Real world outcomes in KRAS G12C mutation positive non-small cell lung cancer

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\textbf{A R T I C L E  I N F O}

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KRAS G12C mutation
Lung cancer
Non-small cell lung cancer

\textbf{A B S T R A C T}

\textbf{Background:} KRAS mutations are found in 20–30 % of non-small cell lung cancers (NSCLC) and were traditionally considered undruggable. KRAS\textsuperscript{G12C} mutation confers sensitivity to KRAS\textsuperscript{G12C} covalent inhibitors, however its prognostic impact remains unclear. This study assesses the frequency, clinical features, prevalence of brain metastases and outcomes in KRAS\textsuperscript{G12C} NSCLC in a real-world setting.

\textbf{Methods:} Patients enrolled in the prospective Thoracic Malignancies Cohort (TMC) between July 2012 to October 2019 with recurrent/metastatic non-squamous NSCLC, available KRAS results, and without EGFR/ALK/ROS1 gene aberrations, were selected. Data was extracted from TMC and patient records. Clinicopathologic features, treatment and overall survival (OS) was compared for KRAS wildtype (KRAS\textsuperscript{WT}) and KRAS mutated (KRAS\textsuperscript{mut}); and KRAS\textsuperscript{G12C} and other (KRAS\textsuperscript{other}) mutations.

\textbf{Results:} Of 1386 NSCLC patients, 1040 were excluded: non-metastatic/recurrent (526); unknown KRAS status (356); ALK/EGFR/ROS1 positive (154); duplicate (4). Of 346 patients analysed, 144 (42 %) were KRAS\textsuperscript{mut}, of whom 65 (45 %) were KRAS\textsuperscript{G12C}. All patients with KRAS\textsuperscript{G12C} were active or ex-smokers, compared to 92 % of KRAS\textsuperscript{other} and 83 % of KRAS\textsuperscript{WT}. The prevalence of brain metastases during follow-up was similar between KRAS\textsuperscript{mut} and KRAS\textsuperscript{WT} (33 % vs 40 %, p = 0.17), and KRAS\textsuperscript{G12C} and KRAS\textsuperscript{other} (40 % vs 41 %, p = 0.74). The proportion of patients receiving one or multiple lines of systemic therapy was comparable. OS was similar between KRAS\textsuperscript{mut} and KRAS\textsuperscript{WT} (p = 0.54), and KRAS\textsuperscript{G12C} and KRAS\textsuperscript{other} (p = 0.39).

\textbf{Conclusion:} Patients with KRAS\textsuperscript{mut} and KRAS\textsuperscript{WT}, and KRAS\textsuperscript{G12C} and KRAS\textsuperscript{other} NSCLC have comparable clinical features, treatment and survival. While not prognostic, KRAS\textsuperscript{G12C} may be an important predictive biomarker as promising KRAS\textsuperscript{G12C} covalent inhibitors continue to be developed.

1. Introduction

The Kirsten rat sarcoma viral oncogene (KRAS) is an oncogenic driver of tumorigenesis in a number of cancer types. \cite{1,2} KRAS mutations are found in 20–30% of non-small cell lung cancer (NSCLC). KRAS\textsuperscript{G12C} is the most prevalent KRAS mutation, and has been identified in approximately 15 % of NSCLC.\cite{2} This mutation results in a glycine to cysteine substitution at amino acid position 12.\cite{3} The resulting defect in GTPase-activating proteins (GAPs) causes accumulation of active GTP-bound KRAS, and thus increased proliferation and survival of tumour cells.\cite{3}

In colorectal cancer, the KRAS\textsuperscript{G12C} mutation is associated with a...
poorer prognosis compared to KRAS wildtype (KRASWT) colorectal cancer. [4–6] Conversely, in lung cancer, the impact of the KRASG12C mutation on clinical outcomes compared to other KRAS mutations differs between studies. [7–10]

To understand the frequency, clinical features and prognostic significance of KRASG12C mutation compared to NSCLC without a KRASG12C mutation in the real-world setting, we describe the clinical features and outcomes in a prospective single-institution database. Importantly, we also assess the prevalence of brain metastases at diagnosis and during follow-up in patients with KRASG12C mutation, which has not been previously reported in prior studies. These findings have potential implications for the development of KRASG12C targeted therapies.

2. Materials and methods

2.1. Population

Patients with advanced lung cancer treated at the Peter MacCallum Cancer Centre (PMCC) between July 2012 and October 2019, were prospectively enrolled on the Thoracic Malignancies Cohort (TMC). The TMC prospectively captures clinicopathologic (including molecular status), treatment and outcome data for all lung cancer patients attending PMCC, a large Australian tertiary referral centre. Ethics approval was obtained from the Peter MacCallum Cancer Centre Clinical Research and Ethics Committee for this project (19/204R) and the TMC (17/70, HREC/17/PMCC/42).

From 2012 onwards, patients at PMCC with metastatic nonsquamous NSCLC were routinely tested for anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) rearrangements using immunohistochemistry and fluorescence in situ hybridisation, and epidermal growth factor receptor (EGFR) mutations (exons 18, 19, 20, 21) and KRAS mutations (exons 2, 3, 4) using the targeted next generation sequencing (NGS) PMCC lung panel mutation analysis.

For this analysis, patients with metastatic or recurrent non-squamous NSCLC, who had available KRAS mutation test results and did not have an EGFR, ALK, or ROS1 gene aberration, were included. The following data points were extracted from the TMC: age, sex, ethnicity, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, histology and molecular status, presence of brain metastases at diagnosis and at any time following initial diagnosis, systemic therapy including start and stop dates, date of diagnosis of metastatic or recurrent disease, date of death and date of last follow up. Never smokers were defined as those who had smoked less than 100 cigarettes in their lifetime. Chart review was undertaken for missing data, including clarification of molecular results from histopathology reports and determination of brain metastases from reviewing radiological scans available on the hospital’s electronic medical records at diagnosis and throughout follow up.

2.2. Statistical analysis

Comparative analyses were performed for patients with KRASWT versus KRAS mutated (KRASmut) tumours, and for patients with a KRASG12C versus other KRAS (KRASother) mutation. Systemic treatment
lines were extracted for the selected patient populations and compiled using Sankey diagrams to display the drug categories from lines one to three. [11] Patients who received a second line immunotherapy drug were identified and the duration of treatment as well as the best response were summarised using swimmer plots. Significance of clinicopathological differences was assessed using Fisher’s exact test for categorical variables and the Mann-Whitney test for continuous variables. Survival analyses were performed using the Kaplan Meier method and differences compared using the log rank test. Hazard ratio (HR) and 95% confidence intervals (CI) were reported. Overall survival (OS) was defined as the time from the date of diagnosis of metastatic disease to the date of death, censored at the date of last review. All statistical analyses were 2-sided and statistical significance was defined as P < 0.05. Statistical analyses were performed using STATA.

3. Results

Of the 1386 patients with non-squamous NSCLC identified in the TMC between July 2012 and October 2019, 346 patients were eligible for analysis (Fig. 1). Two hundred and two (58%) were KRAS WT. Of the 144 patients with KRAS mut NSCLC, 65 patients (45%) had a G12C mutation and 79 (55%) had a KRAS other mutation. The distribution of KRAS mutations is shown in Fig. 2: KRAS G12C was the most common mutation in this cohort.

3.1. Patient characteristics

Patient characteristics are displayed in Table 1. There was a higher proportion of smokers (current or former) in patients with KRAS mut compared to KRAS WT NSCLC (p < 0.01). All patients with KRAS G12C mutant NSCLC were current or former smokers. There were no other significant differences in clinicopathological characteristics between KRAS mut and KRAS WT patients, or KRAS G12C versus KRAS other patients. A similar proportion of patients with KRAS mut and KRAS WT NSCLC had brain metastasis at diagnosis (17% and 23% respectively, p = 0.22) and during follow up (33% and 40% respectively, p = 0.17). Patients with KRAS G12C mutations had higher frequency of brain metastases at diagnosis (28% vs. 17% KRAS WT and 19% KRAS other) but this was not statistically significant.

3.2. Survival

Overall, 251 deaths had occurred at the time of analysis (Fig. 3). Median follow-up time was 9 months.

There was no difference in OS between patients with KRAS mut and KRAS WT NSCLC (HR 1.08; 95% CI 0.83, 1.40; p = 0.54). Additionally, there was no difference in OS between patients with KRAS G12C and KRAS other NSCLC (Appendix figure B).

![Fig. 2. KRAS status. Chart A shows KRAS wildtype versus KRAS mutant. Chart B shows the distribution of KRAS mutations that were present in patients with KRAS mutant NSCLC.](image-url)

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics.</th>
<th>All patients (n = 346)</th>
<th>KRAS Wildtype (n = 202)</th>
<th>KRAS Mutant (n = 144)</th>
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<tr>
<td>Age</td>
<td>Median</td>
<td>66 (32–91)</td>
<td>68 (32–91)</td>
<td>65 (34–83)</td>
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<td></td>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
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<tr>
<td></td>
<td></td>
<td>58% (202)</td>
<td>61% (123)</td>
<td>57% (37)</td>
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<td></td>
<td></td>
<td>42% (144)</td>
<td>39% (79)</td>
<td>43% (28)</td>
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<td>Smoking status</td>
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<td>12% (40)</td>
<td>17% (34)</td>
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<tr>
<td></td>
<td>Ex-smoker</td>
<td>67% (231)</td>
<td>63% (128)</td>
<td>74% (48)</td>
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<td>Current smoker</td>
<td>21% (75)</td>
<td>20% (40)</td>
<td>26% (17)</td>
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<tr>
<td>Duration of smoking</td>
<td>Median (pack years)</td>
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<td>36</td>
<td>39</td>
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<td>Ethnicity</td>
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<td>85% (172)</td>
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<td>Asian</td>
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<td>1–49%</td>
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<td>≥50%</td>
<td>10% (34)</td>
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<td>No</td>
<td>13% (44)</td>
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<td>Brain metastases at any time</td>
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<td>33% (67)</td>
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<td>No</td>
<td>63% (219)</td>
<td>66% (134)</td>
<td>58% (38)</td>
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<tr>
<td>Brain metastases at diagnosis</td>
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<td>82% (166)</td>
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</tr>
</tbody>
</table>

* Other includes: Aboriginal, Torres Strait islander, Pacific Islander, Maori, African, mixed.

KRAS other NSCLC (HR 1.19; 95% CI 0.78, 1.80; p = 0.39).

3.3. Systemic therapy

The proportion of patients with KRAS mut or KRAS WT NSCLC who received first line (75% vs 71%, p = 0.39), second line (44% vs 42%, p = 0.83) and third line (21% vs 19%, p = 0.35) systemic therapy were similar (Appendix figure A). Likewise, the proportion of patients with KRAS G12C or KRAS other NSCLC who received first line (68% vs 73%, p = 0.46), second line (35% vs 48%, p = 0.13) and third line systemic therapy (14% vs 24%, p = 0.14) were also comparable. As shown in Appendix figure A, the types of treatment delivered were similar in all groups, with the majority of patients receiving chemotherapy as first and second line systemic treatment.

In patients who received second line single agent immunotherapy, patients with KRAS mut (N = 15) and KRAS WT (N = 21) NSCLC has similar response rates and duration, and this was the same for KRAS G12C (N = 6) and KRAS other (N = 9) NSCLC (Appendix figure B).

4. Discussion

Our study of non-squamous NSCLC patients treated at a large academic centre identified that 42% of patients had tumours with KRAS
mutations, of which 45% were KRAS*G12C, similar to the prevalence reported in the Catalogue of Somatic Mutations in Cancer (COSMIC) database and in other series. [2] We examined the impact of KRAS*G12C mutations on clinical presentation, such as the prevalence of brain metastases at diagnosis and during follow-up, and treatment outcomes, to explore the biology of this subset of NSCLC and potential implications for the ongoing development of therapies targeting KRAS*G12C.

While the proportion of never smokers with NSCLC has increased over the last two decades, approximately 80–90% of patients with NSCLC are still current or ex-smokers. [12–14] Similar to previous studies, 88% of all patients in this study were smokers and a higher proportion of patients with KRAS*mut NSCLC were current or former smokers compared to KRAS*WT NSCLC. [8,15] The type of KRAS mutation has also previously been associated with different smoking patterns, where transversion mutations (such as KRAS*G12C) were more common in smokers, while never smokers have a higher frequency of transition mutations. [16,17] Congruently, all patients in this study with KRAS*G12C NSCLC were smokers. Additionally, one study demonstrated that KRAS*G12C mutation was more frequently seen in women compared with other KRAS mutations types (43.4% of KRAS*G12C mutant NSCLC were female compared to 9.5–20.1% KRAS*other NSCLC). [16] This difference was not demonstrated in our study, where the proportion of women was similar between KRAS*G12C and KRAS*other (43% and 47% respectively).

Brain metastasis occurs in approximately 16–22% of patients with NSCLC and can cause significant morbidity and mortality. [18,19] While whole brain radiotherapy has shown improvements in intracranial disease control, it does not improve OS and can result in significant long-term toxicities such as memory impairment [20–23]. In EGFR mutant and ALK rearranged NSCLC, 50–60% of patients eventually develop brain metastases [24–26] and first generation tyrosine kinase inhibitors (TKI) have shown inferior intracranial control compared to second and third generation TKIs [27,28]. We assessed the presence of brain metastasis in patients with KRAS*G12C NSCLC, which has not been previously reported in prior studies. The prevalence of brain metastasis was high in patients with KRAS*G12C NSCLC, 28% of patients had brain metastasis at diagnosis, and 40% of patients developed brain metastasis during follow up. The frequency of brain metastasis was similar in KRAS*other NSCLC (19% at diagnosis and 41% during follow up). Therefore, parallel to the lessons learnt from EGFR and ALK aberrant NSCLC, agents that are effective for existing brain metastases, and that prevent or delay new brain metastases will be valuable for targeting KRAS*G12C.

While KRAS mutations were previously considered undruggable, therapies directly targeting KRAS*G12C have shown promising early preclinical and clinical results. [29–31] In KRAS*G12C mutant NSCLC, the mutant cysteine 12 is closely located to the nucleotide pocket and switch regions. [29–31] Small molecule covalent inhibitors, such as AMG 510, ARS-853, ARS-1620 and MRTX849, form covalent bonds with the mutant cysteine and decrease the affinity of RAS for GTP relative to GDP [29–32]. Preliminary data from the dose-escalation phase 1 trial of AMG 510 monotherapy in advanced solid organ tumours with KRAS*G12C mutation, included 34 patients with NSCLC, of which 23 were evaluable for efficacy. [33] Eleven out of these 23 patients achieved partial responses, 11 had stable disease, and 1 patient had progressive disease. The disease control rate was 100% in the 13 patients who received the recommended phase II dose of 960 mg (7 achieved partial responses and 6 achieved stable disease) [33]. Similarly, early data from the phase I/II trial of MRTX849 in advanced solid organ KRAS*G12C mutant tumours demonstrated an objective response rate (ORR) of 50% (3/6) in the evaluable patients with NSCLC. [34] In lung cancer, where patients can deteriorate quickly, sequencing of treatments becomes crucial. In our cohort, while 68% of patients with KRAS*G12C mutations received first line systemic therapy, only 35% and 14% received second- and third-line therapy. Therefore, mutation testing and consideration of KRAS*G12C targeting therapies needs to occur early in the treatment of these patients. If KRAS*G12C covalent inhibitors will be shown to be beneficial, upfront use in first or second line should be considered.

Preclinical studies demonstrated that in immune competent mice, treatment with AMG 510 resulted in a pro-inflammatory tumour microenvironment, and produced durable responses when given as monotherapy or in combination with immune-checkpoint inhibitors, cytotoxic chemotherapy or targeted TKIs. [29] Likewise, MRTX849 has been reported to modulate MHC class I protein expression and factors associated with an immunosuppressive tumour microenvironment; and the combination of MRTX849 and programmed death-1 (PD-1) inhibitor treatment resulted in durable, complete responses in preclinical mouse models [32,35]. In addition, exploratory analysis of the Keynote-042 and Keynote-189 studies suggest that in patients with PD-L1 positive NSCLC, upfront pembrolizumab, with or without chemotherapy, resulted in improved ORR and progression free survival (PFS) compared to chemotherapy alone regardless of the presence of KRAS*G12C mutation. [36,37] In our cohort, the majority of patients received chemotherapy as their first line of systemic therapy, in keeping with the study period extending to 2012, i.e. before first-line immunotherapy with or without chemotherapy was established as standard of care treatment. In patients with KRAS*G12C mutant NSCLC who then received second line single agent immunotherapy, only one out of six responded. The presence of STK11 and KEAP1 co-mutations, which are associated with reduced objective response rates to checkpoint inhibitors and OS in KRAS mutant NSCLC, was not assessed in these patients. [38,39] Exploring combinations of KRAS*G12C targeting agents with checkpoint inhibitors, and upfront use of this combination, may be one method to
increase the response rate and durability of benefit from these therapies in \textit{KRAS}^{G12C} NSCLC.

Lastly, the prognostic value of \textit{KRAS} mutations and \textit{KRAS}^{G12C} mutations is controversial. A 2013 meta-analysis including 1543 patients showed no difference in OS between \textit{KRAS}^{mut} and \textit{KRAS}^{WT} early stage NSCLC. [40] However, in advanced NSCLC, several meta-analyses including up to 6939 patients have demonstrated poorer survival in those with \textit{KRAS}^{mut} NSCLC. [41–44] In addition, a 2017 meta-analysis reported that \textit{KRAS} mutations detected in circulating tumour DNA conferred a worse OS [45]. Conversely, the cBioPortal for cancer genomics, where 2175 out of 4521 patient samples have been tested for \textit{KRAS} mutations, showed no difference in OS between \textit{KRAS}^{WT} and \textit{KRAS}^{mut} NSCLC. [46–48]

There have also been mixed results in studies comparing \textit{KRAS}^{G12C} and other \textit{KRAS} mutations. In advanced NSCLC, while one retrospective single institution European study which included 39 patients with \textit{KRAS}^{mut} NSCLC demonstrated a shorter OS in patients with \textit{KRAS}^{G12C} compared to \textit{KRAS}^{other} mutations [10], another large single centre US study analysing 677 patients with \textit{KRAS}^{mut} NSCLC showed no difference in OS. [7] Our study population was larger than the European study. While the patients with \textit{KRAS}^{mut} in our study had similar demographic features to the US study, the US study did not include \textit{KRAS}^{WT} patients. We did not observe any differences in OS between patients with \textit{KRAS}^{mut} and \textit{KRAS}^{WT} NSCLC, similar to cBioPortal, or between \textit{KRAS}^{G12C} and \textit{KRAS}^{other} NSCLC.

Our study has several limitations. It was a large single centre study with patients treated at an academic centre, and therefore our results may not be generalisable to community patients. In addition, while all patients included in this study had available \textit{EGFR}, \textit{ALK}, \textit{ROS1} and \textit{KRAS} test results, testing for other potentially predictive and prognostic biomarkers, such as \textit{TP53}, \textit{BRAF}, \textit{NTRK}, \textit{RET}, \textit{STK11} and \textit{KEAP1} gene aberrations, was not routinely performed. Therefore, we were not able to dissect differences in subsets of \textit{KRAS} mutated tumours, such as \textit{STK11} or \textit{KEAP1} mutants, with known negative prognostic implications. [38,39]

5. Conclusion

This study describes the frequency, clinical features and outcomes of patients with \textit{KRAS}^{G12C} mutation positive NSCLC in the real-world setting. \textit{KRAS} mutations were found in 42 \% of patients, among which 45 \% had G12C mutations. We confirm that \textit{KRAS}^{G12C} is strongly associated with smoking. While there were no differences in the presence of brain metastases between patients with \textit{KRAS}^{mut} and \textit{KRAS}^{WT} NSCLC, or \textit{KRAS}^{G12C} and \textit{KRAS}^{other}, 40 \% of patients with \textit{KRAS}^{G12C} NSCLC developed brain metastasis during follow up. Therefore, in this group of patients, treatments with good intracranial penetration have important implications for long-term disease control. While we did not observe any prognostic impact of \textit{KRAS}^{G12C} mutations, the development of \textit{KRAS}^{G12C} targeted therapies, which have shown promising early efficacy in \textit{KRAS}^{G12C} NSCLC, are expected to improve outcomes in the population.

Appendix A

Figure A. Lines of treatment received.

Fig. A1–A4

![Fig. A1. Treatments received in KRAS wildtype NSCLC (excluding EGFR/ALK/ROS1). Each column represents a new line of therapy.](image-url)
Fig. A2. Treatments received in KRAS mutant NSCLC (excluding EGFR/ALK/ROS1). Each column represents a new line of therapy.

Fig. A3. Treatments received in KRAS\textsuperscript{G12C} mutant NSCLC (excluding EGFR/ALK/ROS1). Each column represents a new line of therapy.

Fig. A4. Treatments received in other KRAS mutant NSCLC. Each column represents a new line of therapy.

Appendix B

Figure B. Duration of treatment on second line single agent immunotherapy.

Fig. B1, B2
Fig. B1. Duration of treatment on second line single agent immunotherapy for KRAS wildtype versus KRAS mutant NSCLC (excluding EGFR/ALK/ROS1). *Patient 32 underwent radiotherapy to oligo-progressive disease and continued immunotherapy.

Fig. B2. Duration of treatment on second line single agent immunotherapy for KRAS<sup>G12C</sup> vs other KRAS mutant NSCLC (excluding EGFR/ALK/ROS1).