Multi-omic Characterization and Molecular Profiling of NUT Carcinoma

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Introduction

- NUT carcinoma (NC) is a rare and aggressive malignancy characterized by rearrangement of the *NUTM1* gene on chromosome 15q14.
- NC presents as undifferentiated or poorly differentiated squamous cell carcinoma that frequently arises in the head & neck or lungs.
- In approximately two-thirds of cases, *NUTM1* is fused to bromodomain-containing protein (*BRD*) 4 on chromosome 19p13.1.
- Several other partners have been identified, including *BRD3* and nuclear receptor binding SET domain protein (*NSD*3).
- Unlike many cancers, the *NUTM1* rearrangement appears to be the sole driver of tumorigenesis.
- Current trials are evaluating agents that target the *NUTM1::BRD4* fusion protein; however still no effective treatment has been described.
- Overall survival is reportedly low in a few studies – 4.1 months as reported by Xie et al.
- The rarity of this disease has made characterizing shared pathological and clinical features more difficult.
- This project aims to comprehensively characterize the molecular landscape of NC in order to identify potential avenues for future treatments.

Materials and Methods

- DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing was performed at Caris Life Sciences (Phoenix, AZ).
- Tumor Mutational Burden (TMB)-High was defined as ≥10 Mut/Mb.
- Tumoral immune cell fractions were inferred using quanTIseq.
- Pathway enrichment was obtained using Gene Set Enrichment Analysis (GSEA).
- Real-world overall survival (rwOS) was extrapolated from insurance claims data with KM estimates from the time of tissue collection to last date of contact.

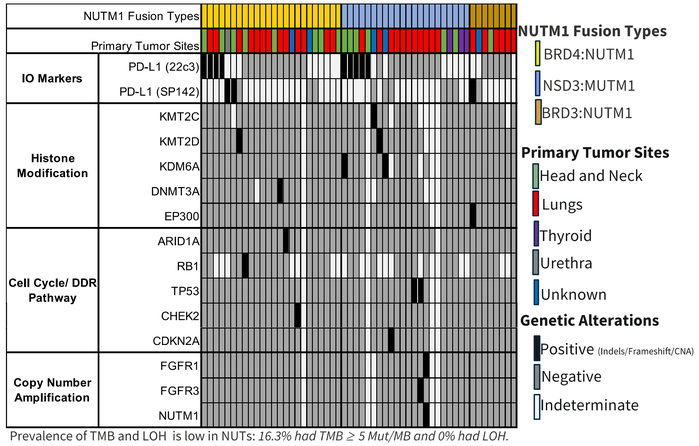
Results

Study cohort

Table 1: Patient demographics and *NUTM1* fusion gene partners

Characteristic	Overall	*BRD4*	*NSD3*	*BRD3*	*p*-value
Total, N	54	24	22	8	
Median Age [Range, years]	54.5 [23-77]	49.5 [23 -72]	56.5 [26 - 76]	61.5 [35 - 77]	0.152
Male, N (%)	31 (57.4%)	13 (54.2%)	12 (54.5%)	6 (75%)	0.609
Female, N (%)	23 (42.6%)	11 (45.8%)	10 (45.5%)	2 (25%)	

Genomic alterations associated with NC



Prevalence of TMB and LOH is low in NUTs: *16.3% had TMB ≥ 5 Mut/MB and 0% had LOH.*

Figure 1: Genomic landscape of NC cases. The most common *NUTM1* fusion partner is *BRD4*, and lung is the most common primary tumor site.

Intratumoral microenvironment composition

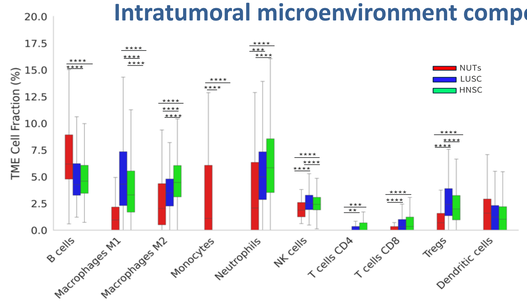


Figure 2: Comparison between the intratumoral microenvironment of NC (NUTs) and squamous cell carcinoma of the head & neck (HNSC) and lung (LUSC). NCs have significantly lower immune cell infiltration compared to squamous cell carcinoma of the lung and head & neck, although B cells/monocytes are significantly higher in NC.

GSEA pathway comparison between NC and squamous cell carcinoma

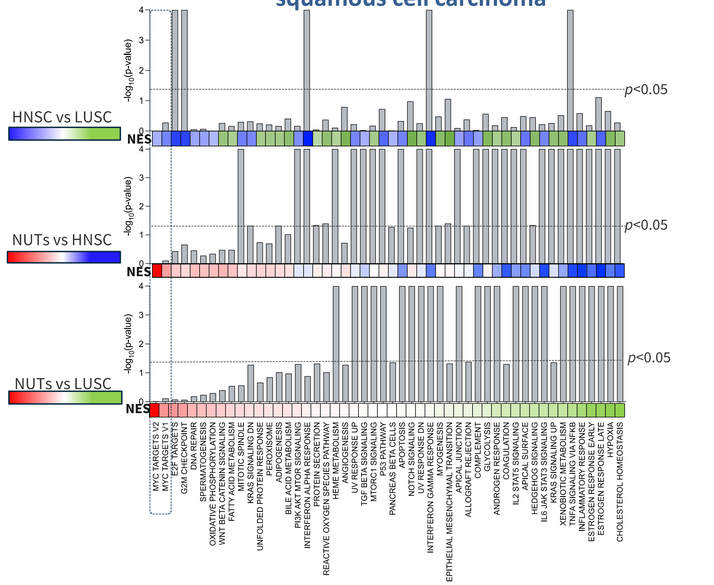


Figure 3: Comparison between Gene Set Enrichment Analysis (GSEA) of NC, lung squamous cell carcinoma (LUSC), and head & neck squamous cell carcinoma (HNSC). GSEA suggests prominent upregulation of the MYC pathway in NC.

Clinical outcomes with or without chemotherapy

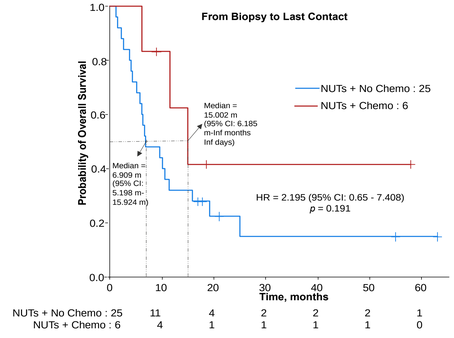


Figure 4: Overall survival from time of biopsy to last contact compared between NC patients (NUTs) treated with and without chemotherapy. NC patients treated with chemotherapy have a tendency for longer overall survival compared to those not treated, although this observation is not statistically significant.

Incidence rate of NC in squamoid tumors of head & neck and lungs

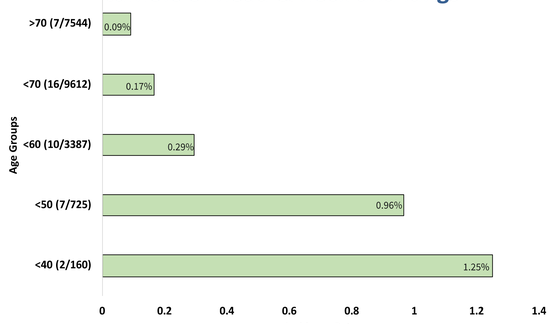


Figure 5: Calculated incidence of NC per age group among all squamoid tumors of the lung and head & neck tested at Caris Life Sciences. NC incidence rate in <50-year-old patients is approximately 1%.

Conclusions

- This large patient cohort demonstrates that NC is characterized by *NUTM1* gene fusions, low mutational burden, and general lack of additional oncogenic drivers.
- The prognosis of NCs remains dismal, and future work could focus on subpopulations of immune cell-rich tumors that might be responsive to immunotherapy.

References

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