Genetic and Clinical Landscape of NUTM1 Structural Variants

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INTRODUCTION

- NUT Carcinoma (NC) is an aggressive, rare cancer, originally described in midline structures of adolescents and young adults driven by a NUTM1 fusion with select partner proteins.
- NC has an estimated incidence of 1,400 cases per year in the U.S. with a median survival of ~6.5 months. However, lack of awareness leads to underdiagnosis, with NC now known to occur in a variety of anatomic sites and a growing number of variant histologies being reported.
- Using the Tempus multimodal real-world database, consisting of de-identified molecular and clinical records, NC diagnoses were evaluated against samples with detected NUTM1 fusions to better understand the molecular and clinical-level features of NC.

METHODS

- From Tempus' de-identified records, patients with a NC diagnosis based on clinically abstracted diagnosis fields were collected in addition to any patients with evidence of a NUTM1 fusion detected by Tempus xT (targeted DNA panel) or Tempus xR (whole-exome capture RNA-seq).
- 227 de-identified records with evidence of a NUTM1 fusion were initially included in the study in addition to 4 records with NC diagnoses that lacked evidence of a detected NUTM1 fusion via Tempus NGS.
- After fusion detection thresholding and QC filtering, 169 records remained representing the cohort of potential NC patients.
- Clinical notes for these records lacking a NC diagnosis were further manually reevaluated for any noted evidence of NC.

NUTM1 Fusion Partner Cohort Characteristics (n=165)

Fusion	Samples (%)	NC Diagnosis (%)	Top Primary Sites (n)	Top Diagnoses (n)
BRD4-NUTM1	59 (36%)	20 (34%)	Unknown primary site (15)	Head and Neck NUT Carcinoma (11)
			Lung (14)	Head & Neck cancer - Other (6)
			Nasal cavity (8)	Lung NUT Carcinoma (6)
			Accessory sinus (4)	Lung Squamous Cell Carcinoma (6)
BRD3-NUTM1	18 (11%)	6 (33%)	Lung (7)	Lung Squamous Cell Carcinoma (4)
			Unknown primary site (4)	Head and Neck NUT Carcinoma (3)
			Nasal cavity (3)	NUT Carcinoma of Unknown primary (2)
			Head, face or neck (1)	Nasal Cavity Squamous Cell Carcinoma (2)
NSD3-NUTM1	29 (18%)	4 (14%)	Lung (11)	Lung Squamous Cell Carcinoma (8)
			Thyroid gland (11)	Thyroid Gland Carcinoma (4)
			Head, face or neck (2)	Thyroid Gland Papillary Carcinoma (4)
			Maxillary sinus (2)	Head and Neck NUT Carcinoma (2)
YAP1-NUTM1	13 (8%)	0 (0%)	Skin (7)	Skin cancer - Non-Melanocytic (4)
			Unknown primary site (3)	Porocarcinoma (2)
			Head, face or neck (1)	Squamous Cell Carcinoma of Unknown Primary (2)
			Lower limb (1)	Adenocarcinoma of Unknown Primary (1)
Other	46 (28%)	2 (4%)	Unknown primary site (11)	Lung Adenocarcinoma (3)
			Lung (6)	Lung NUT Carcinoma (3)
			Colon, NOS (4)	Soft Tissue Sarcoma (3)
			Breast (3)	Acute Myeloid Leukemia (2)

Table 1. Clinical characteristics stratified according to fusion partner.

SUMMARY

- Based on matching abstracted clinical diagnoses with NGS sequencing results from a real-world database, we find that NUT carcinomas may be underdiagnosed the majority of the time.
- Certain cancer types with a high enrichment of *NUTM1* fusions, such as sweat gland adenocarcinomas/porocarcinomas, thyroid cancers, and sarcomas, may benefit from universal NGS sequencing to ensure correct diagnosis.

RESULTS

In a cohort of potential NC patients, 30.7% had clinically-noted evidence of NC

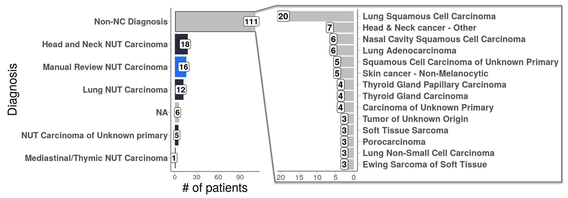

Figure 1. NC-related diagnoses given to patients in the potential NUT Carcinoma cohort (left panel, N=169) and the most prevalent primary diagnoses given to patients lacking a NC diagnosis (right panel). Bars illustrate the number of patients with given diagnosis. Manual Review NUT Carcinoma indicates patients not assigned NC-related diagnosis, but had NC-related clinical notes found after manual curation..

Among patients harboring a canonical NUTM1 fusion partner, 38.8% had clinically-noted evidence of NC

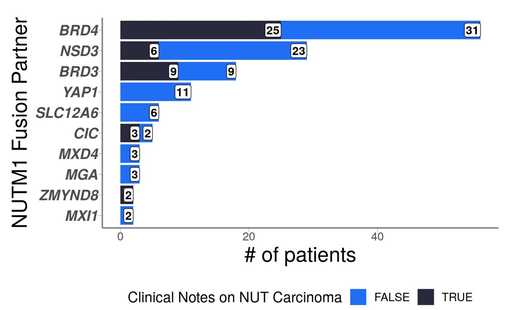

Figure 2. The most prevalent *NUTM1* fusion partners in cohort. Bars illustrate the number of patients for a fusion partner separated by whether abstracted notes from clinical records include references to NC. Canonical NUTM1 fusion partner for NC based on reports in literature (BRD4, NSD3, BRD3).

Patients harboring *NUTM1* fusions exhibit poor outcomes across most partner genes

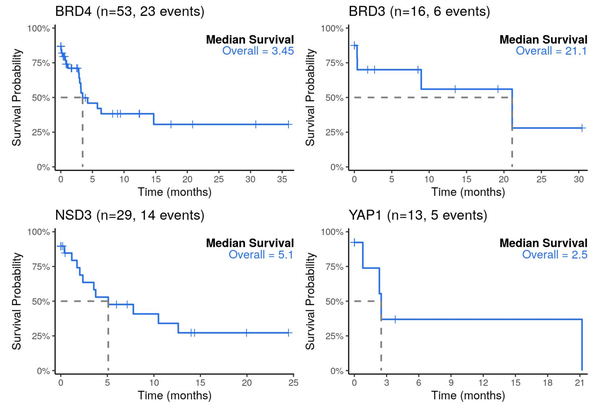

Figure 3. Kaplan-Meier (KM) survival curves illustrate the outcomes real-world overall survival (rwOS) of patients with NUTM1 fusions stratified by fusion partner for the 4 most common fusion partners. Dashed lines highlight the median survival times, x-axis shown in months. The combined rwOS was 5.1 months (n=168, 75 events). Survival data was only available for a subset of patients.

Patients lacking a NC diagnosis are typically older

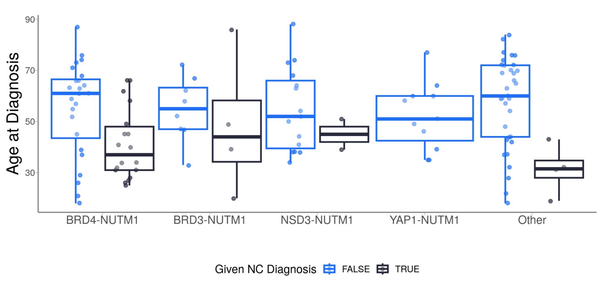

Figure 4. For the top 4 fusion partners by count (and all others combined), we report the age at diagnosis stratified by whether the patient record indicated a NC or not. No YAP1-NUTM1 fusions had a NC diagnosis.

Transcriptome profiling of cohort reveals heterogeneity within *NUTM1* fusion patients

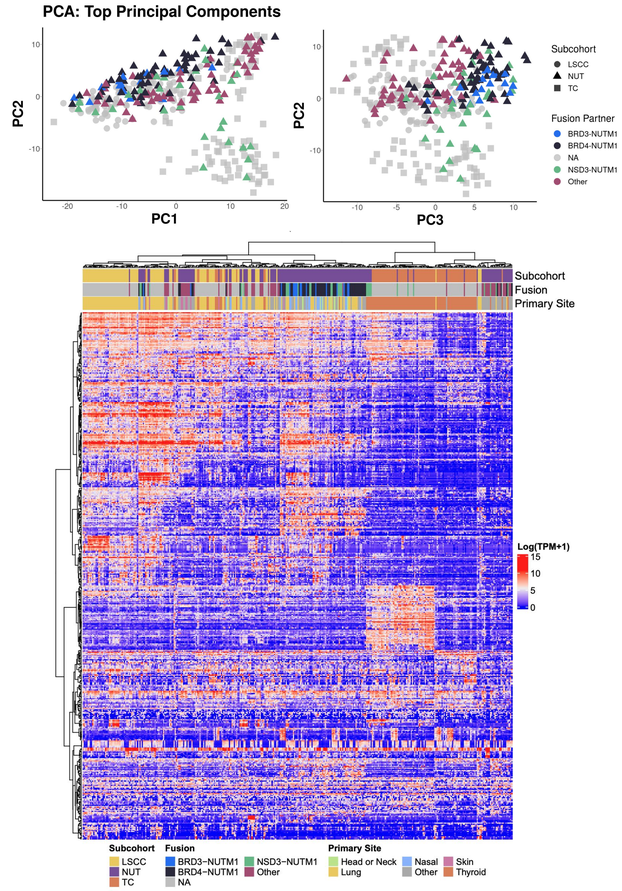

Figure 5. Clustered RNA expression PCA plots (top panels) and heatmap (bottom panel) displaying the 500 most variable genes from the NUTM1 fusion cohort (n = 162) alongside randomly selected samples of poorly differentiated LSCC (n = 100) and thyroid cancer (n = 100) with available whole-transcriptome data.

Abbreviations: NUT Carcinoma (NC); real-world progression-free survival (rwPFS); real-world overall survival (rwOS); Kaplan-Meier (KM); Principal Component Analysis (PCA); Lung Squamous Cell Carcinoma (LSCC); Thyroid Cancer (TC).

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