**Survival difference according to mutation status in a prospective cohort study of Australian patients
with metastatic Non-Small Cell Lung Carcinoma (NSCLC)**

Authors:

Lavinia Tan,¹ Marliese Alexander,^{1,2} Ann Officer,¹ Michael MacManus,¹ Linda Mileschkin,¹ Ross Jennens,¹ Dishan Herath,¹ Richard de Boer,¹ Stephen B Fox,¹ David Ball¹ and Benjamin Solomon¹

¹ Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

² Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Australia

Lavinia Tan, MBBS, FRACP

Marliese Alexander, B. Pharm (Hons), MPH

Ann Officer, RN, B.Ed

Michael MacManus, MB Bch BAO, MD, MRCP, FRANZCR

Linda Mileschkin, MBBS, FRACP, Mbioeth

Ross Jennens, MBBS, FRACP

Dishan Herath, MBBS, FRACP

Richard de Boer, MBBS, FRACP

Stephen B Fox, BSc(Hons), MBChB, FRCPath, FFSc, FRCPA, DPhil, FAHMS

David Ball, MBBS, MD, FRANZCR

Benjamin Solomon, MBBS, PhD, FRACP

Corresponding author:

Benjamin Solomon, Department of Medical Oncology, 305 Grattan Street, Melbourne, VIC, Australia.

Email: ben.solomon@petermac.org

Phone: (03) 85597709

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/imj.13491](https://doi.org/10.1111/imj.13491)

Word count: Abstract: 250 words, Manuscript: 2616 words

Author Manuscript

ABSTRACT

Background and objective:

Non-small cell lung cancer (NSCLC) is a heterogeneous disease comprising not only different histologic subtypes but also different molecular subtypes. Our objective is to describe the frequency of oncogenic drivers in patients with metastatic NSCLC, the proportion of patients tested and survival difference according to mutation status in a single-institution study.

Methods:

Metastatic NSCLC patients enrolled onto a prospective Thoracic Malignancies Cohort (TMC) Study between July 2012 and August 2016 were selected. Patients underwent molecular testing for *EGFR*, *KRAS*, *ROS1*, *BRAF* mutations and *ALK* gene rearrangements. Survival was calculated using Kaplan-Meier method for groups of interest and comparisons were made using the log-rank test.

Results:

A total of 392 patients were included: 43% female with median age of 64 years (28-92). Of 296 patients tested, 172 patients (58%) were positive for an oncogenic driver: 81 patients (27%) *EGFR* positive, 25 patients (9%) *ALK* positive, 57 patients (19%) had *KRAS* mutation and 9 patients (3%) were *ROS1* or *BRAF* positive. Patients with an actionable mutation (*EGFR/ALK*) had a survival advantage when compared with patients who were mutation negative (hazard ratio 0.49; 95% CI 0.33-0.71; $p<0.01$). Survival difference between mutation negative and mutation status unknown was not statistically significant when adjusted for confounding factors in a multivariate analysis (HR 1.29; 95% CI 0.97-1.78, $p=0.08$).

Conclusion:

In this prospective cohort, presence of an actionable mutation was the strongest predictor of overall survival. These results confirm the importance of molecular testing and suggest the likely survival benefit of identification and treatment of actionable oncogenes.

KEY WORDS:

Non-small cell lung cancer (NSCLC), molecular testing, *EGFR*, *ALK*, *KRAS*

ABBREVIATIONS:

NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; PFS, progression free survival; ORR, objective response rate; CI, Confidence Interval, QOL, quality of life; NOS, not otherwise specified, ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *ROS1*, ROS proto-oncogene 1; *BRAF*, B-Raf proto-oncogene; *HER-2*, human epidermal growth factor 2; *NTRK1*, neurotrophic receptor tyrosine kinase 1; *RET*, ret proto-oncogene; *MET*, proto-oncogene MET; TKI, tyrosine kinase inhibitors; TMC, Thoracic Malignancies Cohort.

Figure1.jpg

Figure2.jpg

INTRODUCTION:

Lung cancer remains the leading cause of cancer-related mortality in Australia representing an estimated 9.4% of all new cancers in 2016 and accounting for nearly 1 in 5 (18.8%) cancer deaths.^{1,2}

Approximately 85% of all lung cancer cases are NSCLC, the majority of whom present with locally advanced or metastatic disease.³ These patients have a median survival of 8.0 months despite available standard first-line treatment, with a 5-year overall survival of <14%.^{2,4}

NSCLC includes three major histological subtypes of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, together with NSCLC otherwise specified (NOS).⁵ Adenocarcinoma, the most common histological subtype of NSCLC, has a higher than 50% estimated frequency of potentially identifiable oncogenic driver mutations.⁶ The frequency is much lower in squamous cell and large cell carcinomas. Alterations in several oncogenes including epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), *KRAS*, *ROS1*, *BRAF*, *Her-2*, *NRTK-1*, *RET* and *MET* have been reported in NSCLC. To date, only *EGFR* and *ALK* mutation positive NSCLC have approved targeted therapies in Australia.

Activating *EGFR* mutations are key drivers in NSCLC in approximately 10-15% of Western patients and 30-35% of Asian patients.⁷ The clinically relevant and most frequent *EGFR* mutations are in-frame deletions/insertions of exon 19 (40-50%) and L858R mutation of exon 21 (30-40%). Lung cancers with *EGFR* mutations depend on EGFR signalling for growth and survival which confers sensitivity to treatment with EGFR tyrosine kinase inhibitors (TKIs).⁸ EGFR TKIs gefitinib, erlotinib, and afatinib have been shown in seven randomised phase III trials to improve PFS, ORR and QOL of patients with *EGFR* mutant NSCLC over standard first line doublet chemotherapy. However, an overall survival advantage has not been clearly demonstrated, most likely due to crossover designs confounding survival data.⁹⁻¹⁵ Current treatment guidelines recommend *EGFR* mutation testing in all patients with adenocarcinoma or in whom adenocarcinoma cannot be excluded.¹⁶

ALK gene rearrangements occur in about 3-5% of NSCLC patients with a higher frequency in adenocarcinomas, never or light smokers and younger patients, but can occasionally be found in older

patients and smokers.^{17,18} Crizotinib, a first generation oral TKI inhibiting ALK, ROS1 and MET has been shown to have superior response rates and prolonged PFS over standard chemotherapy and is now the standard first-line treatment of advanced *ALK* rearranged NSCLC.¹⁹ Once again, no survival benefit was identified likely due to a high rate of crossover from chemotherapy to crizotinib arm on progression.

Activating *KRAS* mutations which occurs in about 20-25% of lung adenocarcinomas²⁰ was shown to have a poorer prognosis²¹ with a meta-analysis of 28 studies validating it as an unfavourable prognostic marker.²² More recent data from a pooled analysis of four trials of adjuvant chemotherapy showed that *KRAS* mutation is not significantly prognostic in patients with resected NSCLC.²³ Due to the functional complexity of the RAS-RAF-MEK-ERK signalling pathway, there has been no successful therapeutic treatment for *KRAS* mutant tumours to date despite multiple Phase II studies with agents targeting downstream molecules.^{24,25}

While molecular testing for *EGFR* and *ALK* has been recommended by international guidelines since 2012, the results of molecular testing and the associations with patient outcome have not previously been reported in the Australian setting. Here we describe the frequency of *EGFR*, *KRAS*, *ROS-1*, *BRAF* mutations and *ALK* rearrangements in patients with metastatic NSCLC at diagnosis, together with survival differences according to mutation status using prospectively collected data from an Australian cohort of NSCLC patients. Further, we examined reasons mutation testing was not performed in some patients in this group.

METHODS:

A review was performed on all patients with a diagnosis of Stage IV NSCLC between July 2012 and August 2016 using prospectively collected data from the TMC database at Peter MacCallum Cancer Centre. Ethics approval was obtained from the Peter MacCallum Cancer Centre Clinical Research and Ethics Committee (PMCC 11/88).

Patients with metastatic NSCLC at diagnosis, adenocarcinoma, squamous cell carcinoma, large cell and NOS histology were included. The disease stage was determined by radiological findings according to the TNM classification system and stage IV patients were eligible. Eastern Cooperative Oncology Group (ECOG) performance status²⁶ was determined according to the records for the patients' activity of daily life and the extent of dependence. Molecular status of patients' tumour was determined by histopathology results available in the hospital's electronic medical records and in the database. Results for *EGFR*, *KRAS*, *ROS1*, *BRAF* mutations and *ALK* rearrangements were identified.

The following details were collected for the 392 patients included in the study: age, sex, ethnicity, ECOG performance status, smoking history, respiratory comorbidity, weight loss at diagnosis, histology and molecular pathology, previous treatment, date of last follow-up and date of death.

STATISTICAL METHODS:

Descriptive statistics, including median along with percentages and frequencies for categorical variables were tabulated and presented here. Overall survival was defined as the time from date of diagnosis of metastatic lung cancer to date of death or last follow-up. Patients who were alive at the time of analysis were censored at latest date of assessment.

Survival curves were calculated by the Kaplan-Meier method for groups of interest and were compared using the log-rank test. Hazard ratio (HR) and 95% CI were reported with a p-value less than 0.05 considered to indicate statistical significance. The association between patient- and disease-related variables and overall survival was assessed by univariate and multivariate Cox proportional hazards regression using Stata 14.0 software. All baseline variables collected in the TMC were included in univariate analyses and those demonstrating significant association with survival ($p < 0.05$) were carried forward to multivariate analyses.

RESULTS:

From July 2012 to August 2016, 1352 patients were enrolled into the TMC database including 392 patients with stage IV NSCLC. The cut off date of analysis was 31st of August 2016. Nine patients with

ROS1 and *BRAF* mutations were excluded from survival analyses due to small numbers. 383 patients were included in the survival analysis (103 alive and 280 dead) with a median time on study for all patients of 8.9 months (range 0 to 55 months) and for living patients 17.5 months (range 0 to 55 months).

Patient demographics

The characteristics of the patients are summarised in table 1. The median age of patients at diagnosis were 64 years (28-92), 43% of patients were female with a predominant Caucasian population of 77%. Adenocarcinoma was the most frequent histology (73%) and 24% of patients were never smokers. The majority of patients were ECOG performance status 1 at diagnosis (64%).

Reasons mutation testing not performed

296 out of the 392 patients (76%) were tested for at least one gene. Among these, 124 (124/296, 42%) patients were found to be mutation negative. In 96 patients (96/392, 24%) tumour mutation status was unknown due to molecular testing not being performed with the most common reason being squamous histology (Table 2).

Molecular subtypes

Of the 296 patients who did have testing performed, *EGFR* mutations were the most frequent with 81 patients (81/296, 27%) testing positive, followed by *KRAS* mutations in 57 patients (57/296, 19%), *ALK* rearrangements in 25 patients (25/296, 8%) and 9 patients (9/296, 3%) were either *BRAF* positive (5 patients) or *ROS1* positive (4 patients).

Of the 81 patients with *EGFR* mutation, 68 patients (84%) received first-line TKI while only 9 patients with *ALK* rearrangements (36%) received first-line ALK inhibitor. All patients with identified *EGFR* or *ALK* rearrangements eventually went on to receive a TKI (targeting *EGFR* or *ALK* as relevant) as a subsequent line of treatment. All four patients with *ROS1* positive NSCLC were treated with an ALK inhibitor either in the first-line setting or in a subsequent line of treatment. More than half of the

patients (31/57, 54%) with *KRAS* mutation received systemic therapy while only three out of five patients (40%) with *BRAF* positive NSCLC received chemotherapy.

Survival according to mutation status

Survival by oncogenic driver mutation type compared with patients without a driver mutation (mutation negative and mutation unknown) is shown in Figure 1. Patients who were mutation negative and mutation unknown had median survivals of 9.0 months (range 0 to 46 months) and 5.0 months (range 0 to 37 months) respectively. Patients with *EGFR* mutations had a median survival of 25 months (0 to 53 months), patients with *ALK* rearrangements had a median survival in excess of 24 months (0 to 51 months) and patients with *KRAS* mutations had a median survival of 7.0 months (range 0 to 39 months).

Univariate Analysis

In univariate analyses (Table 3), the following variables were associated with improved overall survival: adenocarcinoma histology, presence of *EGFR* or *ALK* mutation, Asian ethnicity, and absence of smoking history, respiratory comorbidity and no weight loss at diagnosis. Survival differences were not observed between *EGFR* and *ALK* positive patients who were combined as single group for future analyses (actionable mutation positive). Similarly, *KRAS* mutation did not confer any survival benefit compared with mutation negative status and therefore these groups were combined for future analyses (actionable mutation negative).

Multivariate Analysis

In multivariate analysis (Table 4), presence of an actionable mutation (*EGFR/ALK*) conferred a 2-fold survival benefit compared to patients who were mutation negative or not tested. Univariate survival differences between patients not tested and negative for mutation were no longer significant (HR 1.31, 95%CI 0.97 – 7.78, $p=0.08$). Similarly, associations between survival and ethnicity and age were no longer observed in the multivariate model.

DISCUSSION:

Combination platinum-based chemotherapy regimens are still considered standard care for the majority of patients presenting with newly diagnosed metastatic NSCLC, with an improvement in median survival from 4.0 months to 8.0 months.⁴ The discovery of oncogenic drivers together with the development of targeted therapies has revolutionised the management of advanced NSCLC for a subgroup of mutation positive patients leading to improved outcomes. Here, we present the differences in survival of patients with metastatic NSCLC at initial diagnosis according to the presence or absence of an oncogenic driver mutation in the Australian setting.

Our analyses confirmed the known poor survival rates of patients without an oncogenic driver mutation. In this cohort, patients were often older, male, and smokers as reported in previous studies. More than half the patients (74/124, 60%) whose tumours do not harbour a mutation received standard first-line chemotherapy with a median survival of 9.0 months, which is comparable to reported literature. The short survival time of only 5.0 months in patients whose mutation status was unknown could be due to various poor prognostic factors such as older age, smoking history and multiple co-morbidities. More than a third of these patients had a performance status of ≥ 2 , which is a good predictor of shorter survival and the most common reason for not receiving active treatment. It also influences the decision to not requesting mutation testing in patients whom clinicians judge as not fit to receive any form of systemic therapy.

Multivariate analysis confirmed that the presence of an actionable mutation was the strongest predictor of overall survival in this cohort of patients with metastatic NSCLC in which mutation testing was conducted according to international recommendations¹⁶ and targeted therapies were available. The median survival of patients with an actionable mutation (*EGFR/ALK*) in our study was comparable to reported data from the Lung Cancer Mutation Consortium (LCMC).⁶ Additionally, regardless of mutation status, improved survival was associated with female sex and absence of adverse prognostic factors including ECOG ≥ 2 , smoking history, weight loss, and respiratory comorbidity. Evaluation of these patient- and disease-related variables for all patients in the TMC (stages I-IV) has been utilised to improve prognostic estimation at the time of NSCLC diagnosis [Alexander et al, Lung cancer

prognostic index – a risk score to predict overall survival after the diagnosis of Non-Small Cell Lung Cancer in the era of targeted therapies (2017) unpublished manuscript].

Our study recorded that in a setting with available molecular testing, a low but significant number of patients did not have molecular testing performed (96/392, 24%). According to recommended guidelines, *EGFR* and *ALK* testing is not recommended in NSCLC that lacks any adenocarcinoma component, such as pure squamous cell carcinoma or large cell carcinomas. However, if adenocarcinoma component cannot be completely excluded in the setting of limited tissue specimen, *EGFR* and *ALK* testing may be performed in cases showing squamous or large cell histology. Clinical characteristics such as Asian ethnicity and a lack of smoking history may guide decision in this setting.¹⁶ It is currently local practice for molecular testing to be ordered at the time of diagnosis for patients with adenocarcinoma presenting with advanced stage disease. A lung panel consisting of *EGFR*, *ALK*, *KRAS*, *ROS1*, *BRAF* and *MET* are available upon request with *EGFR* mutation and *ALK* rearrangement prioritized over other molecular tests unless clinically indicated or patients are being considered for a clinical trial.

It was noted that while 84% of patients with *EGFR* mutation positive NSCLC received first line *EGFR* TKI, only 36% of patients with *ALK* rearranged NSCLC received an *ALK* inhibitor at diagnosis. This most likely reflects a period of limited availability of crizotinib in Australia, as it was only available on the Pharmaceutical Benefit Scheme (PBS) in August 2015. Nevertheless, all patients subsequently received a targeted therapy (targeting *EGFR* or *ALK* as relevant) in their subsequent line of treatment.

The acquisition of tissue biopsy continues to be a challenge and when available, immunohistochemistry for diagnosis of lung cancer is generally prioritised over molecular testing. In our study, 20% of patients (19/96) had insufficient tissue for molecular testing which is higher compared with the initial Canadian experience with an *EGFR* testing program that found 12% of cases had insufficient tissue.²⁷ The French Cooperative Thoracic InterGroup (IFCT) has shown that routine nationwide molecular profiling for advanced NSCLC is feasible and at least one potentially actionable mutation was detected 50% of the time and changed treatment options for at least half of the

patients.²⁸ Comparatively, 36% of patients in our cohort had at least one potentially actionable mutation (*EGFR/ALK*).

Johnson et al reported that *KRAS* mutation is strongly associated with shorter survival even after adjusting for age, gender and performance status.²⁹ We demonstrated that patients whose tumour harbours *KRAS* mutations had a worse prognosis when compared with those patients with an *EGFR* and *ALK* mutation. The higher frequency of patients with *EGFR* mutations compared with *KRAS* mutations seen in this study is atypical for an Australian population likely due to referral bias to a tertiary cancer centre, with a high number of migrants, who have higher population rates of *EGFR* mutations. The declining rates of smoking in Australia³⁰ may have also contributed to a higher percentage of non-smoking related lung cancer in our study; however it is uncertain if this is due to a declining rate of smokers in general or an increased in lung cancer incidence amongst never smokers.³¹

This study has several limitations, such as the retrospective nature of the analysis, albeit prospectively collected data in a single institution. We only included patients with *de novo* metastatic disease, and survival was measured from date of diagnosis of metastatic disease, selecting out the group of patients with poorest survival. This study was not designed to compare the survival of patients according with the type of treatment received, rather more an observation of the number of patients with an actionable mutation receiving first line targeted therapy. The median survival of patients with *ALK* rearranged NSCLC is longer than expected; however, with only a small number of patients, this should be interpreted with caution.

CONCLUSION:

We conclude that there is a significant difference in survival of patients with an oncogenic driver mutation and treated with a therapeutic targeted agent compared with patients without a mutation. These data confirm that it is imperative to test upfront for somatic mutations in patients diagnosed with metastatic NSCLC, as the identification of an oncogenic driver mutation is prognostic for survival in the context of available targeted therapies.

TABLES:

Table 1: Patient characteristics (n=392)

	Patients without an oncogenic driver mutation		Patients with an oncogenic driver mutation				
No. (%)	Mutation Negative n=124 (32)	Mutation Unknown n=96 (24)	EGFR+ n=81 (21)	ALK+ n=25 (6)	KRAS+ n= 57 (15)	ROS1 n=4 (1)	BRAF+ n=5 (1)
Median age at diagnosis (years):	64	70	59	53	66	34	67
Sex:							
Males	72 (58)	70 (73)	31 (38)	14 (56)	35 (62)	1 (25)	2 (40)
Females	52 (42)	26 (27)	50 (62)	11 (44)	22 (38)	3 (75)	3 (60)
Ethnicity:							
Caucasian	104 (84)	81 (84)	44 (54)	16 (64)	51 (90)	2 (50)	3 (60)
Asian (East/South)	16 (13)	12 (13)	36 (45)	6 (24)	5 (9)	2 (50)	2 (40)
Aboriginal/Torres Strait	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pacific Islander	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
African	1 (1)	0 (0)	0 (0)	2 (8)	0 (0)	0 (0)	0 (0)
Other/Mixed	2 (1)	2 (2)	1 (1)	1 (4)	1 (1)	0 (0)	0 (0)
Histology:							
Adenocarcinoma	87 (70)	42 (44)	75 (93)	22 (88)	50 (88)	4 (100)	5 (100)
Squamous	18 (15)	35 (36)	2 (2)	2 (8)	1 (2)	0 (0)	0 (0)
Large cell	3 (2)	3 (3)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
NSCLC NOS	16 (13)	16 (17)	4 (5)	1 (4)	5 (8)	0 (0)	0 (0)
Smoking History:							
Never smoker [¶]	13 (11)	3 (3)	53 (65)	15 (60)	3 (5)	4 (100)	2 (40)
Current smoker	24 (19)	25 (26)	5 (6)	1 (4)	13 (23)	0 (0)	0 (0)
Past smoker	87 (70)	68 (71)	23 (29)	9 (36)	41 (72)	0 (0)	3 (60)
ECOG PS:[§]							
0	17 (14)	10 (10)	14 (17)	3 (12)	7 (12)	1 (25)	1 (20)
1	78 (63)	52 (54)	55 (68)	21 (84)	39 (69)	3 (75)	4 (80)
2	21 (17)	22 (23)	7 (9)	1 (4)	8 (14)	0	0
3	8 (6)	11 (12)	5 (6)	0 (0)	3 (5)	0	0
Unrecorded		1 (1)					

[¶] Never smoker refers to <100 cigarettes per lifetime

[§]ECOG PS refers to Eastern Cooperative Group Performance Status

Table 2: Reasons for not performing molecular testing (n=96)

Reason	No. (%)
Squamous Histology	35 (36)
Insufficient Tissue	19 (20)
Poor Performance Status	24 (25)
Other	18 (19)
Patient died prior to testing	2
Patient declined systemic treatment	2
Pathology review indicated neuroendocrine tumour	1
Reason not documented	13

Table 3: Association between patient- and disease-related variables and overall survival by univariate Cox proportional hazards regression

Variables	Univariate (n=383)		
	HR	95%CI	p-value ¹
Histology			
Adenocarcinoma	Reference		
Squamous Cell	1.82	1.32-2.54	<0.01
Large Cell	2.87	1.35-6.15	0.01
NSCLC NOS	2.24	1.56-3.21	<0.01
Histology (non-adeno vs. Adeno)²	2.04	1.58-2.65	<0.01
Mutation			
Negative	Reference		
ALK positive	0.28	0.15-0.52	<0.01
EGFR positive	0.40	0.27-0.58	<0.01
KRAS positive	1.27	0.88-1.82	0.20
Not Tested	1.86	1.39-2.50	<0.01
EGFR vs. ALK positive	1.42	0.75-2.71	0.29
Actionable Mutation³			
No	Reference		
Yes	0.34	0.24-0.47	<0.01
Not Tested	1.71	1.31-2.22	<0.01
Ethnicity (Asian vs. non-Asian)	0.53	0.37-0.76	<0.01
ECOG PS (≥2 vs. <2)	1.91	1.46-2.50	<0.01
Smoking Status			
Current	Reference		
Past	0.94	0.70-1.26	0.67
Never	0.28	0.18-0.42	<0.01
Smoking (ever vs. never)⁴	3.43	2.44-4.81	<0.01
Weight loss (0-10% vs. >10%)⁵	1.59	1.20-2.10	<0.01
Respiratory Comorbidity⁶	1.80	1.38-2.33	<0.01
Sex (male vs. female)	1.72	1.34-2.20	<0.01
Age (continuous)	1.00	1.00-1.00	0.11
Age (≤65 vs. >65)	1.74	1.37-2.20	<0.01

1 - p-value for the comparison of overall survival for patients with and without the specified factor, or for actionable mutation as compared with that for patients in the reference group.

2- Adeno refers to adenocarcinoma

3 - Actionable mutation refers to *EGFR* or *ALK* mutation

4 – Ever smoker refers to past or current smokers; never smoker refers to <100 cigarettes per lifetime

5 – Weight loss within 3 months of diagnosis

6 - Colinet definition: Respiratory comorbidity was defined as the presence of one or more of the following: history of tuberculosis, history of pleural effusion or pneumonia, asthma, pulmonary embolism, chronic pulmonary insufficiency as defined by a chronic hypoxemia less than 60mmHg and/or chronic obstructive pulmonary disease (COPD) inducing a FEV1 less than 1.5L.³²

Author Manuscript

Table 4: Association between patient- and disease-related variables and overall survival by multivariate Cox proportional hazards regression

Variables	Multivariate		
	HR	95%CI	p-value ¹
Actionable Mutation²			
No	Reference		
Yes	0.49	0.33-0.71	<0.01
Not Tested	1.31	0.97-1.78	0.08
Histology (non-Adeno vs. Adeno)³	1.21	0.90-1.65	0.20
Ethnicity (Asian vs. non-Asian)	1.10	0.75-1.60	0.62
ECOG PS (≥ 2 vs. < 2)	1.37	1.02-1.84	0.03
Smoking (ever vs. never)⁴	1.60	1.06-2.42	0.03
Weight loss (0-10% vs. $>10\%$)⁵	1.37	1.03-1.83	0.03
Respiratory Comorbidity⁶	1.44	1.10-1.90	0.01
Sex (male vs. female)	1.43	1.11-1.85	0.01
Age (continuous)	1.00	1.00-1.00	0.53

1 - p-value for the comparison of overall survival for patients with and without the specified factor, or for actionable mutation as compared with that for patients in the reference group.

2 - Actionable mutation – *EGFR* or *ALK* mutation

3- Adeno refers to adenocarcinoma

4 – Ever smoker refers to past or current smokers; never smoker refers to <100 cigarettes per lifetime

5– Weight loss within 3 months of diagnosis

6 - Colinet definition: Respiratory comorbidity was defined as the presence of one or more of the following: history of tuberculosis, history of pleural effusion or pneumonia, asthma, pulmonary embolism, chronic pulmonary insufficiency as defined by a chronic hypoxemia less than 60mmHg and/or chronic obstructive pulmonary disease (COPD) inducing a FEV1 less than 1.5L.³²

Figure 1: Survival of All Patients

Mutation negative indicates no mutation; Mutation UK indicates mutation status unknown; EGFR, epidermal growth factor receptor gene; ALK, anaplastic lymphoma kinase gene; KRAS, Kirsten rat sarcoma.

* Nine patients with ROS-1 or BRAF mutations were excluded from survival analyses

Figure 2: Survival of patients without oncogenic driver mutations; mutation negative versus mutation status unknown

Mutation Neg indicates no mutation, Mutation UK; mutation status unknown

*The survival difference shown here is statistically significant by univariate analysis: HR 1.71 (95%CI 1.31-2.22, $p < 0.01$);

however, this result is not statistically significant with multivariate analysis HR 1.29 (95%CI 0.97-1.78, $p = 0.08$) when corrected for confounding factors.

REFERENCES:

1. Australia AloHaWC. Lung cancer in Australia: an overview *Canberra: AIHW* 2011; **64**(CAN 58).
2. Welfare AloHa. Australian Cancer Incidence and Mortality (ACIM) books: lung cancer. *AIHW, Canberra* 2016; (Lung Cancer).
3. Molina J.R., Ying P., Cassivi S.D., Schild S.E., A.A. A. Non-Small Cell Lung Cancer: Epidemiology, Risk Factors, Treatment and Survivorship. *Mayo Clin Proc* 2008; **83**: 584-94.
4. Schiller J.H., Harrington D., Belani C.P., et al. Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. *N Engl J Med* 2002; **346**: 92-8.
5. Li T., Kung H.J., Mack P.C., D.R. G. Genotyping and Genomic Profiling of Non-Small-Cell Lung Cancer: Implications for Current and Future Therapies. *J Clin Oncol* 2013; **31**: 1039-49.
6. Kris M.G., Johnson B.E., Berry L.D., et al. Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs. *JAMA* 2014; **311**: 1998-2006.
7. Sequist L.V., Soria J.C., Goldman J.W., et al. Rociletinib in EGFR-Mutated Non-Small Cell Lung Cancer. *N Engl J Med* 2015; **372**: 1700-9.
8. Janne P.A., Yang J.C-Y., Kim D.W., et al. AZD9291 in EGFR Inhibitor-Resistant Non-small cell Lung Cancer. *N Engl J Med* 2015; **372**: 1689-99.
9. Mok T.S, Wu Y-L., Thongprasert S., et al. Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma. *N Engl J Med* 2009; **361**: 947-57.
10. Inoue A., Kobayashi K., Maemondo M., et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Annals of oncology* 2013; **24**: 54-9.
11. Mitsudomi T., Morita S., Yatabe Y., et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; **11**: 121-28.
12. Rosell R., Carcereny C., Gervais R., et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; **13**: 239-46.

13. Sequist L.V., Yang J., Yamamoto N., et al. Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients with Metastatic Lung Adenocarcinoma With EGFR Mutations. *J Clin Oncol* 2013; **31**: 3327-34.
14. Wu Y.L., Zhou C., Hu C.P., et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 213-22.
15. Zhou C., Wu Y.L., Chen G., et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomized, phase 3 study. *Lancet Oncol* 2011; **12**: 735-42.
16. Lindeman N.I., Cagle P.T., Beasley B., et al. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors. *Arch Pathol Lab Med* 2013; **137**: 828-60.
17. Solomon B., Varella-Garcia M., D.R. C. ALK Gene Rearrangements A New Therapeutic Target in a Molecularly Defined Subset of Non-small Cell Lung Cancer. *J Thorac Oncol* 2009; **4**: 1450-54.
18. Cameron L., Solomon B. New Treatment Options for ALK-Rearranged Non-Small Cell Lung Cancer. *Curr Treat Options in Oncol* 2015; **16**: 1-14.
19. Solomon B., Mok T., Kim D-W., et al. First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. *N Engl J Med* 2015; **371**: 2167-77.
20. Morgansztern D., Campo M.J., Dahlberg S.E., et al. Molecularly targeted therapies in Non-small cell lung cancer annual update 2014. *J Thorac Oncol* 2015; **10**: S1-63.
21. Slebos R., Kibbelaar R.E., Dalesio O., et al. K-RAS oncogene activation as a prognostic marker in adenocarcinoma of the lung. *New England Journal of Medicine* 1990; **323**: 561-5.
22. Mascaux C., Iannino N., Martin B., et al. The role of RAS oncogene in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. *British Journal of Cancer* 2005; **92**: 131-39.
23. Shepherd F.A, Domerg C., Hainaut P., et al. Pooled Analysis of the Prognostic and Predictive Effects of KRAS Mutation Status and KRAS mutation Subtype in Early-Stage Resected Non-Small-Cell Lung Cancer in Four Trials of Adjuvant Chemotherapy *J Clin Oncol* 2013; **31**: 2173-81.

24. Janne P.A., Shaw A., Pereira J., et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *Lancet Oncol* 2013; **14**: 38-47.
25. Blumenschein G.R., Smit E.F., Planchard D., et al. A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC). *Annals of oncology* 2015; **26**: 894-901.
26. Oken M.M, Creech R.H., Tormey D.C., et al. Toxicity and response criteria of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649-55.
27. Ellis P., Verma S., Sehdev S., Younus J., N.B. L. Challenges to implementation of an epidermal growth factor receptor testing strategy for non-small cell lung cancer in a publically funded health care system *J Thorac Oncol* 2013; **8**: 1136-41.
28. Barlesi F., Mazieres J., Merlio J.P., et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: Results of a 1 year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). *Lancet Oncol* 2016; **387**: 1-12.
29. Johnson ML., Sima C.S., Chافت J., et al. Association of KRAS and EGFR Mutations with Survival in Patients with Advanced Lung Adenocarcinomas. *Cancer* 2013; **119**: 356-62.
30. Australia ALoHaWC. Australian's Health Series no 13. *AIHW* 2012; **Aus 156**.
31. Wakelee HA, Chang ET, Gomez SL, et al. Lung cancer incidence in never smokers. *J Clin Oncol* 2007; **25**: 472-8.
32. Colinet B., Jacot W., Bertrand D., et al. A new simplified comorbidity score as a prognostic factor in non-small-cell lung cancer patients: description and comparison with the Charlson's index. *British Journal of Cancer* 2005; **93**: 1098-105.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Tan, L;Alexander, M;Officer, A;MacManus, M;Mileshkin, L;Jennens, R;Herath, D;de Boer, R;Fox, SB;Ball, D;Solomon, B

Title:

Survival difference according to mutation status in a prospective cohort study of Australian patients with metastatic non-small-cell lung carcinoma

Date:

2018-01-01

Citation:

Tan, L., Alexander, M., Officer, A., MacManus, M., Mileshkin, L., Jennens, R., Herath, D., de Boer, R., Fox, S. B., Ball, D. & Solomon, B. (2018). Survival difference according to mutation status in a prospective cohort study of Australian patients with metastatic non-small-cell lung carcinoma. INTERNAL MEDICINE JOURNAL, 48 (1), pp.37-44. <https://doi.org/10.1111/imj.13491>.

Persistent Link:

<http://hdl.handle.net/11343/283420>