Abstract 672P

Nivolumab (Nivo) and ipilimumab (Ipi) combined with radiotherapy (RT) in patients (pts) with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN): updated results on efficacy and correlative analysis

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Background

Immune checkpoint inhibitors are standard of care in recurrent/metastatic SCCHN. We evaluated concurrent radioimmunotherapy (RIT) with Nivo and Ipi in the definitive setting for patients with high-risk LA SCCHN.

Methods

Pts with newly diagnosed, AJCC 7th edition stage IVA-IVB SCCHN of the oropharynx (OP; OP HPV+ were T4, N2c or N3), hypopharynx, and larynx that were eligible for chemotherapy received Nivo (3 mg/kg Q2 weeks x 17) and Ipi (1 mg/kg Q6 weeks x 6) starting 2 weeks prior to IMRT (2 Gy/fraction/day to a total of 70 Gy). The primary endpoint was safety of RIT. Secondary endpoints included progression-free survival (PFS) and overall survival (OS). Exploratory endpoints included the association of baseline PD-L1 expression as well as on-treatment changes in immune bias with treatment outcomes, analyzed by Luminex Millipore (HCYTA-60K).

Table 1. Patient characteristics.

Characteristic	N (%)
Total	24 (100)
Age	
Median (Range)	60.5 (48-77)
Gender	
Male	20 (83)
Female	4 (17)
ECOG performance status	
0	14 (58)
1	10 (42)
Location of primary tumor	
Oropharynx	16 (66)
p16+	14 (88)
p16-	2 (12)
Larynx	6 (25)
Hypopharynx	2 (8)
Stage (AJCC 7th Edition)	
IVA	23 (96)
IVB	1 (4)
Stage (AJCC 8th Edition)	
II	8 (33)
III	6 (25)
IVA	10 (42)
PD-L1 CPS	
<1	5 (21)
1-19	8 (33)
≥ 20	9 (38)
Not available	2 (8)

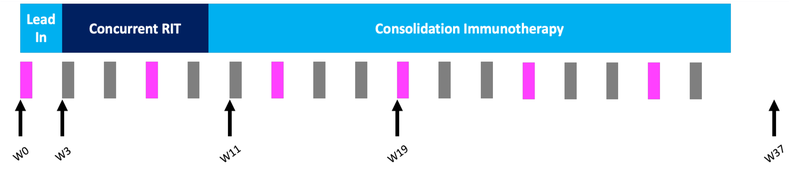

Figure 1. Study schema. Study participants received Nivo (3 mg/kg Q2 weeks x 17) and Ipi (1 mg/kg Q6 weeks x 6) starting 2 weeks prior to IMRT (2 Gy/fraction/day to a total of 70 Gy). Total duration of treatment was 32 weeks. Magenta bars represent concurrent administration of Nivo plus Ipi; grey bars represent administration of single agent nivo; black arrows show timepoints where blood was drawn for correlative studies.

Results

24 pts (16 OP of whom 14 HPV+) were enrolled and followed for a median of 36.1 months. At data cutoff, 7 PFS events were noted, including 5 distant recurrences, 1 regional recurrence and 1 death without evidence of disease progression. The 3-year PFS and OS rates were 74% (95% CI, 58%-94%) and 96% (95% CI, 88%-100%), respectively; 3-year locoregional control rate was 95% (95% CI, 85%-100%). PD-L1 CPS did not correlate with death or disease progression. Among different cytokines, decreased MCSF levels were associated with prolonged PFS at several timepoints (baseline [p=0.038], post-induction [p=0.031], and at the end of RT [p=0.023]); interval decrease in IFNg inducing factor (IL18) within the induction phase was also associated with prolonged PFS (p=0.031), as were post-induction IFNg levels (p=0.041). 5 pts developed in-field ulcerations during consolidation immunotherapy (median time to detection was 3 months post RT completion). PD-L1 CPS did not correlate with ulceration. Interestingly, interval increase in IL9, IL4, IL12, and IL17a during concurrent RIT appeared to protect from in-field ulcerations.

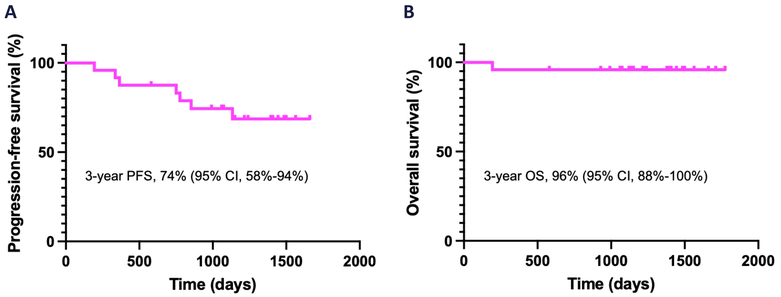

Figure 2. Kaplan-Meier curves showing progression-free survival (A) and overall survival (B) for study participants.

Table 2. Cytokines associated with progression-free survival over subsequent study timepoints.

Cytokine	W0 beta	p value	W3 beta	p value	W11 beta	p value	W19 beta	p value	W37 beta	p value
GCSF	0.00048	0.78	**0.0077**	**0.033**	-0.0076	0.35	-0.00039	0.76	0.0044	0.32
GROa	0.00096	0.22	0.00025	0.91	-0.0015	0.66	0.0025	0.091	**0.0015**	**0.036**
IFNg	0.0074	0.055	**0.011**	**0.043**	-0.014	0.33	-6.00E-04	0.67	0.0024	0.39
IL18	7.30E-05	0.6	**0.00083**	**0.0039**	0.00047	0.077	5.20E-05	0.88	0.00023	0.71
IL1RA	0.0016	0.36	**0.0017**	**0.025**	**0.0022**	**0.036**	-0.00041	0.78	0.0023	0.43
IL22	**0.011**	**0.0078**	**0.0077**	**0.0063**	-0.0015	0.84	-0.00042	0.67	0.0049	0.05
MCSF	**0.021**	**0.03**	**0.0055**	**0.023**	**0.014**	**0.024**	-0.00069	0.76	0.0075	0.13
MDC	**0.00025**	**0.031**	0.00012	0.18	0.00014	0.15	0.00025	0.11	0.00019	0.13
MIP1b	**0.0061**	**0.049**	**0.0071**	**0.035**	0.0059	0.1	-0.00012	0.86	0.0051	0.11
PDGF.AA	**0.00026**	**0.035**	0.00033	0.076	1.00E-04	0.56	0.00021	0.3	0.00015	0.26
sCD40L	**0.00024**	**0.042**	0.00043	0.16	0.00025	0.28	0.00018	0.59	0.00018	0.2
TNFa	**0.025**	**0.028**	**0.045**	**0.03**	-0.019	0.32	-0.0022	0.74	0.011	0.23
TNFb	**0.015**	**0.036**	**0.013**	**0.013**	-0.0032	0.71	-0.00043	0.67	0.0056	0.071

Table 3. Cytokines associated with soft tissue ulceration over subsequent study intervals.

Cytokine	W3/W0 Welch-corr. t	p value	W11/W3 Welch-corr. t	p value	W19/W11 Welch-corr. t	p value	W37/W19 t	p value
Fractalkine	0.23505646	0.821	**2.30894993**	**0.0429**	0.97989715	0.342	-0.1687363	0.869
IFNa2	-0.1313897	0.898	**2.61190606**	**0.0167**	1.3321751	0.202	-0.5193979	0.618
IFNg	1.14239618	0.281	**3.03631895**	**0.0114**	1.08673881	0.294	0.61625964	0.549
IL12p70	-0.6425877	0.547	**3.6509908**	**0.00159**	1.19488118	0.251	0.51974998	0.615
IL13	-0.3228027	0.762	**3.03369606**	**0.00838**	1.1117454	0.284	-0.0658374	0.949
IL15	0.93682721	0.367	**2.4302002**	**0.0246**	1.10200586	0.287	0.60276884	0.557
IL17a	0.59545326	0.563	**3.45271796**	**0.00252**	1.19042653	0.252	-0.6624922	0.529
IL17F	-0.9260364	0.389	**2.75855848**	**0.0122**	1.31098345	0.21	0.48786158	0.637
IL1a	-1.2123327	0.279	**2.81335855**	**0.0124**	1.19197024	0.252	-0.9882743	0.384
IL1b	-0.4790152	0.649	**2.4892668**	**0.0223**	1.15765308	0.265	0.28875094	0.778
IL25	-0.4108391	0.687	**2.77435165**	**0.0128**	1.21859899	0.242	0.55210423	0.592
IL27	0.91351431	0.375	1.71870323	0.105	-0.8296105	0.446	**2.25612971**	**0.0438**
IL3	0.03056741	0.976	0.66481194	0.519	**2.14403418**	**0.0452**	-0.4097819	0.707
IL4	0.23185431	0.824	**4.09151195**	**0.000815**	1.12686235	0.276	-0.2433422	0.821
IL6	-0.9612486	0.381	**2.29081628**	**0.0332**	1.64618329	0.116	-0.0264161	0.98
IL7	-0.4577894	0.667	**2.33934985**	**0.0362**	0.14880823	0.886	-0.3005009	0.787
IL8	-0.2524942	0.808	0.89025023	0.384	**2.12676834**	**0.0494**	-0.7646936	0.492
IL9	-1.0068434	0.333	**4.14564261**	**0.000651**	1.19503076	0.25	-0.0501163	0.962
MIP1b	0.03914274	0.97	**2.59326375**	**0.0207**	0.97569984	0.343	0.89765002	0.387
TNFb	1.07128941	0.31	**2.42434145**	**0.0356**	1.07105091	0.301	-0.1324976	0.898

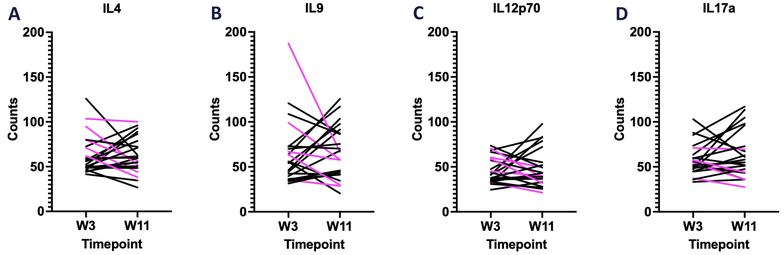

Figure 3. Peripheral decreases in IL4 (A), IL9 (B), IL12p70 (C) and IL17a (D) during concurrent RIT predispose to soft tissue ulceration. Associations are significant after correction for multiple testing.

Conclusions

Definitive RIT has sufficient clinical activity to support further development. Cytokine profiles appear able to predict treatment failure, as well as in-field ulcerations early during treatment.

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