Abstract 6032: Leukocyte Interleukin Injection (LI) immunotherapy extends overall survival (OS) in treatment naïve low risk (LR) locally advanced primary squamous cell carcinoma of the head & neck: the IT-MATTERS Study (Clinicaltrials.gov NCT01265849)

Authors: E. Talor, D. Markovic, P. Lavin, J. Cipriano, J. Timar, A. Karpenko, I. Bondarenko, S. Stosic, H. Sobat, J. Horadugoda, A. Zhukavets, R. Nagarkar, N. Imamovic, C-Y. Chien, M. Bankowska-Wozniak, M. Kisely, R. Feinmesser, J.E. Young, C. Oliver, S-P. Hao

ABSTRACT

Background. The 3-week pre-surgery peritumoral/perilymphatic administration of an investigational proinflammatory cytokine complex biologic (LI) 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) significantly prolonged OS in the NCCN-defined LR intent to treat (ITT) population vs SOC alone. Encouraging phase 2 OS and early responder results motivated this pivotal study IT-MATTERS Clinicaltrials.gov NCT01265849. No safety issues were noted for LI in previous studies.
Methods: Subjects (923 ITT; of which 380 LR [Lower Risk for recurrence] ITT) meeting protocol entry criteria (including AJCC Stage III/IVa OSCC, soft-palate SCCHN, treatment naïve) were randomized 3:1:3 to treatment arms LI (+/- CIZ) + SOC or to Control (SOC alone). LI treated were administered 200IU peritumorally and the same dose peri-lymphatically daily for 3-weeks before surgery. All study subjects were to receive SOC (per NCCN Guidelines). LR for recurrence subjects were to receive RTx 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 LI treated (+/- CIZ) groups were 8.5% (45/529; overall LI) and 16% (34/212; LR LI) vs no SOC PSRs. Early response lowered death rate to 22.2% (ITT LI treated) vs 54.1% for non-PSRs (two-sided Fisher Exact (2FE) p<0.0001), for ITT LR LI PSRs with 17.6% vs 42.7% (2FE p=0.0067), and for ITT LR LI responders (LI+CIZ+SOC) 12.5% vs 41% (2FE p=0.0101). Proportional hazard (PH) ITT LR LI treated HR=0.348 (95% CI: [0.152, 0.801]), ITT LR LI+CIZ+SOC HR=0.246 (95% CI: [0.077, 0.787]). For all ITT LR (n=380), LI+CIZ+SOC demonstrated significant OS advantage vs SOC (log rank p=0.0478; Cox HR=0.68 (95% CI: [0.48-0.95]), Wald p=0.0236 [controlling for tumor stage, tumor location and geographic region]. The absolute OS advantage in ITT LR LI+CIZ+SOC vs SOC was 4.9%/9.5%/14.1%, at 36/48/60 months (M), representing 72.4% vs 67.5% (36 M); 67.3% vs 57.8% (48 M), and 62.7% vs 48.6% (60 M) with a 46.5 M median OS advantage (101.7 M [LI+CIZ+SOC] vs 55.2 M [SOC]). Percent treatment emergent adverse events (TEAEs) were comparable among all treated groups. No excess safety was reported for LI treatment over SOC alone.
Conclusions: LI immunotherapy did not add excess safety issues or TEAEs. Early LI response decreases mortality and predicts OS. ITT LR LI+CIZ+SOC absolute OS advantage over SOC alone increased over time; the 0.68 HR corresponds to a 47% 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).

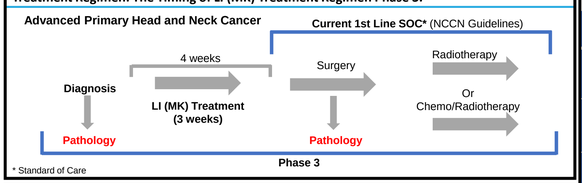
LI (MK) Phase 3 Trial Design (Open Label – OS Primary Endpoint)

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/m² (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

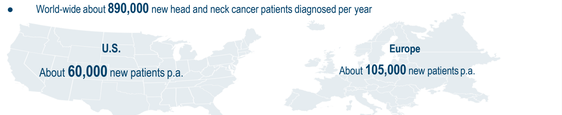
Treatment Regimen: The Timing of LI (MK) Treatment Regimen Phase 3.



* 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)

ITT Demographics: Overall and Lower Risk

Overall (n=923, 99.5%):
- Mean age: 56.6 years
- % Male: 79.3%
- % Caucasian: 79.7%
- % Europe/Eurasia: 41.4%
- % Tongue: 45.8%
- % Stage 3: 56.4%
- % RTx: 42.9%; % CRTx: 42.1%
- % Negative Margin: 77.7%

Lower Risk (n=380, 41.2%):
- Mean age: 57.3 years
- % Male: 79.7%
- % Caucasian: 82.4%
- % Europe/Eurasia: 51.3%
- % Tongue: 42.9%
- % Stage 3: 68.9%
- % RTx: 92.6%; % CRTx: 2.4%
- % Negative Margin: 99.7%

SAFETY:

SAFETY BACKGROUND:
- LI (MK) is only administered for three weeks before surgery
- Planned time to surgery from randomization: SOC alone, 2 weeks vs. LI, 5 weeks
- Disease-directed therapy (DDT) administered after surgery recovery
  - For lower-risk of recurrent per NCCN Guidelines: radiotherapy only
  - For higher-risk of recurrence per NCCN Guidelines: concurrent chemoradiotherapy
  - >80% study adherence
- Adverse event reporting complied with all regulatory requirements.
- No history of safety concerns in previous Phase 1 and 2 LI studies.
- Safety population (treated) in Phase 3: LI (512 subjects) vs Control (367 subjects).

SAFETY SUMMARY:
- LI (MK) was easily administered without negative consequences.
- LI (MK) pre-surgery TEAEs were all local – self resolving, were not present after surgery.
- There were no LI (MK) systemic TEAEs.
- LI (MK) related SAEs (5 cases in total) included edema, bleeding, osteoradionecrosis, atrial fibrillation, and delirium.
- LI (MK) TEAEs leading to discontinuation (2 cases) were edema and pyrexia.
- No deaths or withdrawals attributed to LI (MK).
- LI (MK) pre-surgery TEAEs all resolved after surgery.
- LI (MK) did not delay surgery or interfere with subsequent DDT.
- No TEAE or SAE differences among study groups during or after subsequent DDT.

EFFICACY:

EARLY RESPONDERS (ITT): Early response (from randomization to surgery) in the ITT population (n=923) was only seen in the LI (MK) investigational (neoadjuvant) treated population (n=529) with 45 early responders (5 complete responses). No early response was observed in the SOC only population (n=394). It is noteworthy that, spontaneous disease regression has not been reported in the literature for SCCHN.

Early Response Rates: Overall and NCCN Risk -based.

- Among all 923 subjects and within lower/higher/missing risk populations:

Metric	LI (MK)+CIZ+SOC (n=395)	LI (MK)+SOC (n=134)	Combined LI (MK) (n=529)	SOC (n=394)
Overall ITT	8.1% (32/395)	9.7% (13/134)	**8.5% (45/529)**	**0% (0/394)**
Lower Risk	15.2% (24/158)	18.5% (10/54)	**16.0% (34/212)**	**0% (0/168)**
Higher Risk	3.5% (7/200)	4.3% (3/69)	**3.7% (10/269)**	**0% (0/198)**
Missing Risk	2.7% (1/37)	0% (0/11)	**2.1% (1/48)**	**0% (0/28)**

In the as randomized ITT study population (n=923), the overall early response rate was 8.5% (45/529) for the combined LI (MK) treated groups; the early response rates were 8.1% (32/395) for LI (MK)+CIZ+SOC and 9.7% (13/134) for LI (MK)+SOC. The early response rate was 0% (0/394) for SOC; the difference between LI (MK) treated and SOC early response rate, for all patients as randomized, was highly significant (two-sided Fisher Exact test p=0.00000000001 [one in 100 billion]). The combined LI (MK) treated lower risk population had a 16% (34/212) early response rate and the LI (MK) treated higher risk population had an early response rate of 3.7% (10/269), while a 2.1% (1/48) response rate was noted in the LI (MK) treated subjects who had not been categorized to a risk group in the study. No early responses were observed in the SOC population irrespective of risk group.

Early Response Results in Decreased Death Rate (Prognostic and Predictive of Survival):

In Randomized ITT Population – LI (MK) Early Response (CR/PR) prior to surgery.

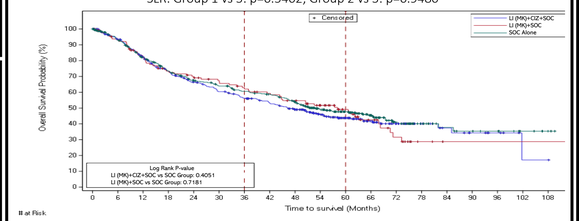
	Early Responders ((CR+PR)/n), (%)	Deaths % LI (MK) Early Responders / Remaining LI (MK)-Treated (n)	Hazard Ratio (HR) [95% CI]
All LI (MK) treated (Lower, Higher, and Missing Risk) (n=529)	45/529 (**8.5%**)	22.2% (10/45) Early Responders vs 54.1% (262/484) Early non-Responders 2-Sided Fisher Exact p-Value [**p<0.0001**]	**HR=0.301** [0.16, 0.566]
Combined Lower Risk LI (MK) treated (n=212)	34/212 (**16.0%**)	17.6% (6/34) Early Responders vs 42.7% (76/178) Early non-Responders 2-Sided Fisher Exact p-Value [**p=0.0067**]	**HR=0.348** [0.152, 0.801]
Lower Risk Group 1 LI (MK)+CIZ+SOC (n=158)	24/158 (**15.2%**)	12.5% (3/24) group 1 Early Responders vs 41.0% (55/134) Early non-Responders 2-Sided Fisher Exact p-Value [**p=0.0101**]	**HR=0.246** [0.077, 0.787]

NOTES: (1) Early response is highly prognostic for future survival. (2) No early responses in the control group.

Early response was prognostic and predictive of survival in the subjects who exhibited early response irrespective of their risk group allocation. These data set the stage for an overall survival advantage confirmation. For the lower risk LI (MK)+CIZ+SOC group, there was a 306% (100 x (1-0.246)/0.246) survival prolongation for 15.2% in this treatment group. Assuming no survival prolongation for the remaining 84.8% in this treatment group, this projects an overall 46.5% survival prolongation (3.06x15.2%); this corresponds to a 0.68 HR (1/1.465) which is exactly what was observed for the LI (MK)+CIZ+SOC group with lower risk classification (See right). The significant 0.68 HR for the lower risk population LI (MK)+CIZ+SOC vs. SOC equates to a 47% survival prolongation, characterized by a 5-year 14.1% absolute OS advantage, and a 46 month median OS advantage over lower risk SOC alone. Thus, a LI (MK) response not only is prognostic but also predicts a favorable survival outcome.

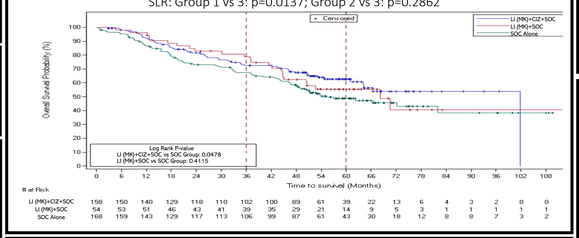
Overall Survival ITT Population (n=923). Kaplan-Meier (K-M) life tables for the study overall population. Group 1 = LI (MK)+CIZ+SOC; Group 2 = LI (MK)+SOC; Group 3 = SOC alone.
ULR = Unstratified Logrank, SRL = Stratified Logrank

OS From Randomization: ITT (n=923; 462 deaths)
ULR: Group 1 vs 3: p=0.4051; Group 2 vs 3: p=0.7181
SLR: Group 1 vs 3: p=0.5402; Group 2 vs 3: p=0.9480



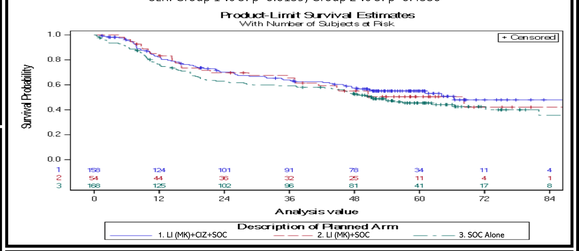
Overall Survival (OS) of the Study Lower Risk Population (n=380). Kaplan-Meier (K-M) life tables for the study lower risk population. Group 1 = LI (MK)+CIZ+SOC; Group 2 = LI (MK)+SOC; Group 3 = SOC alone. ULR = Unstratified Logrank, SRL = Stratified Logrank

OS From Randomization: Lower Risk ITT (n=380; 166 events)
ULR: Group 1 vs 3: p=0.0478; Group 2 vs 3: p=0.4115
SLR: Group 1 vs 3: p=0.0137; Group 2 vs 3: p=0.2862



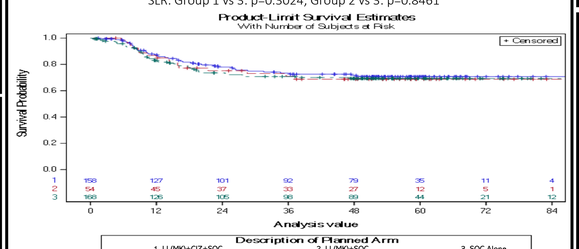
PFS from Randomization. Kaplan-Meier (K-M) life tables for the study lower risk population.

PFS From Randomization: Lower Risk ITT (n=380; 188 events)
ULR: Group 1 vs 3: p=0.1797; Group 2 vs 3: p=0.5175
SLR: Group 1 vs 3: p=0.0159; Group 2 vs 3: p=0.4530



LRC Failure from Randomization. Kaplan-Meier (K-M) life tables for the study lower risk population.

LRC Failure From Randomization: Lower Risk ITT (n=380; 104 events)
ULR: Group 1 vs 3: p=0.6142; Group 2 vs 3: p=0.9784
SLR: Group 1 vs 3: p=0.3024; Group 2 vs 3: p=0.8461



ITT OS Lower Risk: Randomization -> Exit: Ns, P-values, Medians (n=380).

		Endpoint		
	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	0.0137	0.0159	0.3024
Hazard Ratio	LI (MK)+CIZ+SOC vs SOC	0.68 (0.48-0.95)	0.76 (0.55-1.04)	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
Medians (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, & geographic region

OS ITT Lower Risk Entry -> Exit: % Alive 36, 48 and 60 Months (n=380).

		Treatment Group			Delta
Population	Milestone	LI (MK)+CIZ+SOC ('1')	LI (MK)+SOC ('2')	SOC ('3')	'1' vs '3'
ITT (99.5%)	36 months	72.4% (64.4%, 78.9%)	78.8% (65.0%, 87.7%)	67.5% (59.7%, 74.1%)	4.9%
ITT (99.5%)	48 months	67.3% (59.0%, 74.3%)	62.3% (47.4%, 74.1%)	57.8% (49.7%, 65.0%)	9.5%
ITT (99.5%)	60 months	62.7% (54.0%, 70.2%)	55.5% (40.5%, 68.2%)	48.6% (40.4%, 56.4%)	14.1%
Improving Overall Survival Advantage Over Time					

SUMMARY OF IT-MATTERS STUDY RESULTS:

1. ***SAFETY (N=923): no toxicity or safety issues reported in the LI (MK) arms.***
   - incidence of AE and SAE in LI (MK) arms not substantially different from control.
   - treatment was well tolerated and easy to administer (via injection locally around the tumor and peri–lymphatically).
2. ***EFFICACY (N=380): significant OS benefit in the lower-risk treatment cohort confirmed by multiple metrics.***
   - **14.1% absolute OS benefit** in the lower-risk treatment cohort
   - **101.7 months median OS** in lower-risk LI (MK) treatment cohort vs. 55.2 months in SOC control;
   - **16.0% early response rate** in lower-risk LI (MK) treatment cohort vs. 0% in SOC control;
   - **17.6% death rate for early responders** in lower-risk treatment cohort vs. 42.7% for non-responders;
   - histopathology confirms significant LI (MK) treatment effect vs. SOC via 61 markers, ratios, and combinations [Data Not Presented].
   - PFS (0.76 HR) supports OS (0.68 HR).
3. ***Consistent with Phase 2 results showing safety and efficacy.***
4. ***Clinically important: approximately 41% of the study subjects fell within the lower-risk cohort (similar to NCCN):***
   - About 210,000 locally advanced primary SCCHN patients globally annually, (~26,600 in the U.S.)
   - LI (MK) is different from other immunotherapies: Neoadjuvant delivered before SOC (surgery + DDT), as first treatment following diagnosis to previously untreated patients – producing early response (in 3-5 weeks prior to surgery).
5. ***Results of the IT-MATTERS Randomized Phase 3 study in the Advanced Primary SCCHN Lower Risk population, is First to demonstrate effect on OS (at 3-5 years) – No Randomized Studies have shown the same in the past 25+ years in this unmet patient population.***

SAFETY CONCLUSIONS

- LI (MK) easily administered without negative consequences
- LI (MK) pre-surgery TEAEs were all local
- There were no LI (MK) systemic TEAEs
- LI (MK) related SAEs (5 cases) included edema, bleeding, osteoradionecrosis, atrial fibrillation, and delirium
- LI (MK) TEAEs leading to discontinuation (2) were edema and pyrexia
- No deaths or withdrawals attributed to LI (MK)
- LI (MK) pre-surgery TEAEs all resolved after surgery
- LI (MK) did not delay surgery or interfere with subsequent DDT
- No TEAE or SAE differences during or after subsequent DDT

CONCLUSIONS

- Safety results were not significantly different between treatment groups.
- Leukocyte Interleukin, LI(MK) neoadjuvant immunotherapy did not add excess safety issues or TEAEs.
- In the Randomized ITT population, early LI (MK) response decreases mortality and is prognostic/predictive of OS.
- ITT Lower Risk LI (MK)+CIZ+SOC absolute OS advantage over SOC alone (Control) increased over time to 14.1% at 5-years; the 0.68 HR corresponds to a 47% prolongation of median survival, having a 46-month median OS advantage over SOC alone. The SCCHN population studied has been without any new therapy options in decades.

Acknowledgements:
The Sponsor wishes to thank all the study subject volunteers, the Clinical Investigators and sites, and the Study Team and co-developers for a global effort in conducting this Pivotal Study.

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