Clinical and Immunological Profile of Patients with Immune-Related Adverse Effects Following Treatment with Immune Checkpoint Inhibitors

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Background

- Immune-related adverse effects (irAEs) have been associated with survival benefits in melanoma and non-small-cell lung cancer patients on immune checkpoint inhibitors (ICIs), but this association has not been well-established in patients with head and neck squamous cell carcinoma (HNSCC)[1-4].
- Furthermore, little is known about the mechanisms behind irAEs and if there are any predisposing factors to developing irAEs.
  - They are thought to represent bystander effects from activated T-cells or disinhibition of immune checkpoints that protect against autoimmunity[5,6].
  - Variations in T-cell function among patients could contribute to the development of irAEs.

Objectives:

- To investigate the association between irAEs and response to immunotherapy in patients with HNSCC.
- To identify differences in circulating cytokine levels between patients who experienced irAEs and those who did not while on ICI therapy for HNSCC.

Methods

This was a retrospective cohort study that included patients with HNSCC enrolled in one of three immunotherapy-based clinical trials:

A window of opportunity trial of preoperative nivolumab with or without tadalafil in squamous cell carcinoma of the head and neck (NCT03238365) (Nivo-Surg)

- Investigator-initiated, two arm multi-institutional randomized trial
- Patients with newly diagnosed + resectable HNSCC of any stage
- Randomized 1:1 to receive PD-1 inhibitor nivolumab (Bristol Myers Squibb, New York, NY) alone or nivolumab plus tadalafil (Eli Lilly, Indianapolis, IN) with stratification for HPV status
- Definitive surgical resection at 4 weeks

Nivolumab, Ipilimumab, and Radiation Therapy in Treating Patients with Stage III-IVB Head and Neck Cancer (NCT03162731) (Nivo-Ipi-XRT)

- Phase I investigator-initiated single-arm non-randomized trial
- Patients with clinical stage III-IVB (AJCC 8th Ed.) HNSCC
- Subjects received nivolumab (Bristol-Myers Squibb) IV and the CTLA-4 inhibitor ipilimumab (Bristol-Myers Squibb) IV
- Beginning week 3, simultaneous integrated boost intensity-modulated radiation therapy (XRT) or volumetric modulated arc therapy for five days/week over seven weeks

Durvalumab With or Without Metformin in Treating Participants with Head and Neck Squamous Cell Carcinoma (NCT03618654) (Durva-Surg)

- Phase I investigator-initiated, two arm randomized trial
- Patients with any stage resectable HNSCC
- Randomized 3:1 to PD-L1 inhibitor durvalumab (Medimmune/AstraZeneca) + metformin (generic from the hospital's pharmacy) (Arm A) or durvalumab alone (Arm B)
- Definitive surgical resection at 4 weeks

Each trial prospectively collected adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Assessment of Pathologic Treatment Effect:

- Nivo-Surg and Durva-Surg involved definitive cancer resection.
- Pathologic specimens from day of surgery independently graded by two pathologists.
- All slides with tumor (primary and all lymph nodes) included in analysis.

pTE% = Areas of Treatment Effect/Total Tumor Surface Area

- Histologic criteria for pTE included areas of macrophage reaction, multinucleated giant cells and granulomas, fibrosis, and chronic inflammation adjacent to residual tumor nests[7].
- Nivo-Surg: Responder pTE% ≥ 20% and Non-responder pTE% < 20%
- Durva-Surg: Responder pTE% > 10% and Non-responder pTE% ≤ 10%

Cytokine Analysis:

- Peripheral whole blood taken at time of study recruitment (pre-treatment) and four weeks after beginning treatment (post-treatment).
- Samples fractionated via centrifugation and plasma collected and stored at -80°C.
- MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panels (Millipore) used to identify cytokines present in plasma at both timepoints.
- Standardized curves generated for each cytokine, and median fluorescent intensities transformed into concentrations by 5-point, non-linear regression.
- We will present the cytokine profile of the Durva-Surg trial separately from the other two trials that utilized nivolumab as they have different mechanisms of action.

Results

A total of 104 patients were included in this study:

- 43% Nivo-Surg (n = 45)
- 23% Nivo-Ipi-XRT (n = 24)
- 34% Durva-Surg (n = 35)

Table 1 shows the frequency of irAEs experienced stratified by clinical trial.

- Four Grade 3 reactions (all in Nivo-Ipi-XRT)
- Remainder Grade 1-2

Positive p16 status was significantly associated with irAEs (odds ratio [OR] 2.64; 95% CI 0.98-6.62; p = 0.046).

Table 1
Frequency of irAEs by Clinical Trial

	Nivo-Surg (n = 45)	Nivo-Ipi-XRT (n = 24)	Durva-Surg (n = 35)
irAE			
Dermatologic[a]	6 (13%)	10 (42%)	6 (17%)
Endocrine[b]	4 (9%)	5 (17%)	3 (9%)
Gastrointestinal[c]	0 (0%)	2 (4%)	0 (0%)
Multi-Organ IRAE	1 (2%)	4 (17%)	1 (3%)

[a]Dermatologic: dermatitis (n = 22), psoriasis flare (n = 1).
[b]Endocrine: hypothyroidism (n = 9), hyperthyroidism (n = 2), hyperglycemia (n = 1).
[c]Gastrointestinal: colitis (n = 1), lipase elevation (n = 1).

Pathologic Response

- Of patients evaluable for pathologic treatment response, there were 30 responders (38%, n = 78).
- Patients in Durva-Surg were less likely to be pathologic responders than in Nivo-Surg (OR 0.165; 95% CI 0.05-0.52; p = 0.002).
- In the combined cohort, there was a statistically significant association between irAEs and pathologic response to treatment (OR 4.05; 95% CI 1.34-13.32; p = 0.022).
- When stratified by study, there remained a significant association between the presence of irAEs and pathologic response within Nivo-Surg (OR 10.0; 95% CI 1.48-115.6; p = 0.025) but not within Durva-Surg (OR 4.40; 95% CI 0.79-22.3; p = 0.137) (Table 2).

Table 2.
Proportion[a] of Responders and Non-Responders with irAEs

		irAE +	irAE -	P-value	Odds Ratio		
					Value	95% CI (Low)	95% CI (High)
Combined	Responder	37% (11)	63% (19)	0.022	4.05	1.34	13.32
	Non-Responder	13% (6)	87% (42)				
Nivo-Surg	Responder	33% (8)	67% (16)	0.025	10.0	1.48	115.6
	Non-Responder	5% (1)	95% (20)				
Durva-Surg	Responder	50% (3)	50% (3)	0.137	4.40	0.79	22.3
	Non-Responder	19% (5)	81% (22)				

[a]Proportions represented as a percentage of row total.
Abbreviations: irAE, immune-related adverse effects; CI, confidence interval.

Survival

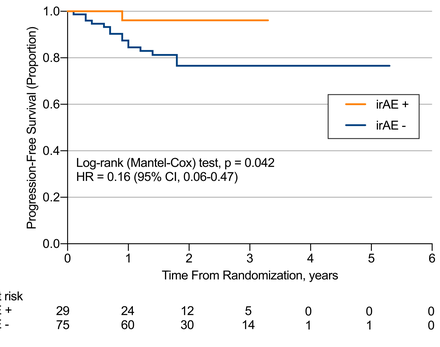

Figure 1. Kaplan-Meier PFS curves for length of time between trial enrollment and recurrence of disease or death are presented for the irAE + and irAE - groups.

There was a significant difference in PFS between the two groups (log-rank test p = 0.042).

At 1 year, the Kaplan-Meier survival probability estimates were 0.96 for patients with irAEs and 0.85 for patients without irAEs.

At 3 years, these estimates were 0.96 for patients with irAEs and 0.77 for patients without irAEs.

Cytokine Analysis

Table 3.
Comparison of Circulating Cytokine Concentrations (pg/mL) Between irAE + and irAE - Patients Treated with Nivolumab

Mean (±SE)	Pre-treatment			Post-treatment		
	irAE -	irAE +	P-value	irAE -	irAE +	P-value
TNF-α	91.7 (±12.2)	152.4 (±19.2)	0.008	105.0 (±9.7)	138.3 (±15.1)	0.062
IFN-γ	98.5 (±30.2)	280.3 (±47.7)	0.002	105 (±18.6)	180.4 (±29.2)	0.031
IL2	62.8 (±8.0)	85.6 (±12.4)	0.123	66.1 (±5.7)	92.2 (±8.9)	0.014
IL3	37.3 (±2.5)	50.3 (±3.9)	0.005	40.7 (±3.6	68.3 (±5.6)	< 0.001
IL4	50.5 (±11.6)	135.2 (±18.3)	< 0.001	54 (±6.0)	88.7 (±9.4)	0.002
IL5	59.9 (±12.8)	124.5 (±20.2)	0.007	63.1 (±8.1)	99.4 (±12.7)	0.017
IL6	88.8 (±14.7)	150.5 (±23.3)	0.027	184 (±24.6)	277.0 (±38.5)	0.043
IL7	42.3 (±3.6)	62.3 (±5.8)	0.004	51.7 (±7.4)	88.2 (±11.6)	0.009
IL10	60.2 (±6.0)	85.1 (±9.5)	0.028	76.7 (±7.7)	142.6 (±12.0)	< 0.001
IL15	57.0 (±4.0)	68.6 (±6.3)	0.119	69.7 (±7.0)	96.7 (±11)	0.040
IL22	219.2 (±43.6)	361 (±52.7)	0.041	219.1 (±27.5)	271 (±32.7)	0.223
IL27	353.3 (±53.4)	605.4 (±64.6)	0.003	596.1 (±112.5)	1186.6 (±133.9)	0.001
IL12p70	36.4 (±6.4)	66.3 (±10.1)	0.013	40.2 (±5.9)	72.8 (±9.2)	0.003

- Concentrations of circulating cytokines were compared between the irAE+ and irAE- groups in Nivo-Surg and Nivo-Ipi-XRT pre-treatment and post-treatment (Table 3).
- Cytokines elevated at both timepoints include IFN-γ, IL3, IL4, IL5, IL6, IL7, IL10, IL27, and IL12p70.
- Patients with irAEs from Durva-Surg did not appear to differ in cytokine concentrations from those without irAEs, apart from IL7 which was significantly higher in the irAE group post-treatment.

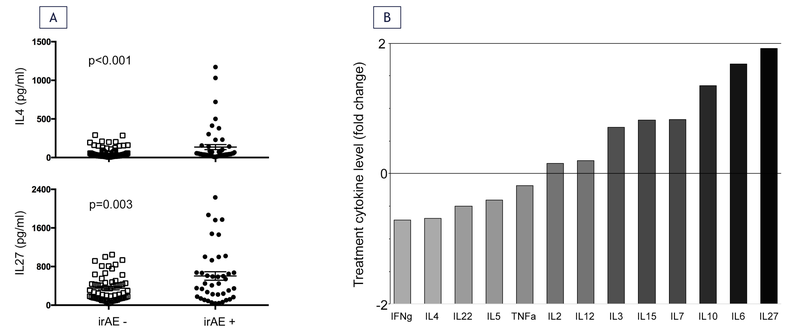

Figure 2. Circulating cytokine concentrations in patients treated with nivolumab. (A) Scatterplot comparing pre-treatment IL4 and IL27 concentrations between patients with and without irAEs. Compared to patients without irAEs, patients with irAEs showed significantly higher concentrations of various circulating cytokines, including IL-4 (p = 0.004) and IL-27 (p = 0.04) pre-treatment. (B) Fold change during the first month of treatment with nivolumab was calculated for each cytokine significantly elevated in patients with irAEs. Over one month, the most significant increase was seen in IL27, with a near two-fold increase, and the most significant decreases were seen in IFN-γ and IL4.

Conclusion

- irAEs may correlate with and serve as biomarkers for improved response to ICIs in patients with HNSCC.
- irAEs may represent greater immune competence and, as a result, greater antitumor efficacy of ICIs.
- In this cohort, irAEs secondary to nivolumab were characterized by elevation of select circulating cytokines that could be used to predict the development of irAEs in future patients.
- The ability to predict and manage irAEs early may help maximize the therapeutic benefit of ICIs in patients with HNSCC and manage patient expectations.

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