ESMO '22 Abstract 690P: Early response to Leukocyte Interleukin Injection (LI) immunotherapy extends overall survival (OS) in locally advanced primary squamous cell carcinoma (SCC) of the head & neck (HN): the IT-MATTERS Study (Clinicaltrials.gov NCT01265849)

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ABSTRACT

Background: The international, randomized, pivotal Phase 3 study (clinicaltrials.gov NCT01265849) evaluated a 3-week pre-surgery administration of an investigational natural cytokine complex biologic LI (MK) with/without CIZ (one-time low dose cyclophosphamide), indomethacin, and zinc multivitamins [both given daily starting with the first LI(MK) administration to 1-day before surgery] as compared to Standard of Care (SOC) in treatment naïve locally advanced SCC of the oral and soft-palate.

Methods: Early response (ER) pre-surgery was evaluated by RECIST for all subjects (923 ITT; 380 Lower Risk [LR], 467 Higher Risk [HR], and 76 Unclassified Risk [UC]) in addition to OS at 5-yrs. Subjects were randomized 3:1:3 to treatment arms LI (MK) (+/- CIZ*) + SOC or to Control (SOC alone). LI (MK) was administered daily for 3-weeks (x5/wk) before surgery. Overall median follow-up was 56 months.

Results: There were 45 objective ERs (5 complete and 40 partial responders) and 462 deaths (50.1%); the 5 complete responders [CRs] were all confirmed by pathology. ERs were only observed in the two LI-treated groups (8.5% combined LI; 16% LR combined LI vs 3.7% HR LI; 15.2% LR LI+CIZ+SOC). ERs were more commonly seen in the LR group (16.0%) vs the HR group (3.7%). No responders were seen in the SOC patients.
In the LI (MK)-treated groups, death rates fell significantly for ERs vs non-responders (54.1% vs 22.2% combined LI; 42.5% vs 17.6% LR combined LI (MK) groups; 40.7% vs 12.5% LR LI (MK)+CIZ+SOC); the corresponding hazard ratios (HZR) were 0.301 (Wald p<0.0001) overall, 0.348 (p=0.0067) for LR LI (MK), and 0.246 (p=0.01) for LR LI+CIZ+SOC in support of ER being prognostic.
Objective ER explained OS advantage in support of prediction; LR LI (MK)+CIZ+SOC exhibited 306% OS prolongation for 15.2% ERs. Assuming no OS prolongation for the remaining 84.8%, this equates to a 46.5% OS gain corresponding to the observed 0.68 HZR (1/1.465) for the ITT Lower Risk LI (MK)+CIZ+SOC group; this was consistent with the observed 46.5-month median OS advantage for LR LI+CIZ+SOC (101.7 months) vs LR SOC (55.2 months). ER was also predictive; among the 45 responders; there were only 10 deaths (22.2%) in contrast to 452 (51.5%) for the overall ITT population. Thus, ER was predictive from both a modeling and outcome perspective.

Conclusions: Objective ER was only observed for the LI (MK) treatments. Multiple ERs were observed across LR (n=34), HR (n=10), and UC (n=1). ER from LI (MK) treatment is not only prognostic but also predicts a most favorable OS outcome.

STUDY DESIGN:

Previously untreated locally 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. Patients 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

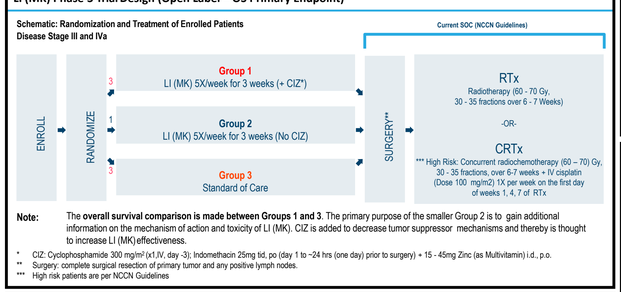
Groups 1 and 3 served as the main comparator arms. Group 2 was included to assess the need for CIZ and the toxicity of LI (MK) alone (i.e., without CIZ). Lower risk patients were to receive RTx; higher risk patients were to receive CRTx.

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

Secondary/other study objectives were to assess PFS, LRC, 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).

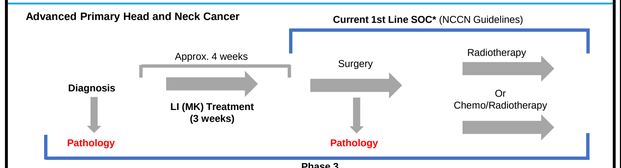
LI (MK) Phase 3 Trial Design (Open Label – OS Primary Endpoint)



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: LI (MK) Treatment Regimen

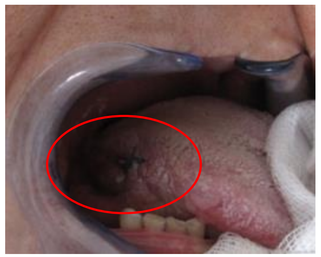


* Standard of Care

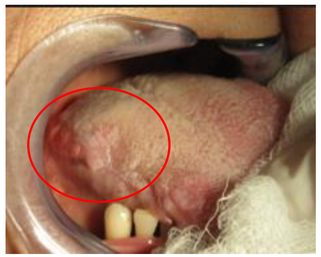
COMPLETE RESPONDER FIGURE 1:

European Subject (#013 non-EU country)

Subject assessed as having **Complete Response** based on Pathology findings immediately following surgery



Screening (Baseline Before Tx)

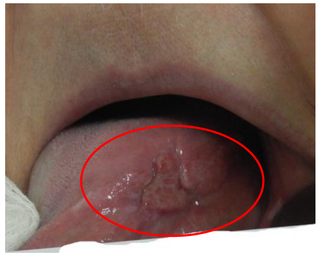


Post LI(MK)-Tx (Prior to Surgery)

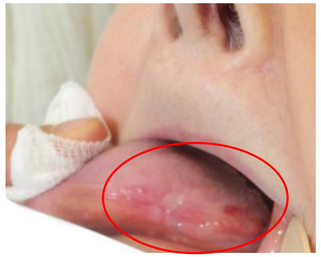
COMPLETE RESPONDER FIGURE 2:

European Subject (#028 non-EU country)

Subject assessed as having **Complete Response** based on Pathology findings immediately following surgery



Screening (Baseline Before Tx)



Post LI(MK)-Tx (Prior to Surgery)

CORRESPONDING COMPLETE RESPONSE (CR) CASE SUMMARIES (Local Pathology Reports):

European Subject (#013 non-EU country), Fig 1: This **59-year-old female** had a total resection of the primary tumor in in Oral Tongue with an elective (partial) resection of right (ipsilateral) neck lymph nodes.

No tumor positive for Squamous Cell Carcinoma (SCC) was identified during surgery: no malignancy cells in tumor tissue were seen as per pathology report. There was no extracapsular nodal spread, no positive margins of resection and no second primary tumor identified at the time of surgery.

Maximum dimension of the resected tumor mass was reported as 6 X 4.5 cm.

A total of 17 right neck ipsilateral lymph nodes were examined; no positive nodes for SCC histology were identified.

TNM staging at pathology report was not provided and indicated Not Done.

The pathology report supports that this patient has Complete Response.

European Subject (#028 non-EU country), Fig 2: This **74-year old female** had a total resection of the primary tumor in Oral Tongue with a total resection of left (ipsilateral) neck lymph nodes.

No tumor positive for Squamous Cell Carcinoma (SCC) was identified during surgery: complete response after treatment was noted at the pathology report. There was no extracapsular nodal spread, no positive margins of resection and no second primary tumor identified at the time of surgery.

Maximum dimension of the tumor mass *(in the resected mass)* was reported as 0X0 cm.

A total of 28 left neck ipsilateral lymph nodes were examined and no positive nodes for SCC histology identified.

TNM staging at pathology was (p)T0N0M0.

OTHER THREE COMPLETE RESPONDERS' SUMMARIES (Local Pathology Reports):

European Subject (#002 EU country): This **43-year old male** had a total resection of the primary tumor in Oral Tongue, and a total resection of both left and right neck lymph nodes.

No tumor positive for Squamous Cell Carcinoma (SCC) was identified during surgery: dysplasia and leucoplasia was noted at the pathology report. There was no extracapsular nodal spread, no positive margins, and no second primary tumor identified at the time of surgery.

Maximum dimension of the resected tumor mass was reported as 2.9 X 1.7 cm.

A total of 33 right neck ipsilateral lymph nodes and 29 left neck contralateral lymph nodes were examined and no positive nodes for SCC histology were identified.

TNM staging at pathology was reported as: (p)T0N0M0.

Asian Subject (#028 South Asia): This **54-year old male** had a total resection of the primary tumor in the right Cheek (Buccal Mucosa) with a total resection of right (ipsilateral) neck lymph nodes.

No tumor positive for Squamous Cell Carcinoma (SCC) was identified during surgery. There was no extracapsular nodal spread, no positive margins, no second primary tumor identified at the time of surgery.

Maximum dimension of the resected tumor mass was not reported in the pathology report.

A total of 16 right neck ipsilateral lymph nodes were examined and no positive nodes for SCC histology identified. Lymph nodes at level 1 to 5 negative for tumor shows reactive changes only.

TNM staging at pathology was reported T4aN0M0 which is the same TNM staging reported at screening and at Post-LI (MK)/Pre-surgery visit. TNM staging at pathology does not correspond with the pathology report which indicates complete response (CR), however oncology practice at some sites is to keep the initial TNM staging as it is during screening/treatment.

The pathology report supports that this patient has Complete Response.

Asian Subject (#022 South Asia): This **38-year old male** had a total resection of the primary tumor in the left Cheek (Buccal Mucosa) with total resection of left (ipsilateral) neck lymph nodes.

No tumor positive for Squamous Cell Carcinoma (SCC) was identified during surgery: no dysplasia or evidence of malignancy was noted in the pathology report. There was no extracapsular nodal spread, no positive margins of resection, and no second primary tumor identified at the time of surgery.

Maximum dimension of the tumor mass *(in the resected mass)* was reported as 0X0 cm.

A total of 9 left neck ipsilateral lymph nodes were examined and no positive nodes for SCC histology identified.

TNM staging at pathology was reported as: (p)T0N0M0.

EFFICACY: RESPONSE RATES, DEATH RATES, AND HAZARD RATES: RESPONDERS VS NON-RESPONDERS

- **Significantly, early objective responders were observed only for LI (MK) versus SOC alone (None observed in SOC)**

	Site Determined Risk Classification			
	Early Response Rate			
Treatment Group	**Lower Risk**	**Higher Risk**	**Unclassified**	**Totals**
LI (MK)+CIZ+SOC	15.2%	3.5%	2.7%	8.1%
LI (MK)+SOC	18.5%	4.3%	0%	9.7%
Combined LI (MK)	**16.0%**	**3.7%**	**2.1%**	**8.5%**
SOC alone (Control)	**0%**	**0%**	**0%**	**0%**
2-sided Fisher Exact Test	P<0.0001	P=0.0062	NS	P<0.0001

	Death Rate		
Response Outcome	**Combined LI (MK)**	**LR Combined LI (MK)**	**LR LI (MK)+CIZ+SOC**
Responders	22.2%	17.6%	12.5%
Non-responders	54.1%	42.5%	40.7%
2-sided Fisher Exact Test	P<0.0001	P=0.0068	P=0.01

	Hazard Ratio		
	Combined LI (MK)	**LR Combined LI (MK)**	**LR LI (MK)+CIZ+SOC**
Hazard Ratio	0.301	0.348	0.246
2-sided 95% CI	0.16, 0.566	0.152, 0.801	0.077, 0.787
2-sided Wald Test	P<0.0001	P=0.0067	P=0.01

OVERALL SURVIVAL: ITT LI (MK)+CIZ+SOC VS SOC; RESPONDERS VS NON-RESPONDERS

Consistent survival advantages were observed for responders vs. non-responders, as well as vs. SOC

	ITT Group 1 (LI(MK)+CIZ+SOC, N=395)		ITT Group 3 (SOC, N=394)		
Time to Survival (months)	**(A) Responders (N=32)**	**(B) Non-Responders (N=363)**	**(C) SOC Control, (N=394)**	**Observed Difference**	
	OS% [95% CI]	OS% [95% CI]	OS% [95% CI]	(A) – (C)	(B) – (C)
12	**100.0** [89.5, 100.0]	80.4 [75.7, 84.2]	81.9 [77.5, 85.5]	**+18.1**	-1.5
24	**90.0** [72.1, 96.7]	64.3 [58.9, 69.1]	67.5 [62.4, 72.1]	**+22.5**	-3.3
36	**86.5** [68.0, 94.7]	53.5 [47.9, 58.7]	60.6 [55.2, 65.5]	**+26.0**	-7.1
48	**83.1** [64.0, 92.6]	45.9 [40.3, 51.2]	53.7 [48.3, 58.8]	**+29.4**	-7.9
60	**72.9** [50.3, 86.4]	41.0 [35.4, 46.5]	47.7 [42.2, 53.0]	**+25.2**	-6.7

FIGURE 3: OVERALL SURVIVAL (OS): ITT POPULATION (N= 923) - OVERALL RISK RESPONDERS VS NON-RESPONDERS VS SOC

LOG RANK: RESPONDERS VS NON-RESPONDERS, P=0.0007; RESPONDERS VS SOC, P=0.0037; NON-RESPONDERS VS SOC, P=0.1070

- **Early Response is prognostic for Overall Survival**

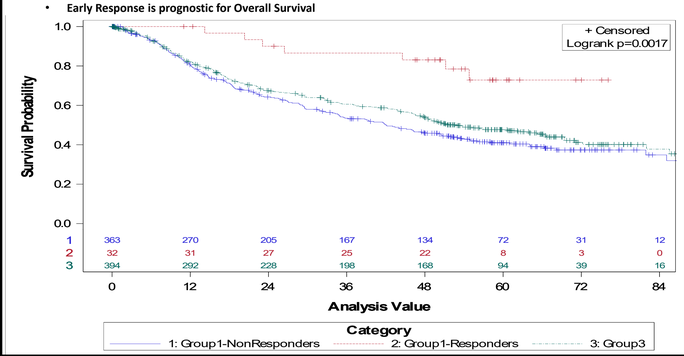
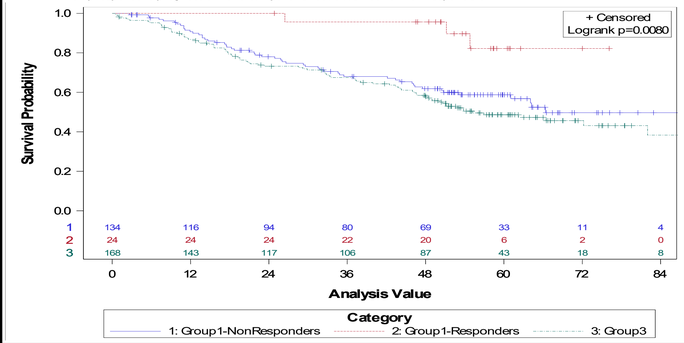


FIGURE 4: OVERALL SURVIVAL: ITT POPULATION - LOWER RISK [LR] (N= 380) RESPONDERS VS NON-RESPONDERS VS SOC

LOG RANK: LR-RESPONDERS VS LR-NON-RESPONDERS, P=0.0104; LR-RESPONDERS VS LR-SOC, P=0.002; LR-NON-RESPONDERS VS LR-SOC, P=0.2853

- **Early response is prognostic with a carryover effect observed for non-responders**



EARLY RESPONSE (ER) PREDICTIVE VALUE:

Objective ER explained OS advantage in support of prediction; LR LI (MK)+CIZ+SOC exhibited 306% OS prolongation for 15.2% ERs. Assuming no OS prolongation for the remaining 84.8%, this equates to a 46.5% OS gain corresponding to the observed 0.68 hazard ratio - HR (1/1.465) for the ITT Lower Risk LI(MK)+CIZ+SOC group; this was consistent with the observed 46.5-month median OS advantage for LR LI(MK)+CIZ+SOC (101.7 months) vs LR SOC (55.2 months).

Among the 45 early responders, there were only 10 deaths (22.2%) as of database lock in contrast to 452 (51.5%) for the overall ITT population. The causes of death for the 45 early responders included 4 progressions (8.9%) in contrast to 517 progressions (56.0%) for the overall ITT population.
Thus, ER was predictive from both a modeling and outcome perspective.

CONCLUSIONS:

- Early Response to LI(MK)-Treatment is noted BEFORE surgery (occurring at median 5 weeks post-randomization) adding credibility to the isolated impact of early response
- Early Response provides a positive signal to both patients and care providers (early in the treatment course)
- Early response was ONLY noted in the LI(MK) treatment groups
- Early response occurs in both the Lower Risk and Higher Risk groups for recurrence (Risk as defined per NCCN Guidelines)
- Early response is prognostic and <u>predictive</u> for overall survival in:
  - Overall, and
  - Lower Risk populations
- Benefit was also seen in LI(MK)-treated Lower Risk non-responders

Conflict of interest/ funding statement: Philip Lavin consults to the study sponsor (CEL-SCI Corp) through Lavin Consulting, LLC

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