Histopathology population (HPP) confirms Multikine [Leukocyte Interleukin Injection (LI)] treatment (Tx) outcome in naïve locally advanced primary head & neck squamous cell carcinoma (SCCHN)

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Abstract (Poster #1231)

Background: In a Phase 3, randomized, controlled pivotal study, pre-surgery administration of investigational proinflammatory biologic Multikine (LI) with CIZ (single low dose cyclophosphamide IV, indomethacin (po tid) and Zinc (po, daily) multivitamins + Standard of Care (SOC) to oral and soft-palate SCCHN subjects, resulted in significantly prolonged overall survival (OS) in the NCCN Guidelines defined low risk (LR) intent to treat (ITT) population vs SOC alone (IT-MATTERS Study, Clinicaltrials.gov NCT01265849).

Methods: Available HPP ITT subjects (453 ITT; 210 LR ITT) meeting entry criteria (AJCC Stage III/IVa OSCC, soft-palate SCCHN, Tx naïve) randomized 3:1:3 to Tx arms LI (+/- CIZ) + SOC or SOC alone. LI was injected 200IU peritumorally and 200IU peri-lymphatically daily, 3-weeks before surgery. All study subjects were to receive SOC (per NCCN, LR RTx, high risk CRTx post-surgery). Follow-up was comparable (55-56 months median per Tx group). Tumor HP samples were stained/quantitated for 20 biomarkers (5 tumor cell, 15 tumor microenvironment); 2 ratios; 14 marker combinations were prospectively defined, including low/high thresholds for each biomarker, ratio; combinations defined as +ve or -ve. Defined prospective interactions models (all subjects) allowed three-way interactions for risk groups, biomarker/combination level to analyze Tx efficacy for tumor response and OS, PFS, LRC hazard ratios (HR) using proportional hazard models.

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: LI(MK)+CIZ+SOC; n=395, LI(MK)+SOC; n=134, SOC alone; 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).

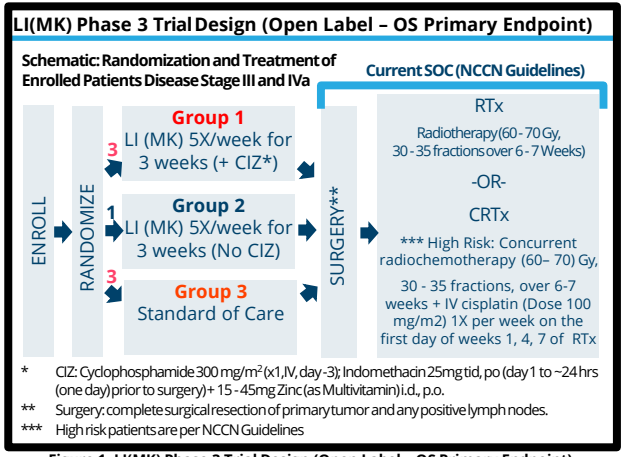

Figure 1. LI(MK) Phase 3 Trial Design (Open Label – OS Primary Endpoint)

Subject Disposition – HP Population

Nearly half (49.1%; 453/923) of the ITT population had histopathology (HP) data. The histopathology population was representative of the ITT population for all baseline characteristics.

As per NCCN Guidelines, there were 847 subjects with risk group classification. Among the 453 subjects with HP data, there were 210 Lower risk subjects and 242 Higher risk subjects (plus one LI(MK)+CIZ+SOC subject with no risk classification).

Results:

Efficacy – Responders

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

The response rates were consistent for the ITT and HP populations; there were no SOC response reported. LI(MK) responses were observed in both higher and lower-risk. LR subjects achieved a 20% response rate, consistent with Phase 2.

Table 1. Response rates for ITT (n=923) and HP (n=453) populations as well as for the corresponding Lower-risk groups.

	LI(MK)+CIZ+SOC n (%)	LI(MK)+SOC n (%)	SOC Alone n (%)
ITT Response Rate: Overall	**8.1% (32/395)**	**9.7% (13/134)**	**0% (0/395)**
ITT Response Rate: Lower-risk	**15.2% (24/158)**	**18.5% (10/54)**	**0% (0/168)**
HP Response Rate: Overall	**7.1% (14/196)**	**13.6% (9/66)**	**0% (0/191)**
HP Response Rate: Lower-risk	**17.1% (14/82)**	**27.3% (9/33)**	**0% (0/95)**

Results.

The HPP (n=453) and the LR HPP (n=210) were representative of the overall population (n=923). LR efficacy (OS, PFS, LRC) was favorable for LI+CIZ+SOC vs SOC as shown below:

Table 2. LR HPP

LR HP (n=210)	Overall Survival	Prog-Free Survival	Local Regional Control
HR (95% CI)	0.64 (0.41 - 1.01)	0.67 (0.44 - 1.02)	0.62 (0.35 - 1.09)
Cox p-value	0.0569	0.0632	0.0961
5-year success	63.9% vs 44.4%	56.9% vs 41.1%	73.1% vs 63.6%

Efficacy for the 36 analysis sets favored LI+CIZ+SOC vs SOC (FLI) significantly more often than favoring SOC (FSOC) (conditional binomial; p<0.0001); see below:

Table 3. Efficacy for the 36 analysis sets

	Proportion Statistically Significant, one-sided p<0.025	
	Overall (n=453)	LR (n=210)
Overall Survival	26/93 (FLI) vs 1/93 (FSOC)	21/93 (FLI)
Prog-Free Survival	17/93 (FLI) vs 2/93 (FSOC)	16/93 (FLI)
Local Reg Control	18/93 (FLI) vs 2/93 (FSOC)	17/93 (FLI)
Totals	61/279 (21.9%>>2.5%) vs 5/279 (1.9%)	54/279 (19.4%>>2.5%)
All LR advantages favored LI+CIZ+SOC vs SOC (FLI)		

Conclusion

LI neoadjuvant Tx followed by surgery and NCCN-directed DDT confirmed efficacy (OS, PFS, LRC) in the HP subset, independent of multiple biomarkers (tumor: p16, PDL1, TME: CD4, CD8, CD3, FOXP3, CD20, CD68, CD163, CD1A, immune cells: PD1, CTLA4, PDL1, and CD25), ratios (CD4/CD8, CD8/FOXP3), and pre-defined combinations. LI + Surgery + DDT prolongs OS in SCCHN patients with no new Treatment options in decades.