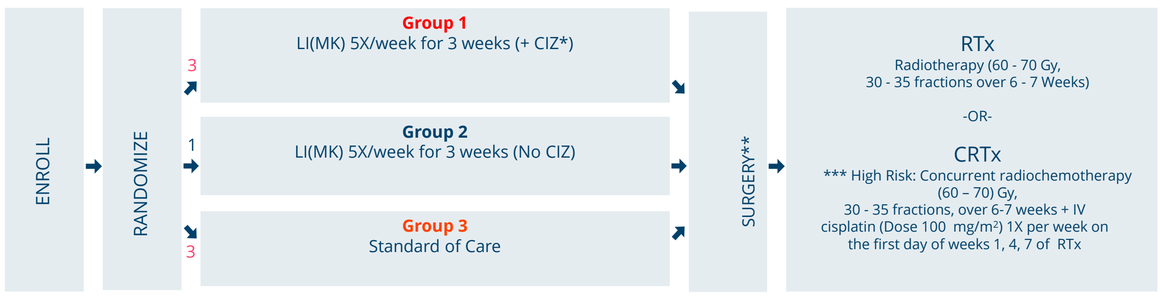
Secondary (and other) study objectives were to assess the rate of PFS and LRC failure, Quality of Life, histopathological nature of cellular tumor infiltrate, and tumor response to LI(MK)+CIZ+SOC vs SOC

Study Power: The study had 80% power and two-sided 5% Type I error to detect a 0.721 hazard ratio which corresponded to a 10% absolute advantage at 3 years assuming exponential survival. For this comparison (Group 1 vs Group 3), the log rank test required a minimum of 298 deaths in the combined comparator arms of the study (Group 1 and Group 3).

LI(MK) Phase 3 Trial Design (Open Label – OS Primary Endpoint)

Schematic: Randomization and Treatment of Enrolled Patients

Disease Stage III and IVa



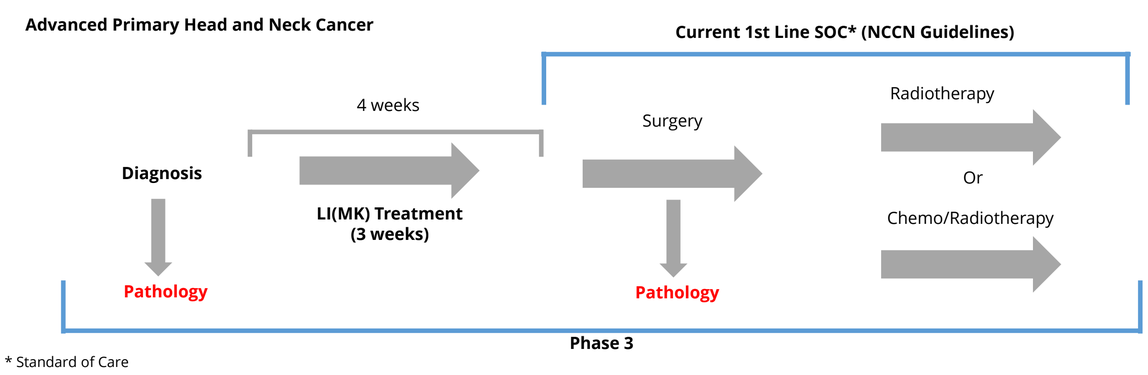
Note: The **overall survival comparison is made between Groups 1 and 3**. The primary purpose of the smaller Group 2 is to gain additional information on the mechanism of action and toxicity of LI(MK). CIZ is added to decrease tumor suppressor mechanisms and thereby is thought to increase LI(MK) effectiveness.

* CIZ: Cyclophosphamide 300 mg/m^2 (x1,IV, day -3); Indomethacin 25mg tid, po (day 1 to ~24 hrs (one day) 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

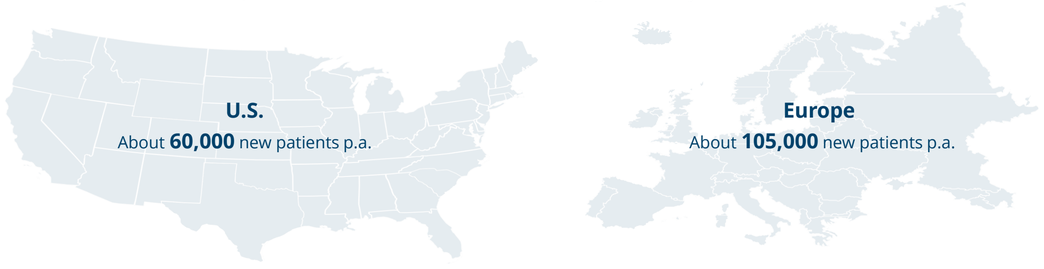
Treatment Regimen: The Timing of LI(MK) Treatment Regimen Phase 3



* Standard of Care

Disease State Globally and Patient Population. Head and Neck Cancer Population.

- World-wide about **890,000** new head and neck cancer patients diagnosed per year



- 90% of head and neck cancers are squamous cell carcinomas
- About 66% are Advanced Primary
- Of the **Advanced primary about 40%** will receive only RTx following surgery (i.e., about 211,000 patients annually)

Subject Disposition - ITT

As per the NCCN Guidelines and Protocol, Higher risk subjects were to receive chemoradiotherapy (CRTx) and Lower risk [LR] subjects were to receive radiotherapy (RTx) as Disease Directed Therapy (DDT).

The following table displays the relationship between DDT (RTx, CRTx) and Risk Group for the ITT population.

There were 396 subjects that received RTx. There were 352 Lower Risk subjects and 42 Higher Risk subjects that only received RTx (instead of CRTx) as per subject/physician choice. Two additional RTx subjects were excluded below since they were unable to be classified for risk group.

	LI(MK)+CIZ+SOC (N=395)		LI(MK)+SOC (N=134)		SOC Alone (N=394)	
Disease-Directed Therapy	**LOWER RISK n (%)**	**HIGHER RISK n (%)**	**LOWER RISK n (%)**	**HIGHER RISK n (%)**	**LOWER RISK n (%)**	**HIGHER RISK n (%)**
RTx	**141 (35.7)**	**10 (2.5)**	**53 (39.6)**	**9 (6.7)**	**158 (40.1)**	**23 (5.8)**
CRTx	**4 (1.0)**	**171 (43.3)**	**1 (0.7)**	**52 (38.8)**	**4 (1.0)**	**156 (39.6)**
Total	**145 (36.7)**	**181 (45.8)**	**54 (40.3)**	**61 (45.5)**	**162 (41.1)**	**179 (45.4)**

RESULTS:

EFFICACY - RESPONDERS

The RECIST 1.0 Criteria were used to determine response between screening/entry and subsequent surgery (5 weeks period for the two LI(MK) treatments, and 2 weeks period for SOC treatment).

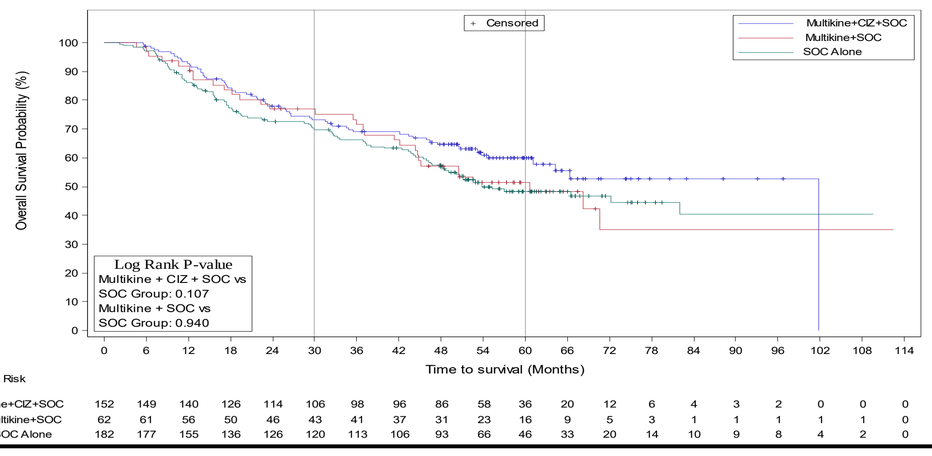
The following table displays the response rate for the ITT RTx population (n=396). There were 34 ITT RTx subjects that responded. The response rates were 15.1% for RTx LI(MK)+CIZ+SOC and 17.7% for RTx LI(MK)+SOC. There were no SOC responders reported.

	RTx LI(MK)+CIZ+SOC (N=152) n (%)	RTx LI(MK)+SOC (N=62) n (%)	RTx SOC Alone (N=182) n (%)
Responders	**23 (15.1)**	**11 (17.7)**	**0 (0)**

The following table displays the response rate for the ITT LR RTx population (n=352). There were 32 ITT LR RTx subjects that responded. The response rates were 15.6% for ITT LR RTx LI(MK)+CIZ+SOC and 18.9% for ITT LR RTx LI(MK)+SOC. There were no SOC responders reported.

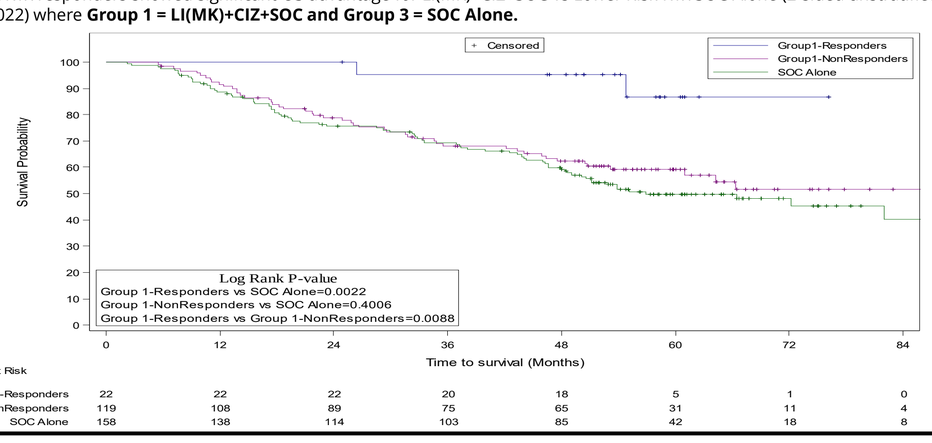
	Lower Risk RTx LI(MK)+CIZ+SOC (N=141) n (%)	Lower Risk RTx LI(MK)+SOC (N=53) n (%)	Lower Risk RTx SOC Alone (N=158) n (%)
Responders	**22 (15.6)**	**10 (18.9)**	**0 (0)**

EFFICACY - ITT RTx OVERALL SURVIVAL



EFFICACY - RESPONSE IMPACT ON ITT LOWER RISK RTx OVERALL SURVIVAL

ITT Lower Risk RTx responders showed significant OS advantage for LI(MK)+CIZ+SOC vs Lower Risk RTx SOC Alone (2-sided unstratified logrank p=0.0022) where **Group 1 = LI(MK)+CIZ+SOC and Group 3 = SOC Alone.**



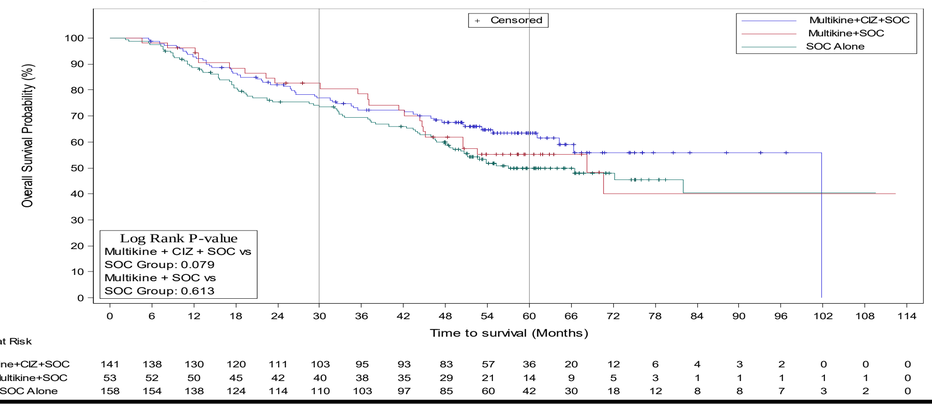
EFFICACY - RESPONSE IMPACT ON LOWER RISK DEATH RATES

Early response lowered death rates from, 48.7% (77/158) for ITT LR RTx SOC Alone (non-responders) in contrast to 15.6% (5/32) for ITT LI(MK)-treated LR RTx responders (two-sided Fisher Exact p=0.0027) and 43.8% (71/162) for LI(MK)-treated LR RTx non-responders (carryover evidence).

	Lower Risk RTx LI(MK) Responders % (n/N)	Lower Risk RTx LI(MK) Non-responders % (n/N)
LI(MK)+CIZ+SOC Death Rate	**9.1% (2/22)**	**42.0% (50/119)**
LI(MK)+SOC Death Rate	**30% (3/10)**	**48.8% (21/43)**
Combined Death Rate	**15.6% (5/32)**	**43.8% (71/162)**
Two-sided Fisher Exact Test		**P=0.0027**

EFFICACY - LI(MK) RESPONSE BENEFIT CARRIED OVER TO LOWER RISK OVERALL SURVIVAL

Overall Survival: ITT LR RTx favored LI(MK)+CIZ+SOC vs ITT LR SOC Alone (2-sided unstratified logrank p=0.079).
There was a 15.6% absolute OS advantage at 60 months.



EFFICACY - OVERALL SURVIVAL ACCELERATION: Increasing advantage for LI(MK)+CIZ+SOC vs SOC Alone: Month 36->48->60

The absolute OS advantage in ITT LR RTx LI(MK)+CIZ+SOC vs ITT LR SOC Alone was 2.8%/8.3%/15.6% at 36/48/60 months, representing 72.3% vs 69.5% at Month 36; 67.6% vs 59.3% at Month 48, and 65.3% vs 49.7% at Month 60. There was a 33.5-month median OS advantage (101.7 Months for ITT LR RTx LI(MK)+CIZ+SOC vs 68.2 Months for ITT LR RTx SOC Alone).

Time Post-randomization	Lower Risk RTx LI(MK)+CIZ+SOC (n=141)	Lower Risk RTx SOC Alone (n=158)	LI(MK)+CIZ+SOC Survival (%) Advantage over SOC Alone
Month 36	**72.3%**	**69.5%**	**+2.8%**
Month 48	**67.6%**	**59.3%**	**+8.3%**
Month 60	**65.3%**	**49.7%**	**+15.6%**

The proportional hazard model for ITT Lower Risk RTx reached statistical significance (two-sided Wald p=0.047) favoring LI(MK)+CIZ+SOC vs SOC (controlling for tumor stage, tumor location and geographic region).

The hazard ratio was 0.70 (95% CI: [0.49 - 1.00]) which represents a 43% prolongation.

EFFICACY - PROGRESSION-FREE SURVIVAL

The corresponding PFS advantage was 8.4% at 60 Months for ITT LR RTx LI(MK)+CIZ+SOC vs ITT LR RTx SOC Alone.

The HR was 0.81 (95% CI: [0.58 - 1.13]) in support of multi-dimensional efficacy.

SAFETY

- LI(MK) was easily administered without negative consequences
- LI(MK) pre-surgery TEAEs were all local; all resolved after surgery
- There were no LI(MK) systemic TEAEs
- Three LI(MK) related SAEs (3 separate cases) were reported inclusive of bleeding, osteoradionecrosis, and recurrent disease
- No LI(MK) TEAEs led to discontinuation
- No deaths or withdrawals were attributed to LI(MK)
- LI(MK) did not delay surgery or interfere with subsequent Disease-Directed Therapy (DDT)
- No TEAE/SAE excesses were seen during/after subsequent DDT for LI(MK)-treated vs. SOC

CONCLUSION

LI(MK) neoadjuvant immunotherapy treated SCCHN (oral cavity and soft-palate) enabled favorable efficacy outcomes (OS and PFS) including early objective response (per RECIST 1.0) prior to surgery in LR subjects receiving RTx post-surgery. There were no LI(MK)-related excess safety issues or TEAEs. ITT LR RTx LI(MK)+CIZ+SOC absolute OS advantage over SOC alone increased over time; the 0.70 HR corresponds to a 43% prolongation of median survival (equating to >12 months) in a population without any new therapy options in decades.

First author discloses financial interests

Author Contact Information: Eyal Talor, PhD; etalor@cel-sci.com