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Introduction

- Neoadjuvant chemoimmunotherapy has emerged as a standard of care treatment for patients (pts) with resectable stage II-IIIa non-small cell lung cancer (NSCLC).
- Immune checkpoint inhibitors (ICIs) are associated with the development of immune-related adverse events, including ICI-associated sarcoid-like granulomatous reactions (SLGR).
- SGLRs may manifest as new or progressive lymphadenopathy or pulmonary lesions that mimic disease progression. These findings can potentially impact surgical and clinical decision-making.
- Real-world data regarding granulomatous inflammation and presumed SLGRs in NSCLC patients who received neoadjuvant chemoimmunotherapy remains limited.
- We conducted an international retrospective study from The Ohio State University (OSU), University of Virginia (UVA), and National Cheng Kung University (NCKU). This study evaluates the baseline characteristics and prevalence of granulomatous inflammation, including but not limited to SLGRs, following neoadjuvant chemoimmunotherapy and surgery.

Results

Number of patients	112
Median age at diagnosis (range)	66 years (37 to 85)
Sex, n (%)	
Male	69 (61.6%)
Female	43 (38.4%)
Histology	
Adenocarcinoma	46 (41.1%)
Squamous cell carcinoma	45 (40.2%)
Adenosquamous	3 (2.7%)
Poorly differentiated	11 (9.8%)
Other	7 (6.3%)
Race	
White	73 (65.3%)
Asian	30 (26.8%)
African American	7 (6.3%)
Other	2 (1.8%)
Smoking status	
Former	61 (54.5%)
Current	27 (24.1%)
Never	24 (21.4%)

Methods

- Patient characteristics:
 - Stage IIA-IIIC NSCLC
 - Received neoadjuvant chemoimmunotherapy consisting of a platinum-based doublet chemotherapy plus a PD-1/PD-L1 inhibitor
 - Underwent definitive surgical resection.
- Exclusion criteria:
 - EGFR or ALK alterations present
 - Received perioperative chemoimmunotherapy
- Pathologic responses were defined as pathologic complete response (pCR: 0% viable tumor) or major pathologic response (MPR: ≤10% viable tumor)
- Post-chemoimmunotherapy and surgical pathology specimens were reviewed for granulomatous inflammation.
- Kaplan–Meier curves and Cox proportional hazards were used to compare survival outcomes between patients with and without granulomas. Fisher’s exact test was used to examine associations between the presence of granulomas and pathologic responses.

Clinical stage	
IIA	11 (9.8%)
IIB	27 (24.1%)
IIIA	58 (51.8%)
IIIB	13 (11.6%)
IIIC	3 (2.7%)
PD-L1	
0	21 (18.8%)
1-49	34 (30.4%)
≥ 50	34 (30.4%)
Unknown	23 (20.5%)
Neoadjuvant immunotherapy	
Nivolumab	69 (61.6%)
Pembrolizumab	36 (32.1%)
Durvalumab	7 (6.3%)
Neoadjuvant chemotherapy	
Carboplatin + pemetrexed	32 (28.6%)
Carboplatin + paclitaxel	47 (42.0%)
Other	33 (29.5%)
Pathologic response	
MPR	58/93 (62.4%)
pCR	35/112 (31.3%)

Results

- 26.8% (30 out of 112) of the patients had granulomas identified in their surgical specimens after neoadjuvant chemoimmunotherapy.
- Among patients with granulomas identified, 23.3% (7 out of 30) of the patients had post-chemoimmunotherapy CT or PET-CT findings showing increased lymphadenopathy or increased FDG-avidity concerning for disease progression.
- No association was observed between granulomatous reactions and MPR (p=0.81), pCR (p=0.61), progression-free survival (p=0.38), or overall survival (p=0.23).
- Only 1 patient had a granulomatous reaction reported on their initial biopsy at diagnosis, though baseline sampling was limited to fine-needle or core biopsies.

Granuloma Characteristics

Granuloma characteristics		
Necrotizing		15/30 (50.0%)
Non-necrotizing		14/30 (46.7%)
Unknown		1/30 (3.3%)
Granuloma etiologies		
Infectious		6/30 (20.0%)
Non-infectious		22/30 (73.3%)
Unknown		2/30 (6.70%)
Proportion of patients with granulomas at each institution		
OSU		18/49 (36.7%)
UVA		8/34 (23.5%)
NCKU		4/29 (13.8%)
Proportion of infectious granulomas at each institution		
	Patients positive for infection, n (%)	Patients tested for infection¹
OSU	5 (31%) ²	16
UVA	0 (0%)	4
NCKU	0 (0%)	4

¹ AFB (Acid-fast bacillus), GMS (Grocott's Methenamine Silver)

² Positive for Histoplasma

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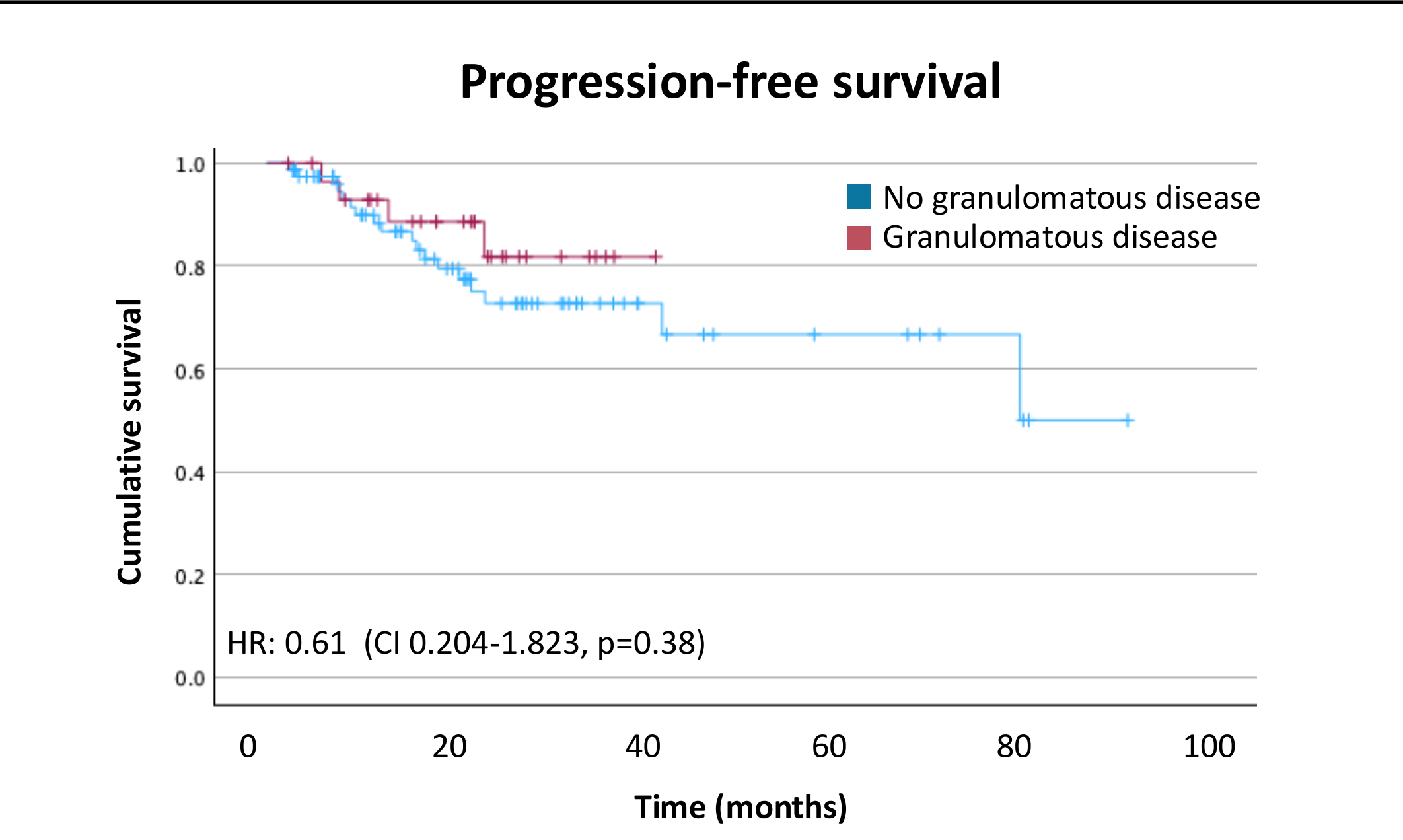


Figure 1. Kaplan-Meier curves of progression-free survival of patients with or without granulomatous reactions on biopsy or postoperative specimens.

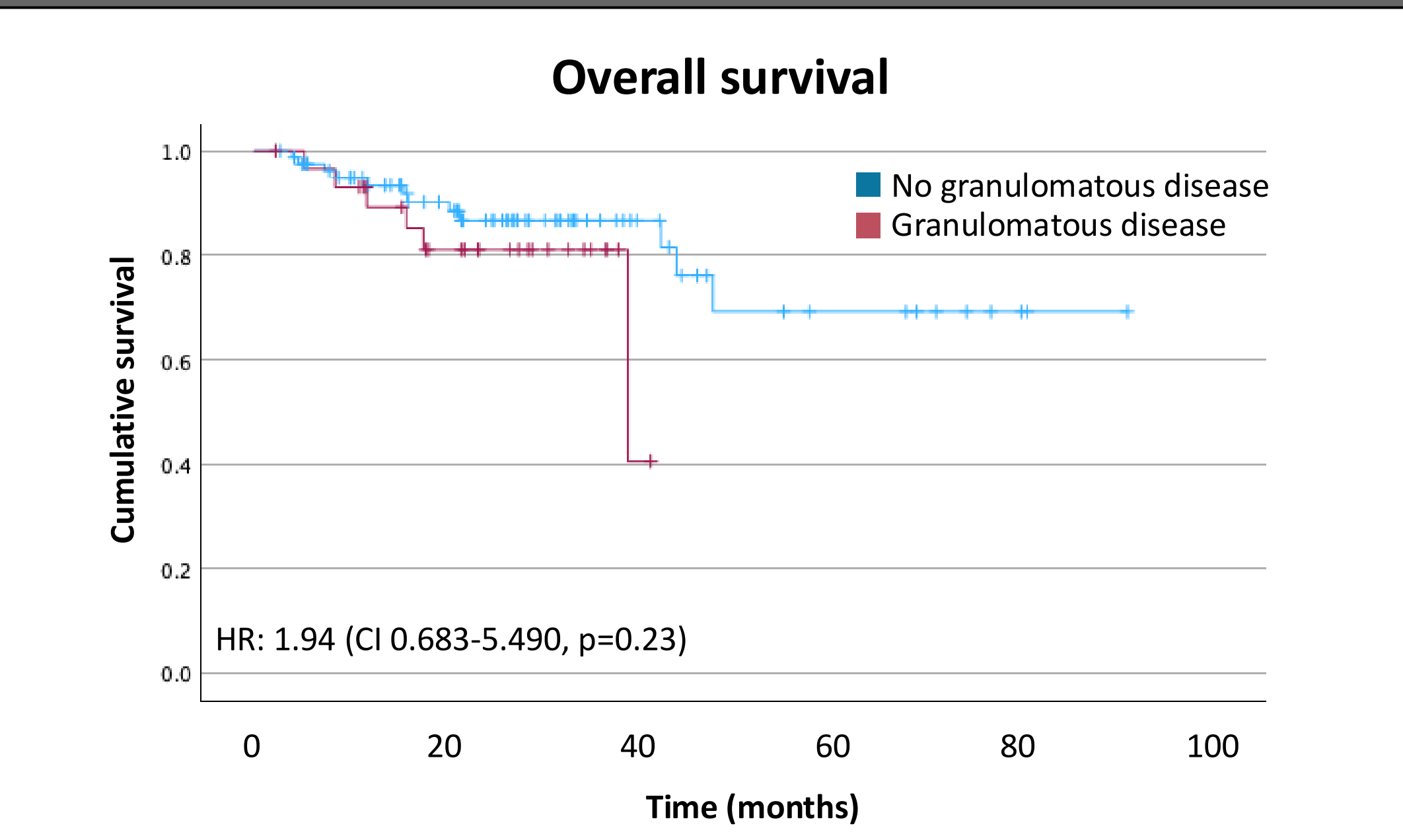


Figure 2. Kaplan-Meier curves of overall survival of patients with or without granulomatous reactions on biopsy or postoperative specimens.

Conclusions

- Granulomatous reactions are prevalent in NSCLC patients after treatment with neoadjuvant chemoimmunotherapy.
- Granulomas represent a heterogeneous entity that includes both infectious etiologies and immune-related etiologies such as SGLRs.
- Given the potential of granulomatous reactions to mimic disease progression on imaging, careful pathological and clinical evaluation is critical to guide appropriate management.