Impact of tumour genomic characteristics on healthcare resource utilisation and real-world outcomes in patients with non-small cell lung cancer: A real world study using linked whole genome-clinical databases

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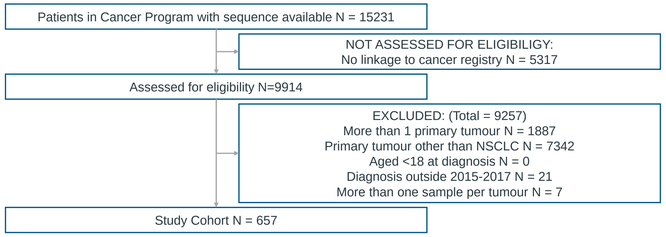
Background and objectives

- Non-small cell lung cancer (NSCLC) is a leading cause of mortality worldwide, accounting for 85% of total lung cancer deaths[1,2]
- The aim of this study was to establish the feasibility of using the Genomics England (GE) database to generate real-world evidence about cancer patients to support the development of targeted therapies
- The database contains somatic and germline whole genome sequencing data from patients with cancers and rare diseases in the UK, linked to real-world clinical databases

Objective: To use linked genomic-clinical data to describe the association between genetic features and outcomes (Overall survival and healthcare resource utilisation) in patients with non-small cell lung cancer

Figure 1: Study Attrition



Methodology

- A retrospective cohort study of 657 participants with a NSCLC diagnosis between 2015-2017 and whole genome sequencing in the GE database, with clinical information from the Cancer Outcomes and Services Dataset (COSD), Systemic Anti-Cancer Therapy Dataset (SACT) and Hospital Episode Statistics Dataset (HES). See Figure 1 for study attrition
- Tumour mutational burden (TMB), defined as total number of non-synonymous, somatic mutations identified per megabase of the genome, was calculated for all study participants. TMB is emerging as a biomarker to select patients that could benefit from immune checkpoint blockade therapies such as PD-L1 inhibition[3]
- Descriptive statistics and Kaplan-Meier analyses for overall survival were performed. For some analyses, TMB was stratified into low and high based on a threshold found in literature[3] of 10 mut/Mb. Rounding and masking has been applied to obscure small numbers (≤5)

Limitations

- SACT data availability is limited, only 25% of the cohort had SACT information available.
- Stage distribution is biased toward early stage cancer (Stage I-IIIA) compared to late stage cancer (Stage IIIB-IV)
- As we restricted to a cohort with registry data, robust diagnosis and tumour information was available for all participants, however, a lot of patients were excluded and to include these patients in future studies research must be done on synthesizing and reconciling various sources of non-registry diagnostic information

Conclusions

- Overall survival was similar among NSCLC patients stratified by TMB high (above 10) and TMB low (below 10). However, among patients with advanced NSCLC (Stage IIIB-IV), there is some suggestive evidence that median survival is longer for TMB high patients compared to TMB low
- There was no difference in HealthCare Resource Use and SACT therapy between TMB high and low
- Longitudinal epidemiological studies using linked genomic-clinical data from the Genomics England database are feasible, including outcomes such as HCRU and survival. Further studies with this database could include drug efficacy and safety studies, biomarker testing, and drug discovery

Results

Figure 2: Overall Survival Kaplan Meier

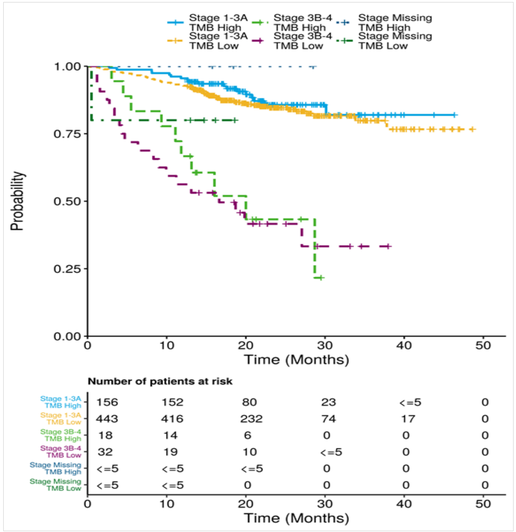
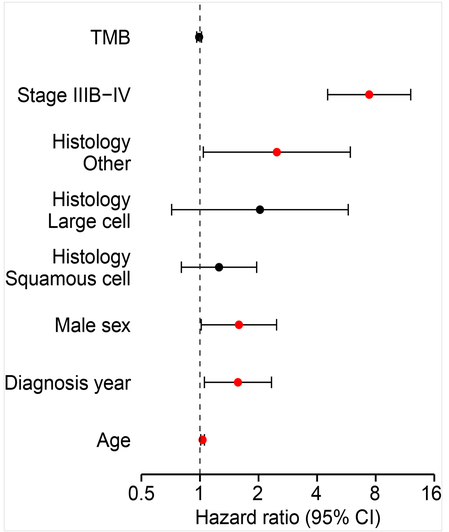


Figure 3: Overall Survival Cox Model



Results (cont'd)

Table 1: Demographic and Clinical Characteristics

		Overall		Low TMB		High TMB	
N		657	100.00%	480	73.06%	177	26.94%
Age at diagnosis	18 – 44	10	1.52%	≥5	~0.00%	≤5	~0.00%
	45 - 64	215	32.72%	154	23.44%	55	8.37%
	65 - 74	261	39.73%	189	28.77%	75	11.42%
	75 - 84	154	23.44%	115	17.50%	42	6.39%
	85+	17	2.59%	≥12	~0.00%	≤5	~0.00%
Sex	Female	316	48.10%	232	35.31%	84	12.79%
	Male	341	51.90%	248	37.75%	93	14.16%
Ethnicity	White	614	93.46%	443	67.43%	171	26.03%
	Other	≥10	~0.00%	≥9	~0.00%	≤5	~0.00%
	Missing/Unknown	≥10	~0.00%	≥10	~0.00%	≤5	~0.00%
Stage	1 - 3A	599	93.76%	443	92.29%	156	88.13%
	3B - 4	≥48	~6%	≥26	~4%	≥10	~2%
	Missing/Unknown	≥5	~0.00%	≤5	~0.00%	≤5	~0.00%
Histology	Squamous Cell Carcinoma	220	33.49%	156	23.74%	64	9.74%
	Adenocarcinoma	≥352	~55.00%	≥262	~41.00%	≥81	~10.00%
	Other	19	2.89%	12	1.83%	7	1.07%
	Unconfirmed	39	5.94%	31	4.72%	8	1.22%
	Large Cell Carcinoma	≥8	~0.00%	9	1.37%	≥5	~0.00%
	NOS	≤5	~0.00%	≤5	~0.00%	0	0.00%
Tumour Mutational Burden	Mean (SD)	8.00 (8.04)		4.42 (2.81)		17.72 (9.45)	
	Median (Q1-Q3)	5.92 (2.70 - 10.46)		4.26 (1.99 - 6.84)		14.20 (11.50 - 20.24)	
	Min-Max	0.00 - 74.86		0.00 - 9.94		10.00 - 74.86	
Charlson Comorbidity Index (Calculated From HES)	0	0	0.00%	0	0.00%	0	0.00%
	1-2	484	73.89%	347	52.98%	137	20.92%
	3-4	144	21.98%	110	16.79%	34	5.19%
	>=5	27	4.12%	≥18	~0.00%	≤5	~0.00%

Table 2: Therapy and HCRU

		Overall		Low TMB		High TMB	
N		657	100.00%	480	73.06%	177	26.94%
Resource Utilization							
Any hospitalization episode	FALSE	25	3.81%	19	3.96%	6	3.39%
	TRUE	632	96.19%	461	96.04%	171	96.61%
Number of hospitalization episodes per patient	Mean (SD)	8.05 (7.36)		7.81 (7.32)		8.67 (7.43)	
	Median (Q1-Q3)	6.00 (3.00 - 12.00)		6.00 (3.00 - 11.00)		6.00 (3.00 - 13.00)	
Treatments							
SACT data available	SACT data available	167	25.42%	121	25.21%	46	25.99%
	SACT data unavailable	490	74.58%	359	74.79%	131	74.01%
Number SACT regimens	Mean (SD)	1.20 (0.43)		1.21 (0.43)		1.17 (0.44)	
	Median (Q1-Q3)	1.00 (1.00 - 1.00)		1.00 (1.00 - 1.00)		1.00 (1.00 - 1.00)	
Most common first SACT after diagnosis	CARBOPLATIN + VINORELBINE	38	22.75%	32	26.45%	6	13.04%
	CISPLATIN + VINORELBINE	69	41.32%	47	38.84%	22	47.83%
	CISPLATIN + PEMETREXED	17	10.18%	8	6.61%	9	19.57%
	CARBOPLATIN + PEMETREXED	7	4.19%	7	5.79%	0	0.00%

Table 1 contains descriptive and clinical characteristics of the overall, low and high TMB cohort. Compared to the NSCLC population overall [1,2,5] the GE sequenced cohort is younger, and diagnosed at an early stage, indicating a possible selection bias

Table 2 contains summaries of therapy data and HCRU. There is no difference in HCRU or treatment between low and high TMB cohorts

Figure 2 shows a Kaplan Meier overall survival estimate, stratified by TMB and stage. There is some suggestive evidence of longer survival among patients with high TMB. Clinical studies [4] have shown high TMB is associated with improved response to immunotherapy, which may contribute to a longer overall survival in high TMB patients. The unadjusted survival is also longer than observed for NSCLC in general (median survival <1 year[1,2]) possibly due to the largely early stage population in this cohort

Figure 3 contains a Cox overall survival model. TMB is encoded as a continuous variable. Significant ($p<0.05$) variables are shown in red. Reference categories are Stage I-IIIA, Histology Adenocarcinoma and Female sex. Adjusted hazard ratios are plotted on the log scale. TMB does not significantly influence risk of death in this study. Advanced stage (Stage IIIB-IV), male sex and other histology are associated with increased risk of death

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