ESMO '23 Abstract 893P: Tumor Node stage shift following Leukocyte Interleukin Injection (LI) neoadjuvant extends overall survival in treatment-naïve locally advanced primary squamous cell carcinoma of the oral cavity/soft palate

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ABSTRACT (ESMO '23 Abstract# 893P)

Background: A 3-week pre-surgery peri-tumoral/peri-lymphatic administration of an investigational pro-inflammatory cytokine complex biologic (LI) + CIZ (single low dose cyclophosphamide IV (300 mg/m^2), indomethacin (po 25mg tid) and zinc multivitamins (po 15-45mg zinc)) + Standard of Care (SOC) to treatment-naïve oral/soft palate (OSP) locally advanced primary SCC, resulted in CRs/PRs prior to surgery (RECIST 1.0, pathology confirmed) significantly extend overall survival (OS) in NCCN-defined low risk (LR) intent to treat (ITT) population vs SOC alone. Joint TN (jTN) distribution determined at screening, prior to planned surgery, confirmed at surgery. (IT-MATTERS; Clinicaltrials.gov NCT01265849).
Methods: Subjects (923 ITT; 380 [LR], 467 higher-risk [HR] for recurrence) AJCC Stage III/IVa OSCC, treatment naïve were randomized 3:1:3 to treatment (Tx) arms LI (+/- CIZ) + SOC or Control (SOC only). LI treated (Tx) received 400IU daily, ½ dose 200IU peritumorally + ½ dose 200IU peri-lymphatically x5/wk for 3-consecutive weeks before surgery. Each treatment group had comparable (55-56 months median) follow up. jTN = the sum of the TN score at screening and prior to surgery.
Results: TN data were available at screening and surgery for 815/923 ITT subjects; and 43 pre-surgery responders (R), a general trend of worsening jTN (W) entry to surgery with 6-7% more improved jTN (I) for both LI-Tx vs SOC. No significant differences at screening for subsequent Response vs non-Response; significant improvement in jTN stage from screening to surgery for LI R (88% improved); jTN differences (p<0.0001) between LR vs HR allowing differentiation of LR from HR at entry. LI-Tx subjects with jTN (I) had ~65% 5-year overall survival (OS) vs ~55% for SOC. LI+CIZ+SOC 5-yrs OS (I vs W) p <0.0001 and (Same vs W) p=0.0135. LR vs HR stage distribution p<0.0001 for both overall and for LI+CIZ+SOC.
Conclusions: jTN differentiated LR vs HR at entry enabling to search for LR subjects as ideal for neoadjuvant LI-Tx to extend OS. LI neoadjuvant jTN improvement is highly associated with OS joining pre-surgery response to LI as another surrogate marker for OS.

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 + CIZ + SOC n=395
Group 2 – LI + 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 alone (i.e., w/o CIZ). Low risk subjects (per NCCN Guidelines) were to receive RTx; high risk subjects were to receive CRTx.

- **Primary study objective** was to assess OS superiority of LI+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+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 (Group 1 vs Group3) which corresponded to a 10% absolute advantage at 3 years assuming exponential survival. For this comparison, the log rank test required a minimum of 298 deaths in the study combined comparator arms (Groups 1 and 3).

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

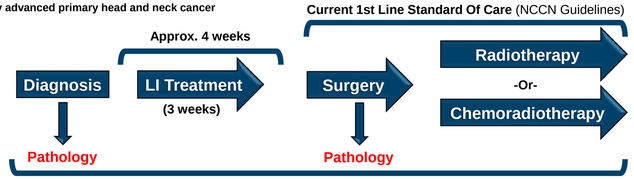
Schematic: Randomization and Treatment of Enrolled Patients
Disease Stage III and IVa

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.
- CIZ is added to decrease tumor suppressor mechanisms and thereby is thought to increase LI 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 is complete surgical resection of primary tumor and any positive lymph nodes.
*** High risk patients are per NCCN Guidelines

Treatment Regimen: LI Treatment Regimen

Locally advanced primary head and neck cancer



METHODS:

American Joint Committee on Cancer (AJCC) staging has long been accepted as a validated marker for survival outcome; there are established rules to define AJCC Stage according to tumor classification with node classification.

AJCC Stage was assessed at both screening/entry and at surgery using the respective tumor (T) and node (N) classifications. To standardize the AJCC Stage determination relative to the downstaging reported in the literature, the sponsor retrospectively mapped these TN scores to AJCC Stage using the AJCC TNM Staging Manual, 7th edition. This approach was used rather than using site-reported AJCC which could contain inaccurate stage mapping.

In addition, the AJCC Stage at screening/entry was examined to determine whether -there was AJCC Stage separation between lower risk and higher risk groups. The prognosis analyses for OS were performed by treatment group for the AJCC Stage shift classified as a downstage, no change, or upstage with prognostic analyses (death rates, time to death, Wald p-values, hazard ratios, two-sided 95% CIs, unstratified log rank tests) were conducted.

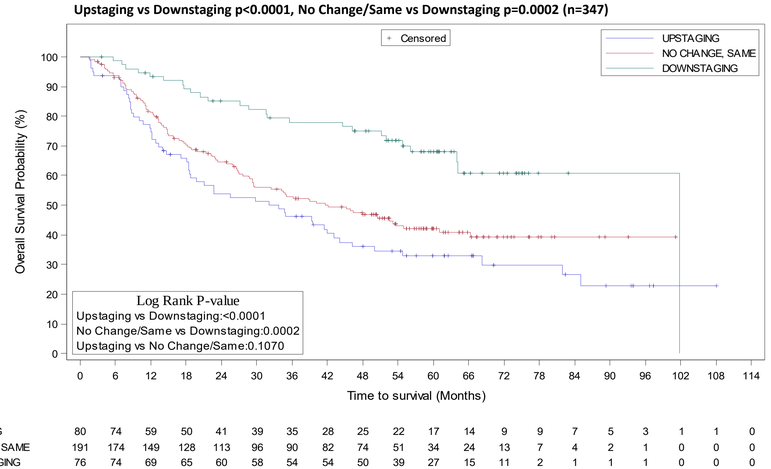
Joint Tumor-Node (jTN) Score is a new measure not yet validated. It was introduced to provide further insights into the numerical quantification of tumor and node classification. The sum of the tumor and node classification was computed at screening/entry and compared to that at surgery. This approach relies directly upon site determination of tumor and node classifications with no need to recompute this measure. The same analyses for Joint TN Score were performed as for AJCC.

Surgery Outcome Relative to Screening/Entry

- Significant worsening of condition in the control group from screening/entry to surgery is reflected in both AJCC Stage change (p=0.0052) and joint TN score change (p=0.00094) for control; however, in the LI treatment groups, there was no significant worsening of condition observed from either metric.
- In low-risk subjects (not shown), pre-surgical AJCC Downstaging (PSD) rate was significantly higher (p=0.0015) in the LI+CIZ+SOC group *vs* control (38.2% vs 21.3%).

	Surgery Outcome Relative to Screening/Entry				
	AJCC Stage Surgery Outcome Relative to Screening/Entry				
Treatment Group	Upstage (U)	No Change	Downstage (D) (PSD)	p-value (U *vs* D)*	p-value vs SOC**
LI+CIZ+SOC	80 (23.1%)	191 (55.0%)	76 (21.9%)	0.8103	0.002
LI+SOC	19 (16.59%)	72 (62.6%)	24 (20.9%)	0.5424	0.0499
Combined LI	99 (21.4%)	263 (56.9%)	100 (21.6%)	1.0000	0.0017
SOC alone (Control)	78 (22.1%)	229 (64.9%)	46 (13.0%)	0.0052***	N/A
*Exact two-sided conditional binomial test comparing (U) vs (D) (50% null hypothesis), **Two-sided Fisher Exact test of U and not-U distribution vs SOC alone, *** (U) vs (D) significant for SOC only					
	Joint TN Surgery Outcome Relative to Screening/Entry				
Treatment Group	Worse (W)	Same	Improved (I)	p-value (W vs I)*	p-value vs SOC**
LI+CIZ+SOC	118 (34.0%)	134 (38.6%)	95 (27.4%)	0.1315	0.0521
LI+SOC	40 (34.8%)	43 (37.4%)	32 (27.8%)	0.4096	0.1577
Combined LI	158 (34.0%)	177 (38.3%)	127 (27.5%)	0.0754	0.0333
SOC alone (Control)	121 (34.2%)	158 (44.8%)	74 (21.0%)	0.00094***	-
*Exact two-sided conditional binomial test comparing (W) vs (I) (50% null hypothesis), **Two-sided Fisher Exact test of I and not-I distribution vs SOC alone, *** (W) vs (I) significant for SOC only					

Overall ITT LI+CIZ+SOC Kaplan-Meier (K-M) Curve For AJCC PSD, No Change, and Upstage
Upstaging vs Downstaging p<0.0001, No Change/Same vs Downstaging p=0.0002 (n=347)



SUBJECT SELECTION MOVING FORWARD

Going forward, the LI target population can be defined according to the criteria 1 and 2 (below) to select at screening/entry patients with lower disease burden and inferred low risk per NCCN Guidelines classification*. These inclusion criteria are:

Criterion 1. Only locally advanced patients with N0 nodal status (and no extracapsular spread), as determined by PET-CT/MRI.

Criterion 2. Only those with low tumor PD-L1 expression defined as Tumor Proportion Score (TPS) < 10.

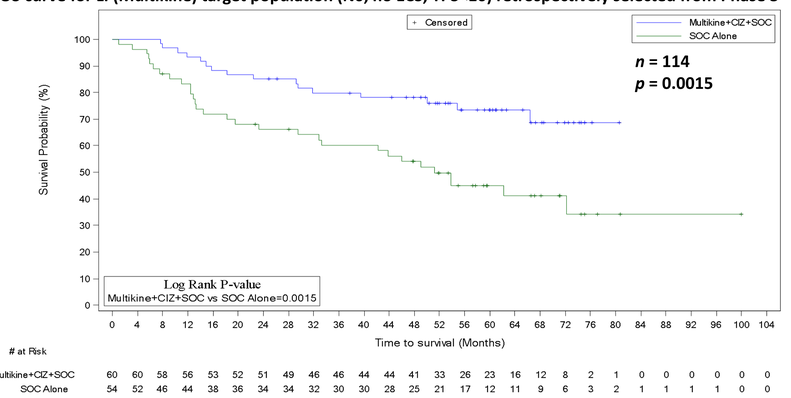
It is estimated that ~25% of all locally advanced primary SCCHN patients meet these criteria ~145,000 patients per year globally.
*Other inclusion criteria are consistent with those used in the pivotal Phase III study of LI.

Significant Survival Benefit In the LI Target Population (n=114) (N0, no extracapsular spread, and low tPD-L1 expression (TPS<10)*

Metric	LI + CIZ + SOC (N=60)	SOC Alone (N=54)	*p*-value
Pre-surgical response rate (clinical → pathological response per RECIST)	13%	0%	0.0065 (two-sided Fisher Exact)
Pre-surgical downstaging rate (AJCC stage change from screening/entry to surgery)	35%	13%	0.0085 (two-sided Fisher Exact)
5-year Overall Survival rate (28.6% absolute benefit)	73.4% 95% CIs [59.5, 83.2]	45% 95% CIs [30.6, 58.1]	0.0015 (unstratified log rank)
5-year Overall Survival (hazard ratio) (LI + CIZ + SOC vs SOC alone)	HR = 0.349 (95% CIs [0.184, 0.660], Wald *p*=0.0012)		
5-year Progression Free Survival (hazard ratio) (LI + CIZ + SOC vs SOC alone)	HR = 0.531 (95% CIs [0.307, 0.920], Wald *p*=0.0240)		

* Based on Phase III subjects retrospectively analyzed with N0 at screening, no ECS at surgery (inferred no ECS at screening) and with histopathology analysis to determine TPS<10

K-M OS curve for LI (Multikine) target population (N0, no ECS, TPS<10) retrospectively selected from Phase 3



CONCLUSIONS:

- A highly significant differential distribution of baseline joint TN score in the low-risk (LR) vs high risk (HR) groups supports the use of baseline TN scores to select patients with lower disease burden at screening/entry.
- LI treated subjects demonstrated a significant shift in AJCC downstage from baseline to surgery in the LI+CIZ+SOC vs SOC
- The joint TN score results correlate/support the computed established AJCC stage results.
- Patients with lower disease burden at screening/entry are the ideal candidates for the proposed indication for use of LI, in view of the Phase 3 ITT low risk LI-treated subjects who had HR=0.68 (95% CIs [0.48, 0.95]) vs SOC (control).
- Patients with low tPD-L1 expression (TPS <10) are also good candidates for the proposed indication for use of LI-Tx, in view of the Phase 3 subjects with histopathology analysis (n=453) who had HR=0.60 (95% CIs [0.36, 1.00]) vs SOC (control).
- Taken together, the ideal candidates for the proposed indication for use of LI are patients presenting at baseline with N0 and no ECS determined via PET-CT/MRI and having low tPD-L1 expression (TPS <10) determined by biopsy.
- The joint TN score analysis, as confirmed by AJCC stage analysis, shows that these ideal LI candidates should be readily identifiable at baseline by the oncology care provider with current imaging practices (e.g., PET-CT/MRI) and pathology.

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