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# Prognostic value of KRAS G12C in advanced non-small cell lung cancer with high PD-L1 expression treated with upfront immunotherapy: a systematic review and meta-analysis

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## Summary

AIM: This study aims to evaluate the prognostic role of the KRAS G12C mutation in patients with advanced non-small cell lung cancer and PD-L1 expression ≥50% who are treated with immune checkpoint inhibitor monotherapy.

METHODS: We conducted a systematic review of clinical studies fulfilling the following criteria: (1) enrolling patients with advanced/metastatic non-small cell lung cancer with high PD-L1 tumour expression receiving first-line therapy with anti-PD-(L)1 immune checkpoint inhibitors; (2) comparing the outcomes of patients with the KRAS G12C mutation to those without this mutation, and (3) reporting overall survival and progression-free survival (PFS). The electronic databases Medline, EMBASE, Cochrane and Google Scholar, along with reference lists, were systematically searched.

RESULTS: We identified four publications that fulfilled the inclusion criteria, comprising a total of 469 patients. Of these, two studies reported hazard ratios (HR) for PFS, resulting in a final pooled patient sample of 163 for the meta-analysis. In patients with non-small cell lung cancer who received anti-PD-(L)1 monotherapy, the presence of a KRAS G12C mutation was associated with improved PFS compared to patients with KRAS wild-type tumours, with a pooled hazard ratio of 0.39 and a 95% Confidence Interval (CI) of 0.25–0.63. Among all patients with KRAS mutations, those harbouring a KRAS G12C mutation had improved PFS compared to patients with any other KRAS mutation (pooled HR 0.33, 95% CI 0.19–0.57).

CONCLUSIONS: Patients with non-small cell lung cancer who have the KRAS G12C mutation and high PD-L1 expression demonstrate favourable PFS with first-line PD-(L)1 immune checkpoint inhibitor monotherapy compared to patients with KRASwt or other KRAS mutations and high PD-L1 expression.

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## Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for an estimated 1.80 million deaths in 2020 [1]. New therapeutic options for patients with metastatic non-small cell lung cancer (NSCLC) have significantly improved survival outcomes [2]. According to current guidelines, the selection of first-line therapy is based on histological subtyping, molecular analysis, and the expression of biomarkers that are predictive of immunotherapy response. These biomarkers include epidermal growth factor receptor (EGFR), B-raf murine sarcoma viral oncogene homolog B1 (BRAF), mesenchymal-epithelial transition factor (MET), and gene fusions involving anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), rearranged during transfection (RET), or neurotrophic tyrosine receptor kinase (NTRK) 1, 2 and 3, as well as the expression level of programmed death ligand 1 (PD-L1) on tumour cells [3–5].

The KEYNOTE-024 trial established pembrolizumab as the first-line treatment for metastatic non-small cell lung cancer with a PD-L1 expression ≥50%, demonstrating improved outcomes in terms of overall survival (OS) and progression-free survival (PFS) compared to platinum-based chemotherapy [6]. Conversely, the KEYNOTE-189 and KEYNOTE-407 phase III clinical trials, involving patients with non-squamous and squamous non-small cell lung cancer, respectively, established the combination of chemotherapy and pembrolizumab independently of PD-L1 expression level, thus becoming the standard treatment for patients with PD-L1 <50% [7,8].

**ABBREVIATIONS**

**KRAS mutation** all KRAS mutations
**KRASwt** KRAS wild-type
**KRAS others** all other mutations except G12C
**non G12C** KRAS others and KRASwt

Several other biomarkers have been proposed to guide better treatment decision-making, including tumour mutational burden (TMB) and tumour infiltration by immune cells [9, 10]. However, these biomarkers are rarely included in clinical practice guidelines and are not routinely tested in all institutions [6–8].

The presence of specific driver alterations has been shown to reduce the likelihood of response to immunotherapy, despite high PD-L1 expression. This phenomenon can partially be explained by the fact that most driver alterations occur among non-smokers, who often present with a disease characterised by low TMB [11–13].

Mutations in KRAS are the most commonly reported in lung adenocarcinoma (20–25% of cases), with the KRAS G12C variant constituting the majority [14]. At present, the KRAS G12C variant is the only one for which targeted treatments are available, namely sotorasib and adagrasib [15, 37]. Consequently, clarifying the association between KRAS G12C and the efficacy of immune checkpoint inhibitor (ICI) therapy is essential to evaluate the best combination, integration and sequencing of treatment strategies. We conducted this systematic review and meta-analysis to summarise the current evidence on the prognostic role of the KRAS GC12 mutation in patients receiving first-line treatment with checkpoint inhibitors.

## Materials and methods

We aimed to summarise and assess published evidence on the prognostic value of the KRAS G12C mutation in terms of progression-free survival and overall survival in patients with advanced/metastatic lung cancer and PD-L1 expression ≥50% receiving their first systemic treatment with immune checkpoint inhibitor monotherapy.

### Literature search

We systematically searched Medline, EMBASE, the Cochrane database and Google Scholar from July to September 2022. Reference lists were manually checked to identify additional studies. Named electronic databases were systematically searched. The search performed in the MESH database from the National Institute of Health used the terms ("KRAS protein, human" [Supplementary Concept]) AND "Immune Checkpoint Inhibitors" [Mesh], yielding 32 articles, of which three were selected. The search terms "G12C AND immunotherapy AND lung" retrieved 51 results, among which five met the selection criteria. Another search term combination, "G12C AND other mutations AND pembrolizumab", led to two results, one of which was eligible for inclusion. Further searches using combinations of KRAS, G12C, variants, immune checkpoint inhibitor (ICI), progression-free survival, PFS, overall survival, OS, non-small cell lung cancer (NSCLC), PD-L1, high-expression, pembrolizumab, nivolumab, cemiplimab, atezolizumab, durvalumab and avelumab did not alter the number of included publications.

Studies were included if they met the following inclusion criteria: (1) patients with advanced non-small cell lung cancer and PD-L1 ≥50%; (2) upfront single-agent therapy with checkpoint inhibitors (pembrolizumab, nivolumab, cemiplimab, atezolizumab, durvalumab or avelumab); and (3) presence of the KRAS G12C mutation. The detailed search strategies are listed in figure 1, and the PICO process used to develop a focused search strategy is shown in table S1 in the appendix.

### Article selection criteria

An initial screening was conducted to select all relevant publications concerning patients with advanced non-small cell lung cancer, KRAS mutation and first-line immunotherapy treatment. Studies that included treatments other than single-agent immunotherapy were excluded. The second screening focused on articles reporting diagnosis, age, PD-L1 expression status, KRAS mutation status and subtype, type of immunotherapy used, progression-free survival and/or overall survival. All study designs from any source (peer-reviewed journals, non-peer-reviewed sources or scientific meeting abstracts) were considered, provided they contained complete information as previously defined. For studies with overlapping patient populations, only the most comprehensive publications were included.

### Data extraction and quality assessment

Two investigators, Luciano Wannesson and Caroline Erhart, independently extracted data and then compared and merged it. A third investigator, Benjamin Kasenda, reviewed the results. Extracted data included study name, authors, year of publication, sample size, patient characteristics, disease stage, PD-L1 status, KRAS mutation status and subtype, treatment, progression-free survival, overall survival, and, if available, hazard ratios (HRs) of progression-free survival and overall survival. The quality of the studies was evaluated using the "Risk of Bias in Non-randomized Studies of Exposure (ROBINS-E 2022)" [16] (figure S1 in the appendix). For this systematic review, data were synthesised into a tabulation of characteristics and outcomes. Missing data were represented by the abbreviation "NA".

### Outcome measures and statistical methods

After selecting suitable studies, data were extracted and entered into standardised Excel spreadsheets. The endpoints considered were progression-free survival and overall survival. We aimed to conduct two separate comparisons: patients with a KRAS G12C mutation versus those with no KRAS mutation (KRASwt), and patients with a KRAS G12C mutation versus those with other KRAS mutations (any KRAS mutation except G12C).

One of the publications was a previous study from the same group (IOSI), allowing us to calculate the hazard ratio (HR) based on datasets still available to us [17]. We pooled the aggregated HR with the HR reported in the other publications and created forest plots using the statistical program R version 4.1.2(2021-11-01) with the statistical package meta. We analysed the heterogeneity between studies using the I2 statistic.

## Results

### Search and selection process

After screening and full-text appraisal, we included four studies (figure 1, table 1). All four studies received no

funding [17–20]. The median age of patients ranged from 65 to 69 years. The distribution of gender, smoking status and Eastern Cooperative Oncology Group (ECOG) performance status was relatively similar across the studies. Patients were stratified according to their PD-L1 expression status in all trials, and progression-free survival and/or overall survival was reported in all papers.

Two studies fully reported the hazard ratio [17, 18]. In contrast, the other two studies had insufficient data to determine the HR of progression-free survival among KRAS G12C, KRASwt or other KRAS mutations [19, 20].

### Narrative summary of reported endpoints

Three of the four studies included in the systematic review suggested that KRAS G12C mutations were associated with a better response to immunotherapy among patients with PD-L1 expression ≥50%. Table 2 summarises the endpoints of these studies.

Cefalì et al. identified that KRAS G12C was associated with better progression-free survival compared to other KRAS mutations in non-small cell lung cancer patients with PD-L1 ≥50% [17] (HR 0.27; 95% CI 0.1–0.76, p = 0.01). In the same study, a second analysis compared PFS in patients with any KRAS mutation versus those with wild-type KRAS gene status. The trend towards better PFS

**Figure 1:** Detailed search strategies according to the PRISMA 2020 flow diagram (http://www.prisma-statement.org; Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71).

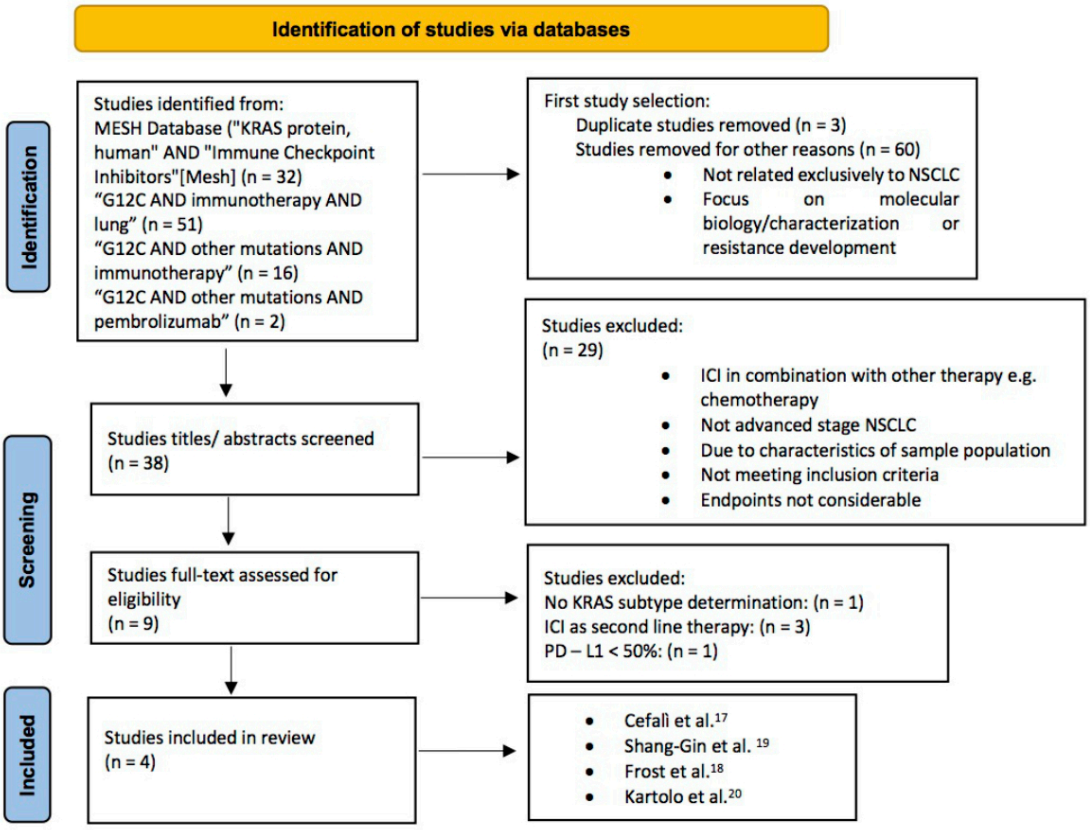



**Table 1:**
Baseline characteristics of the study populations.

| Author | Cefalì et al. [17] | Frost et al. [18] | Shang-Gin et al. [19] | Kartolo et al. [20] |
|---|---|---|---|---|
| Country of origin | Switzerland | Germany | Taiwan | Canada |
| Patients, n | 44 | 119 | 228 | 78 |
| Median age | 69 | 68 | 66 | >65 |
| Male, n (%) | 25 (57%) | 68 (57%) | 159 (69%) | 37 (47%) |
| Smoker, n (%) | 42 (95) | 98 (82) | 144 (63) | 74 (94) |
| KRAS mutation, n | 25 | 62 | 228 | 30 |
| KRAS G12C mutation, n (%) | 11 (44) | 32 (51) | 143 (63) | 11 (37) |
| Hazard ratio (progression-free survival) KRAS G12C vs KRAS other (95% CI [p-value]) | 0.21 (0.06;0.72 [0.01]) | 0.37 (0.20;0.68 [0.01]) | NA | NA |
| Hazard ratio (progression-free survival) KRAS G12C vs KRASwt (95 CI [p-value]) | 0.33 (0.12;0.91 [0.03]) | 0.41 (0.24; 0.69 [0.01]) | NA | NA |
| Included in meta-analysis | Yes | Yes | No | No |

in the KRAS-mutated subgroup was not statistically significant (log-rank $\chi2(1) = 1.8$, $p = 0.18$) [17].

A study conducted in Taiwan by Shang-Gin et al. concluded that the G12C mutation was associated with improved immune checkpoint inhibitor treatment effectiveness in patients with non-small cell lung cancer. For the 143 patients with advanced-stage non-small cell lung cancer, overall survival was significantly different between patients with the KRAS G12C mutation and those with other KRAS mutations (7.7 months versus 6.0 months, respectively; $p = 0.018$). Notably, the KRAS G12C subgroup had a higher proportion of male individuals (80%; $p = 0.018$) and smokers (81.3%; $p <0.001$) [19].

Another study supporting the favourable role of KRAS G12C was conducted in Germany. Frost et al. demonstrated that KRAS subtypes and TP53 mutations differentiate between prognostic groups (HR 0.23; 95% CI, 0.08–0,72, $p = 0.01$; KRAS G12C/TP53 mutant cases against KRAS others and TP53 wt cases) [18]. Notably, the KRAS G12C/TP53 co-mutation was frequently associated with high PD-L1 expression [18].

In contrast, Kartolo et al. did not find a positive prognostic effect of KRAS G12C [20]. There was no significant difference in median overall survival between KRAS mutant and KRASwt patients (12.9 vs 19.3 months, $p = 0.879$). There was a non-significant trend towards worse outcomes in KRAS G12C cases compared to KRAS others and KRASwt (progression-free survival 3.3 vs 8.1 vs 5.4 months, $p = 0.442$; and overall survival 11.4 vs 44.9 vs 19.3 months, $p = 0.772$). The study population was characterised by older age and included a significant percentage of smokers, as well as a higher proportion of patients with worse ECOG performance status [20].

### Study level meta-analysis

Only two of the four identified studies qualified for the study-level meta-analysis. We reused unpublished data from the study by Cefalì et al. to calculate the HR for comparing the KRAS G12C positive group, KRASwt and other KRAS mutations. This enabled us to pool the data from Frost et al. and Cefalì et al., resulting in the forest plots shown in figures 2A and 2B.

The first forest plot indicates that a KRAS G12C mutation is associated with improved progression-free survival compared to KRASwt tumours. The second forest plot shows that a KRAS G12C mutation is associated with better progression-free survival than other KRAS mutations.

In contrast, Shang-Gin et al. provided the hazard ratio for overall survival for KRAS G12C versus other KRAS mutations but not for KRAS G12C versus KRASwt. Kartolo et al. only reported the HR for progression-free survival when comparing the KRAS mutant and KRAS wild-type groups.

## Discussion

Our systematic review and meta-analysis suggest that patients with advanced non-small cell lung cancer harbouring a KRAS G12C mutation and high PD-L1 expression have a favourable prognosis when receiving first-line immunotherapy with a checkpoint inhibitor. However, the predictive role of the KRAS G12C mutation – specifically, whether patients with this mutation and high PD-L1 expression benefit more from checkpoint inhibitors compared to chemotherapy – could not be evaluated due to the absence of interaction analysis in the identified publica-

**Table 2:**
Efficacy endpoints. Progression-free survival in months.

| References | Cefalì et al. | Cefalì et al. [17]retrieved data | Frost et al. [18] | Shang-Gin et al. [19] | Kartolo et al. [20] |
|---|---|---|---|---|---|
| No. of patients | 44 | 44 | 119 | 228 | 78 |
| No. of KRAS G12C | 11 | 11 | 32 | 143 | 11 |
| Median age | 69 | 69 | 68 | 55 | >65 |
| Design | Retrospective | Retrospective | Retrospective | Retrospective | Retrospective |
| Median overall survival KRAS G12C (months) | Not evaluable | | Not evaluable | 7.7 | 12.9 |
| Median overall survival KRAS others (months) | 14.7 | | 18.9 | 6.0 | 19.3 |
| Median progression-free survival KRAS G12C (months) | 14.6 | | 19.8 | 4.8 | 3.3 |
| Median progression-free survival non-G12C (months) | 12.5 | | NA | NA | NA |
| Hazard ratio for progression-free survival KRAS G12C vs KRAS non-G12C | 0.27 | | NA | NA | NA |
| 95% CI (p-value) | 0.1–0.76 (0.01) | | | | |
| Median progression-free survival KRAS mutation (months) | 8.6 | | 13.3 | NA | 6.0 |
| Median progression-free survival KRASwt (months) | 6.0 | 6.0 | 6.2 | NA | 5.4 |
| Hazard ratio for KRAS mutation vs KRASwt | 0.46 | | 0.66 | NA | 1.184 |
| 95% CI (p-value) | 0.22–0.95 (0.04) | | 0.44–1.0 (0.05) | | 0.571–2.455 (0.651) |
| Hazard ratio for KRAS G12C vs KRASwt | NA | 0.33 | 0.41 | NA | NA |
| 95% CI (p-value) | | 0.12–0.91 (0.03) | 0.24–0.69 (0.001) | | |
| Median progression-free survival KRAS others | 6.5 | 6.5 | 5.8 | 2.1 | 8.1 |
| Hazard ratio for KRAS G12C vs KRAS others | NA | 0.21 | 0.37 | NA | NA |
| 95% CI (p-value) | | 0.06–0.72 (0.01) | 0.20–0.68 (0.01) | | |

NA: unavailable; KRASwt: KRAS wild-type; KRAS mutation: all KRAS mutations; KRAS others: all other mutations except G12C; non-G12C: KRAS others and KRASwt.

tions. Overall, the quality of evidence is relatively low, and most studies lack sufficient reporting to derive definitive conclusions.

Due to its structural and biochemical properties, the KRAS protein has long been considered an "undruggable" target. The main challenges include its high affinity for GTP, limited active binding sites and the complexity of its downstream pathways. Additionally, there is little structural difference between wild-type and mutant KRAS, making it difficult to target the mutant form without affecting the normal protein [21, 26]. However, breakthrough technological advances led to the discovery of a small inhibitory molecule (ARS-1620) capable of binding exclusively to a site near the effector region of mutant KRAS G12C that is not present in wild-type KRAS [22, 23]. Since this initial breakthrough, several other small inhibitory molecules have been discovered. Sotorasib is the first KRAS G12C inhibitor to demonstrate sustained clinical benefit in patients with pre-treated non-small cell lung cancer harbouring a KRAS G12C mutation [24, 25]. Based on preclinical data, a phase I/II study assessed the safety, tolerability, pharmacokinetics and efficacy of sotorasib monotherapy in heavily pretreated patients with locally advanced or metastatic KRAS G12C mutant solid tumours [27].

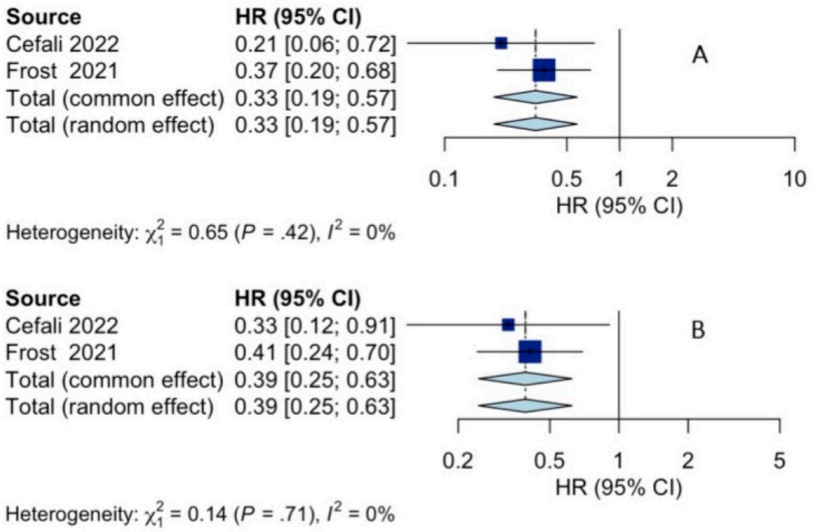
Recent research suggests that KRAS mutations are correlated with an inflammatory tumour microenvironment and increased immunogenicity, providing a rationale for their superior response to PD-(L)1 inhibitors [28]. Therefore, several clinical trials have analysed the efficacy of anti-PD-(L)1 immunotherapy in KRAS-mutant non-small cell lung cancer. These studies indicate that patients with KRAS mutations are more sensitive to PD-(L)1 inhibitors than those with wild-type KRAS [29–32]. However, a systematic investigation of the prognostic and predictive roles of the KRAS G12C mutation has not yet been conducted. Thus, this systematic review focused exclusively on the potential prognostic and predictive roles of the KRAS G12C mutation in relation to anti-PD-(L)1 therapy.

To avoid potential selection bias, we evaluated several relevant papers not included in the final analysis [33–36] (table S2 in the appendix). The main reasons for exclusion were that these papers did not focus exclusively on PD-L1 expression ≥50% and/or first-line immune checkpoint inhibitors. Moreover, studies were excluded if they analysed KRAS mutations in general rather than specifically concentrating on the KRAS G12C mutation.

A study conducted in Italy separated the study population of 22 patients into two groups based on first-line (1L) and second-line (2L) immune checkpoint inhibitor therapy [33]. In the 1L group, the median progression-free survival for KRAS G12C mutated patients was 20 months, compared to 14.5 months for non-KRAS G12C mutated patients (p = 0.76) [33]. In the 2L group, better outcomes were observed in patients with a KRAS G12C mutation compared to non-G12C, with median progression-free survival reaching 23 months compared to only five months (p = 0.03) [33]. These results support our findings, considering that our study population only included first-line immune checkpoint inhibitor therapy. This study was excluded from the analysis due to the lack of information about PD-L1 expression [33].

In contrast, a large German prospective study using the CRISP registry found no prognostic value for KRAS G12C [34]. This study was excluded because it did not exclusively focus on immune checkpoint inhibitor-based first-line therapy. The authors recruited patients with advanced

**Figure 2:** Forest plot for KRAS G12C vs KRAS others (progression-free survival) (A); forest plot for KRAS G12C vs KRASwt (progression-free survival) (B)



non-small cell lung cancer and KRAS mutations. Within the study population, 15.4% of patients had KRAS G12C, 24.2% had non-G12C mutations and 60.4% had KRASwt. High PD-L1 expression, defined as Tumor Proportion Score (TPS)>50%, was documented for each subgroup at 43.5%, 28.9%, and 28.0%, respectively. Meanwhile, 89.3%, 87.7% and 68.8%, respectively, received first-line treatment combined with an immune checkpoint inhibitor [34]. There were no differences in clinical outcomes between KRAS G12C, other KRAS mutations and KRASwt. Interestingly, patients with G12C mutations tended to have higher PD-L1 expression and were more often treated with immune checkpoint inhibitors. This highlights the need for more extensive analyses of patients stratified by their respective treatments to definitively elucidate the prognostic role of PD-L1 in KRAS G12C mutant non-small cell lung cancer [34].

A study conducted by Arbour et al. [35] involving 1,194 patients with non-small cell lung cancer harbouring a KRAS mutation reported that, in the subgroup with PD-L1 expression ≥50%, the median progression-free survival for patients with KRAS G12C was 4.7 months compared with 14.4 months for patients with non-G12C mutations ($p = 0.07$) [35]. Contrary to our findings, they hypothesised a negative impact of KRAS G12C on progression-free survival under immune checkpoint inhibitor therapy. Potential limitations of this study include the heterogeneity of the population, particularly the conflation of first- and second-line data without stratification [35].The statistical analysis did not account for the balance between first- and second-line therapy with immune checkpoint inhibitors, possibly contributing to the observed negative impact of KRAS G12C.

Finally, Jeanson et al. analysed a French cohort of 282 patients with advanced non-small cell lung cancer harbouring KRAS mutations without focusing exclusively on the KRAS G12C mutation. No significant differences in response rate, progression-free survival or overall survival were observed between the KRAS subgroups [36]. Notably, only 9% of the patient population had PD-L1 expression ≥50%. Nevertheless, a significant trend towards improved progression-free survival was observed in KRAS mutant NSCLC with PD-L1-positive versus PD-L1-negative tumours, with increased benefit correlating with a higher proportion of PD-L1-positive tumour cells (≥50%). This association between PD-L1 expression and outcomes with immune checkpoint inhibitors was not observed in NSCLC without KRAS mutations, suggesting that PD-L1 overexpression is even more relevant in KRAS-mutant NSCLC [36]. Hence, this finding strengthens our hypothesis that patients with a KRAS G12C mutation and high PD-L1 expression benefit more from upfront immunotherapy.

Recent research is beginning to reveal the effect of co-mutations on tumour biology and response to different therapeutic strategies [18, 37–39]. Co-mutations are significant because recent findings indicate that treatment with KRAS G12C inhibitors (such as sotorasib) can trigger the development of co-mutations, thereby compromising the effectiveness of immune checkpoint inhibitors (anti-PD1/PDL1) [40].

Data from a Spanish study suggest that the most frequent KRAS co-mutations are in TP53 (39%), serine/threonine kinase 11 (STK11) (20%) and kelch-like ECH-associated protein 1 (KEAP1) (13%) [37]. Interestingly, the study by Frost et al. found significantly better outcomes in patients receiving first-line immune checkpoint inhibitors who harboured a KRAS G12C/TP53 co-mutation [18].Another study by Assoun et al. (2019) hypothesised that TP53 mutational status may correlate with response to immune checkpoint inhibitors and suggested a synergistic interaction between PD-L1 expression, KRAS mutation, TMB and TP53 mutation. Their study population included non-small cell lung cancer patients treated with immune checkpoint inhibitors in the first line and subsequent lines of therapy. Their data showed that a TP53-mutated status predicted an overall survival benefit in advanced NSCLC treated with immunotherapy [13].

Further investigation is necessary to clarify the influence of co-mutations in KRAS G12C-positive non-small cell lung cancer [41], identify the optimal combination of predictive biomarkers for immune checkpoint inhibitor therapies and reevaluate and improve the current therapy allocation process. Moreover, new pan-KRAS inhibitors are under investigation and may offer broader therapeutic options because they do not distinguish between different KRAS mutants [42].

## Conclusion

In conclusion, preliminary evidence suggests that the presence of a KRAS G12C mutation is associated with a favourable prognosis in patients with advanced non-small cell lung cancer and high PD-L1 expression treated with upfront immunotherapy. However, this observation needs validation in additional, well-designed studies. Future treatment sequencing or combination strategies may be explored based on these results.

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**Author contributions:** Caroline-Claudia Erhart: Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review and editing. Marco Cefali: Investigation; Writing – review and editing; Supervision. Dylan Mangan: Formal analysis; Writing – review and editing. Benjamin Kasenda: Formal analysis; Writing – review and editing; Visualization. Luciano Wannesson: Conceptualization; Supervision; Writing – review and editing.

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**Potential competing interests**

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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# Appendix

**Figure S1:** Risk Of Bias In Non-randomized Studies – of Exposure (ROBINS-E), 2023 [16]. Domains: D1: Bias due to confounding. D2: Bias arising from measurement of the exposure. D3: Bias in selection of participants into the study (or into the analysis). D4: Bias due to post-exposure interventions. D5: Bias due to missing data. D6: Bias arising from measurement of the outcome. D7: Bias in selection of the reported result.

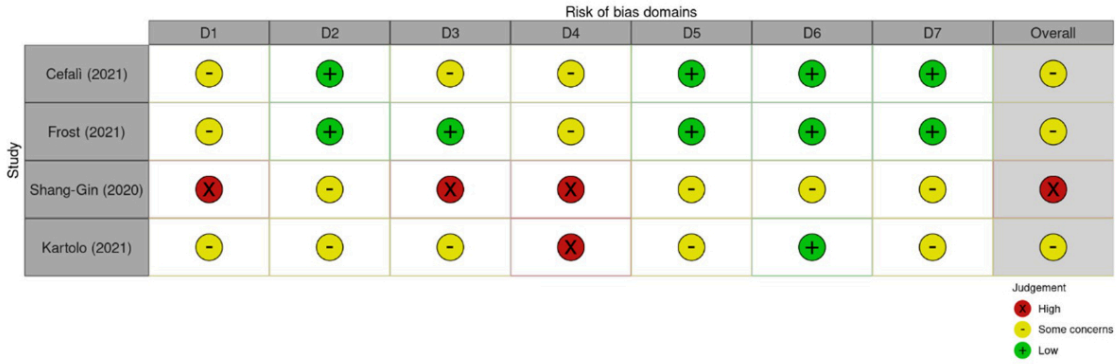


**Table S1:**
PICO criteria.

| | |
|---|---|
| **P** | Advanced non-small cell lung cancer with PD-L1 >50% receiving upfront immunotherapy |
| **I** | KRAS G12C mutation |
| **C** | Non-G12C KRAS mutations and KRAS wt |
| **O** | Progression-free survival (PFS) and overall survival (OS) |

**Table S2:**
Additional studies.

| Authors | Results | Reasons for exclusion |
|---|---|---|
| Sciortino et al. (2022) [33] | In the subgroup treated with second-line immune checkpoint inhibitors, patients with KRAS-G12C mutations had a median progression-free survival of 23 months compared to 5 months for non-KRAS G12C mutated cases (p = 0.03) | No explicit mention of PD-L1 expression ≥50%; only 9 patients with G12C mutation treated in first line |
| Sebastian et al. (2019) [34] | No differences in clinical outcomes between patients with KRASwt, G12C and non-G12C mutations, with progression-free survival of 5.7 months (95% CI 4.9–6.6) for KRASwt non-squamous, 6.0 months (95% CI 3.2–8.4) for KRASwt squamous, 5.7 months (95% CI 4.2–8.2) for KRAS G12C, and 5.4 months (95% CI 4.5–6.5) for KRAS non-G12C | Did not exclusively focus on first-line immune checkpoint inhibitor-based therapy |
| Arbour et al. (2021)[35] | mPFS was 3.7 months in patients with G12C vs 3.3 months in those with non-G12C mutations (p = 0.89) | Statistical analysis does not separate first- and second-line immune checkpoint inhibitors |
| Jeanson et al. (2019) [36] | Trend towards better ORR and longer progression-free survival was observed for KRAS mutant non-small cell lung cancer with PD-L1–positive versus PD-L1-negative tumours, with increased benefit for a higher rate of PD-L1-positive tumour cells (≥50%) | Analysis of PD-L1 expression between the KRAS mutation groups but no statistical analysis correlating with immune checkpoint inhibitors |
| | | Statistical analysis of immune checkpoint inhibitor effect focusing only on KRASwt and KRAS mutations |