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### ► To cite this version:

Agathe Dehem, Julien Mazieres, Ali Chour, Florian Guisier, Marion Ferreira, et al.. Characterization of 164 patients with NRAS mutated non-small cell lung cancer (NSCLC). Lung Cancer, 2023, 186, 10.1016/j.lungcan.2023.107393 . hal-04294653

**HAL Id: hal-04294653**

**<https://hal.science/hal-04294653v1>**

Submitted on 1 Dec 2023

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# Characterization of 164 patients with *NRAS* mutated non-small cell lung cancer (NSCLC)

Publish in *Lung Cancer* 186 (2023) 107393

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## ABSTRACT

**Background:** *NRAS* mutations are observed in less than 1% of non-small cell lung cancer (NSCLC). Clinical data regarding this rare subset of lung cancer are scarce and response to systemic treatment such as chemotherapy or immune checkpoint inhibitors (ICI) has never been reported.

**Methods:** All consecutive patients with an *NRAS* mutated NSCLC, diagnosed between August 2014 and November 2020 in 14 French centers, were included. Clinical and molecular data were collected and reviewed from medical records.

**Results:** Out of the 164 included patients, 106 (64.6%) were men, 150 (91.5%) were current or former smokers, and 104 (63.4%) had stage IV NSCLC at diagnosis. The median age was 62 years, and the most frequent histology was adenocarcinoma (81.7%). *NRAS* activating mutations were mostly found in codon 61 (70%), while codon 12 and 13 alterations were observed in 16.5% and 4.9% of patients, respectively. Programmed death ligand-1 expression level <1%/1–49%/≥50% were respectively found in 30.8%/27.1%/42.1% of tumors. With a median follow-up of 12.5 months, median overall survival (OS) of stage IV patients was 15.3 months (95% CI 9.9–27.6). No significant difference in OS was found according to the type of mutation (codon 61 vs. other), HR= 1.12 (95% CI 0.65–1.95). Among stage IV patients treated with platinum-based doublet (n = 66), ICI (n = 48), or combination of both (n = 10), objective response rate, and median progression free survival were respectively 45% and 5.8 months, 35% and 6.9 months, 70% and 8.6 months

**Conclusion:** *NRAS* mutated NSCLC are characterized by a high frequency of smoking history and codon 61 mutations. Further studies are needed to confirm the encouraging outcome of immunotherapy in combination with chemotherapy.

## 1. Introduction

Over the last decades, advances in cancer biology have allowed the discovery of molecular alterations driving the oncological process in non-small cell lung cancers (NSCLC) [1–3]. These progresses have led to the development of targeted therapies revolutionizing management and outcomes of patients with metastatic NSCLC harboring actionable mutations (*EGFR*, *MET* exon 14, *KRAS* G12C, or *BRAF* V600E) or rearrangements (*ALK*, *ROS1*, *RET*) [4]. More recently emergence of immunotherapy with the development of immune checkpoint inhibitors (ICI) targeting the programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) pathway has also profoundly changed the therapeutic strategy in metastatic NSCLC. Interestingly, differences in ICI efficacy have been observed in NSCLC according to the type of oncogenic driver, with notably reduced activity in patients with *ALK* rearrangement or *EGFR* mutation [5].

*Neuroblastoma rat sarcoma viral oncogene homolog* (*NRAS*) belongs to the RAS-GTPase family like *KRAS* and *HRAS*. The RAS-GTPases transduce signals from transmembrane tyrosine kinase receptors and are involved in several biological processes like cell proliferation, embryonic development and tumorigenesis [6]. Approximately 19% of all patients with cancer harbor *KRAS*, *NRAS* or *HRAS* activating mutations [7]. Whereas *KRAS* mutations are frequent in NSCLC, *NRAS* mutations are mostly found in melanoma, myeloma, chronic myeloid leukemia, acute myeloid leukemia, thyroid carcinoma [7–9]. These alterations disrupt the guanine exchange cycle of the RAS protein and favor an active GTP bound state, which leads to the activation of downstream signaling pathways involved in proliferation and cell survival such as the MAPK or the PIK3/AKT/mTOR pathways [8,10–12].

About 67% of the patients in our study had at least one genomic co-alteration associated with the *NRAS* mutation. These co-alterations could be found in tumor suppressor genes or in genes coding for proteins involved in the MAPK pathway, for proteins of the PI3K pathway, or for tyrosine kinase receptors. In their *NRAS* mutated NSCLC series, Ohashi et al. also described co-alterations with one patient harboring a *KRAS* G12A mutation and another one a *MET* amplification associated to *NRAS* mutations [10]. In *KRAS* mutated NSCLC, the most frequently reported co-alterations were mutations in the *TP53*, *SKT11* and *KEAP1* genes [20,39]. These co-alterations may have an impact on the biology of *KRAS* mutated NSCLC and the prognosis of patients [40]. Thus, NSCLC with a *KRAS/TP53* co-mutations harbored an increase of inflammatory markers and immune checkpoint effector molecules and could have an important clinical benefit of ICI therapy [40,41]. A significant decrease in overall survival has been also described in metastatic *KRAS* mutated NSCLC in case of co-mutation of *STK11* or *KEAP1*

Only 0.6 to 1% of NSCLC patients harbor *NRAS* activating mutations [7,10,13–16] and clinical data on these patients are scarce with only 30 cases described in a previously published cohort [10]. The response of *NRAS* mutated NSCLC to systemic treatment like chemotherapy or immunotherapy remains unknown. In this study, our objective was to determine the clinical and molecular characteristics of patients with *NRAS* mutated NSCLC and to analyze their responses to anti-tumoral systemic therapy.

## 2. Methods

### 2.1. Study population and data collection

Consecutive adult patients, from 14 French centers (12 university hospitals and 2 cancer centers), with an *NRAS* mutated NSCLC, diagnosed between August 2014 to November 2020 were systematically included in the present study. Clinical and molecular data were extracted from medical records and submitted by investigators from June 2020 to January 2021 to a database hosted by Lille University Hospital. Patient demographics (sex, age, smoking status, Performance Status (PS) at NSCLC diagnosis), tumor characteristics (histological and molecular analyses, Tumor Node Metastasis (TNM) stage) and systemic treatment history (type of drug, start and end date of treatment, best response according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria, cause of treatment discontinuation, date of disease progression) were documented.

### 2.2. Molecular analysis

*NRAS* mutations had to be identified by Next Generation Sequencing (NGS) in a French ISO 15189 accredited laboratory. For each patients the molecular analysis report and the existence of co-molecular alterations had to be recorded by each center in the study database. The 18 NGS panels used in the study are described in Supplementary Table 1. Patients with an *NRAS* mutation classified as variant of undetermined significance, benign, or probably benign, according to the American College of Medical Genetics and Genomics (ACMG) classification as of March 20,2021, were excluded from the present study [17].

### 2.3. Study oversight

This non-interventional study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and per CNIL (French National Data Protection Authority) MR004 (Reference Methodology 004) guidelines. This study has been declared to local Data Protection Officer in accordance with European Union GDPR (General Data Protection Regulation). All participating departments approved the study protocol and all alive included patients received information from their referring physician, with an opportunity not to participate.

### 2.4. Outcomes and statistical analysis

Qualitative variables were described as number and percentages. Quantitative variables were described by median and range or inter-quartile range (IQR). Only patients harboring a stage IV NSCLC without *EGFR* mutation or *ALK* rearrangement and with available follow up data were included in survival and treatment efficacy analyses. For each treatment (platinum doublet, ICI, platinum doublet and ICI), objective response rate (ORR) was defined as the percentage of patients with partial or complete response to the indicated treatment according to RECIST 1.1 evaluated by investigators. Disease control rate (DCR) was defined as the percentage of patients with partial or complete response or stable disease according to RECIST 1.1 evaluated by investigators. Progression free survival

(PFS) was measured from the date of treatment initiation to the date of progression according to RECIST 1.1 or the date of death from any cause. Rechallenges, with platinum doublet or ICI, alone or in combination, were not included in treatment analysis. Overall survival (OS) was calculated from the date of diagnostic of metastatic disease to the date of death from any cause. The Kaplan- Meyer method was used to carry out survival analyses. Survival curves were compared by log-rank test and Cox proportional hazard model was used to derive the corresponding hazard ratios and associated 95% confidence intervals. P values of 0.05 or lower were considered statistically significant. R software (windows version 4.3.1) was used for statistical analysis.

### 3. Results

#### 3.1. Clinical and pathological characteristics

A total of 173 consecutive patients with an *NRAS* mutated NSCLC diagnosed between August 2014 and November 2020 were identified, across 14 centers. We excluded 9 patients whose *NRAS* mutation was classified as a variant of undetermined significance and 164 patients were included in the study (Supplementary Fig. 1). Most patients were men (64.6%), and current or former smokers (91.5%) (Table 1). The median age was 62 years (range: 35–92). At diagnosis, the majority of patients were PS 0 or 1 (75%) and displayed a stage IV NSCLC (63.4%). The most common histology was adenocarcinoma (81.7%). PD-L1 tumor proportion scale (TPS) was available for 81.1% of included patients with 30.8%/27.1%/42.1% of them harboring respectively a low (<1%) / intermediate (1–49%) / high (≥50%) PD-L1 tumor expression.

#### 3.2. Molecular features

*NRAS* mutations were identified on samples collected at NSCLC diagnosis before any anticancer therapy in 161 patients (98.2%). Conversely, in 3 patients harboring either an *EGFR* mutation or an *ALK* rearrangement, the *NRAS* mutation was detected on a re-biopsy collected after the initiation of anticancer treatment (Supplementary Table 2). Most patients (69.5%) included in the study displayed an *NRAS* mutation within the codon 61 while the codons 12 and 13 were only involved in 16.5% and 4.9% of the patients, respectively (Fig. 1). The most frequent *NRAS* mutation subtype was *NRAS* Q61L found in 32.9% of patients followed by Q61R (18.3%) and Q61K (14.6%). *NRAS* codon 12 and codon 13 alterations were mainly represented by *NRAS* G12D, G12C, G12A and G13R mutations. Interestingly, mutations outside codons 61, 13 and 12 were observed in 15 patients (9.1%). Co-occurring molecular alterations were reported in 109 patients, *TP53* mutations being the most common (Supplementary Table 3). Other co-alterations were found in genes involved in the MAPK pathway (*KRAS*, *HRAS*, *BRAF*, *MAP2K1*, *MAP2K2*), or in the PI3K pathway (*PTEN*, *PIK3CA*), or in genes coding for tyrosine kinase receptors (*MET*, *EGFR*, *ALK*, *PDGFRA*, *FGFR2*) or in tumor suppressor genes (*STK11*, *CDKN2A*, *SMAD4*).

#### 3.3. Overall survival and prognosis

The median follow-up from the date of stage IV *NRAS* mutated NSCLC was 12.5 months (IQR 5.8–23.6). The median overall survival from the date of stage IV *NRAS* mutated NSCLC was 15.3 months (95% confidence Interval (CI) 9.9–27.6) (Fig. 2). No significant difference in OS was found according to the type of mutation (codon 61 vs. other, HR= 1.12; 95% CI 0.65–1.95), according to the PD-L1 status (PD-L1  $\geq$  50% vs. PD-L1 < 1%, HR = 1.06; 95% CI 0.54–2.07 and PD-L1 1%–49% vs. PD-L1 < 1%, HR = 1.76; 95% CI 0.84–3.66) or according to the smoking status (former or current smokers vs. never smokers, HR = 0.71; 95% CI 0.28–1.77) (Supplementary Fig. 2A).

#### 3.4. Systemic treatment activity in metastatic *NRAS* mutated NSCLC

Among patients displaying a metastatic *NRAS* mutated NSCLC without *ALK* rearrangement or *EGFR* mutation, 66 patients received a platinum doublet chemotherapy (median follow-up of 14.9 months, IQR 8.1–33.7), 48 patients an ICI (median follow-up of 15.5 months, IQR 9.3–23.4) and 10 patients a platinum doublet chemotherapy combined with ICI (median follow-up of 6.1 months, IQR 4.6–8.4) (Table 2). The ORR and DCR to platinum doublet chemotherapy, ICI, and platinum doublet chemotherapy combined with ICI were respectively 45% and 59%, 35% and 54% and 70% and 90%. For patients treated with platinum doublet chemotherapy, ICI, and platinum doublet chemotherapy combined with ICI, the medians PFS were respectively 5.8 months (95% CI 4.5–7.1), 6.9 months (95% CI 4–27.6) and 8.6 months (95% CI 8.6–NR). The ORR on ICI for patients with a low (<1%) / intermediate (1–49%) / high ( $\geq$ 50%) PD-L1 tumor expression were respectively 17%, 29% and 41% (Table 3). The ORR for patients who had received ICI in first or second line were respectively 36.4% and 39.1%. Among the 3 patients who received ICI in third line no objective response was reported (Table 3). Twenty patients with a PD-L1 tumor expression  $\geq$  50% received pembrolizumab as 1st line treatment. The pembrolizumab median PFS and the median OS for these patients were respectively 7.2 months (95% CI 5.6–NR) and 25.2 months (95% CI 11.3 – NR). No significant difference in ICI PFS was found according to the PD-L1 status (PD-L1  $\geq$  50% vs. PD-L1 < 1%, HR = 0.72; 95% CI 0.24–2.18 and PD-L1 1–49% vs. PD-L1 < 1%, HR = 1.52; 95% CI 0.39–5.8), the treatment line (second line vs. first line, HR = 1.06; 95% CI 0.51–2.21), the type of *NRAS* mutation (codon 61 vs. other, HR = 1.13; 95% CI 0.46–2.78), or to the smoking status (former or current smokers vs. never smokers, HR = 0.58; 95% CI 0.20–1.72) (Supplementary Fig. 2B). There was also no significant difference in platinum doublet chemotherapy PFS according to the type of *NRAS* mutation (codon 61 vs. other, HR = 0.78; 95% CI 0.44–1.39) or to the smoking status (former or current smokers vs. never smokers, HR = 0.78; 95% CI 0.28–2.18) (Supplementary Fig. 2C). Finally, among the 33 patients who received an ICI and had an NGS panel covering *TP53*, there was no significant difference in ICI PFS according to the *TP53* mutation status (presence of *TP53* mutation vs. absence of *TP53* mutation, HR = 0.7; 95% CI 0.29–1.64).

#### 3.5. *NRAS* mutations in patients with *EGFR* or *ALK* co-alterations and treated with a targeted therapy

Out of the 5 patients with an *NRAS* mutation associated to an *EGFR* mutation or an *ALK* rearrangement, 2 received a genotype directed targeted therapy (Supplementary Table 2). One of these 2 patients was a never-smoker woman with a metastatic lung adenocarcinoma harboring an *EML4-ALK* rearrangement associated with a Q61R *NRAS* mutation. The molecular analysis of the rebiopsy collected at progression on alectinib did not detect any *NRAS* mutation but showed instead a *MET* amplification (FISH: ratio *MET/CEP7* = 5.34) associated to the *EML4*- allowing a partial response and was still ongoing after 2.6 months. The second patient treated with a targeted therapy, was a non-smoker woman displaying a metastatic lung adenocarcinoma with a L858R *EGFR* mutation. After progressing on gefitinib 1st line with T790M *EGFR* mutation, she received osimertinib 2nd line for 6.4 months. A Q61K *NRAS* mutation associated to a L858R *EGFR* mutation was identified on the tumor sample obtained after progression on osimertinib and the T790M *EGFR* mutation was no longer detected.

#### 4. Discussion

This study showed that *NRAS* mutated NSCLC patients have common clinical, pathological, and molecular features characterized by a high prevalence of smoking history, lung adenocarcinoma histology and codon 61 mutations. We also reported the presence of oncogenic genomic co-occurring alterations associated to *NRAS* mutations. Additionally, we described the efficacy of platinum-based chemotherapy, immunotherapy and immunotherapy combined with chemotherapy in patients with metastatic *NRAS* mutated NSCLC. Finally, we detected a codon 61 *NRAS* mutation in a patient with an *EGFR* mutated NSCLC at progression on osimertinib, suggesting that this molecular alteration could be a mechanism of acquired resistance to 3rd generation EGFR TKI.

In our study, patients displaying an *NRAS* mutated NSCLC were mostly men and current or former smokers. The median age at diagnosis was 62 years and the most common histology was adenocarcinoma. These characteristics are close to those found in the *NRAS* mutated NSCLC series from Ohashi *et al.* [10]. A similar profile is also observed in *KRAS* mutated NSCLC with a median age at diagnosis of 60–70 years associated with a high prevalence of smoking and a high frequency of lung adenocarcinoma [18–23]. Interestingly, among the 7 patients with a *HRAS* mutated NSCLC described in the literature the median age was 61 years, all were current or former smokers, and the most frequent histology was adenocarcinoma [24]. This suggests a common clinico-pathological profile across NSCLC harboring a mutation in a RAS GTPase coding gene.

To date, the level of PD-L1 expression in *NRAS* mutated NSCLC has only been described in 7 patients with only one having an expression level  $\geq 50\%$  [25]. In our study, among the 133 patients with interpretable assessment of PD-L1 expression by IHC, 42.9% had PD-L1 expression levels  $\geq 50\%$ . By comparison, in real-life studies the proportion of patients with PD-L1 expression levels  $\geq 50\%$  varies in unselected NSCLC from 22% to 36% [25–29] and in *KRAS* mutated NSCLC from 33% to 45% [18,19,21,25]. Several studies have also described a significant association between PD-L1 high expression and *KRAS* mutations in NSCLC [30–33]. As the proportion of *NRAS* mutated NSCLC with PD-L1

expression levels  $\geq 50\%$  seems to be close to that observed in *KRAS* mutated NSCLC, this suggests a possible association

between *NRAS* mutations and a high level of PD-L1 expression. However, our study did not include a control group without *NRAS* mutation, therefore we cannot specifically answer this question.

The majority of *NRAS* mutations identified in our study occurred in codon 61 the most frequent being Q61L, Q61R, and Q61K. Codon 12 and codon 13 mutations represent only 16.5% and 4.9% of the patients respectively. Ohashi *et al.* reported a similar molecular profile for *NRAS* mutated NSCLC with 80% of mutations occurring within codon 61 [10]. Furthermore, among codon 61 mutations described in this study, the most frequent were also the Q61L/R/K mutations. Codon 61 *NRAS* mutations also represent the majority of *NRAS* mutations in melanoma, thyroid carcinoma and solid tumors in general [6,34–36]. This molecular profile is opposed to that of *KRAS* mutations which occur mainly in codon 12 in lung cancers and in solid tumors in general [6,7,37]. These differences could be related to a lower oncogenicity of codon 12 *NRAS* mutations compared to codon 61 *NRAS* mutations and codon 12 *KRAS* mutations as suggested by preclinical data in melanoma [38].

*NFE2L2* [20,39]. In our study, the *KEAP1* and *NFE2L2* genes were not covered by the NGS panels while *TP53* and *STK11* were only partially covered. Consequently, the exact prevalence of these co-alterations and their impact on systemic treatment efficacy remains difficult to estimate. Additional studies using harmonized NGS panel systematically covering *STK11*, *KEAP1*, *NFE2L2* and *TP53* are needed to evaluate the exact frequency of these co-alterations and their impact on the prognosis of *NRAS* mutated NSCLC.

One patient in our study had an *EGFR* mutated NSCLC with an *NRAS* Q61K mutation at progression on osimertinib. Several studies have shown in *EGFR* mutated cellular models that *NRAS* mutations such as Q61K can induce resistance to 1st and 3rd generation *EGFR* TKIs [42–45]. However, to the best of our knowledge, no publications have identified so far codon 61 *NRAS* mutations in patients with an *EGFR* mutated NSCLC progressing on *EGFR* TKI. Interestingly, *NRAS* mutations have also been described as a common mechanism of resistance in *KRAS* G12C NSCLC treated with sotorasib or adagrasib [46–48]. Although preclinical data suggest that inhibition of the MAPK pathway by MEK inhibitors could overcome the resistance mediated by *NRAS* mutations, there is currently no validated strategy in clinical setting for the management of this type of resistance mechanism [42–44,47]. The impact of *NRAS* mutations on resistance to targeted therapies could also vary according to the type of targeted therapy or the genetic background of the tumor. Thus, another patient of our study had an *NRAS* mutation associated with an *ALK* rearrangement prior to initiation of alectinib therapy and only a *MET* amplification was detected on the alectinib progression biopsy suggesting that the initial *NRAS* mutation was not the cause of *ALK* TKI resistance.



No data was available regarding the prognosis and the efficacy of systemic therapies in metastatic *NRAS* mutated NSCLC patients. In our study, the median OS of metastatic *NRAS* mutated NSCLC patients was 15.3 months. This result is close to the 13 months median OS observed in *KRAS* mutated metastatic NSCLC [19]. Tumor response rates and median PFS with platinum-based chemotherapy, immunotherapy alone, and immunotherapy plus chemotherapy in our cohort were 45% and 5.8 months, 35% and 6.9 months, and 70% and 8.6 months, respectively. Compared to historical data from phase 3 trials evaluating immunotherapy alone or in combination with chemotherapy in non-squamous NSCLC, these results do not suggest any negative effect of *NRAS* mutations on systemic therapy efficacy [49–53]. However, comparison of real-world data with phase 3 trials remains difficult and larger studies with a non-mutated *NRAS* control group are needed to assess properly the impact of *NRAS* mutations on the efficacy of platinum-based chemotherapy and immunotherapy associated or not with chemotherapy.

Several new therapeutic approaches are currently being developed to target the RAS proteins [6]. However, to date, no trial has specifically evaluated these strategies in *NRAS* mutated NSCLC. In unresectable *NRAS* mutated melanoma, the randomized multicenter phase III trial NEMO reported a modest but significant increase of median PFS in patients treated with a MEK inhibitor, binimetinib, compared to patients receiving chemotherapy (2.8 months vs 1.5 months ( $p < 0.001$ )) [54]. Preclinical data also showed an efficacy of MEK inhibitors in several cellular models of *NRAS* mutated NSCLC [10]. This raises the question of evaluating MEK inhibitors in the management of advanced *NRAS* mutated NSCLC after failure of conventional therapies. When selecting patients, future studies evaluating this strategy will probably have to take into account the possible association of *NRAS* mutations with other oncogenic co-alterations.

This study displays several limitations mainly related to its retrospective design. Thus, patient follow-up and NGS panels used for molecular analyses have not been harmonized and depend on the local practices in each study centers. Also, we were not able to centralize tumor response assessment and molecular analyzes. Finally, the absence of an *NRAS* non mutated control group limits the evaluation of *NRAS* mutation impact on patient prognosis. However, it represents the largest series reported so far regarding *NRAS*-mutated NSCLC.

## 5. Conclusion

In conclusion, patients with *NRAS* mutated NSCLC are mostly males, current or former smokers, with a lung adenocarcinoma and a median age of 62 years. *NRAS* mutations are mainly located in codon 61 and may be associated with other co-mutations in oncogenes or tumor suppressor genes. Our study identified the *NRAS* Q61K mutation as a potential resistance mechanism to osimertinib in a patient with an *EGFR* mutated NSCLC. Finally, despite promising results observed in patients treated with immunotherapy combined with chemotherapy, further studies are needed to assess the effect of *NRAS* mutations on anti-tumoral systemic therapy efficacy

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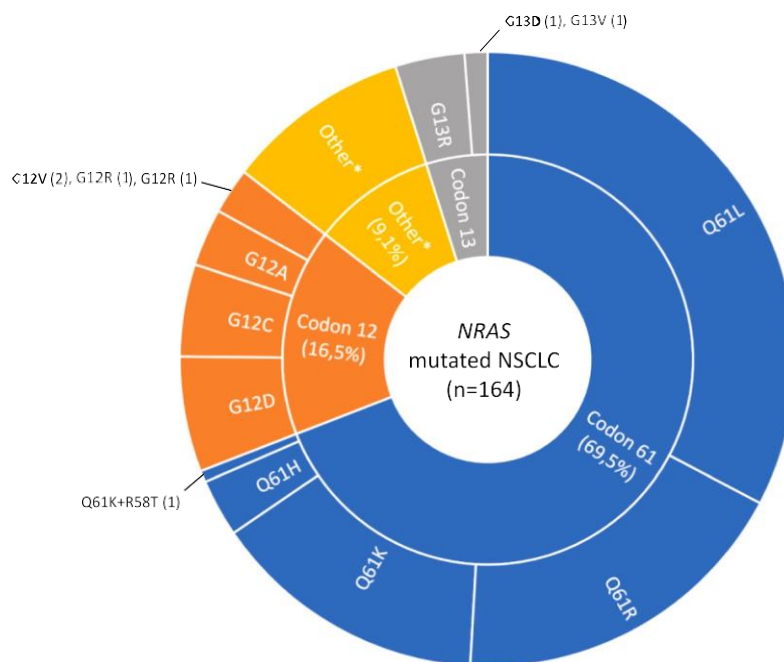
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**Table 1**

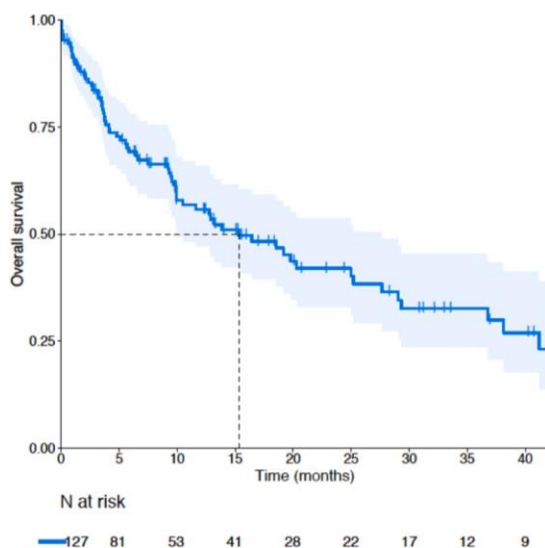
Demographics of the cohort.

Characteristics	<i>n = 164 (%)</i>
<b>Sex</b>	
Male	106 (64.6)
Female	58 (35.4)
<b>Median age (years, range)</b>	62 (35–92)
<b>Smoking status</b>	
Current smokers	82 (50.0)
Former smokers	68 (41.5)
Never smokers	10 (6.1)
Unknown	4 (2.4)
<b>PS at diagnosis</b>	
0–1	123 (75.0)
2–3	21 (12.8)
4	2 (1.2)
Unknown	18 (11.0)
<b>NSCLC stage at diagnosis</b>	
I-II	30 (18.3)
III	24 (14.6)
IV	104 (63.4)
Unknown	6 (3.7)
<b>Metastatic disease at diagnosis or during follow-up</b>	
Yes	132 (80.5)
No	31 (18.9)
Unknown	1 (0.6)
<b>Histology</b>	
Adenocarcinoma	134 (81.7)
Undifferentiated carcinoma	18 (11.0)
Squamous carcinoma	5 (3.0)
Sarcomatoid carcinoma	5 (3.0)
Other*	2 (1.2)
<b>PD-L1 tumor proportion scale</b>	
≥50%	56 (42.1)
≥1% <50%	36 (27.1)
<1%	41 (30.8)
Unknown	31

\* Mixed (adenocarcinoma + squamous cell carcinoma) and large cell carcinoma.



**Fig. 1.** NRAS activating mutations in NSCLC. Codon 61 (114 – 69.5%): Q61L (54–32.9%), Q61R (30–18.3%), Q61K (24–14.6%), Q61H (5–3%), Q61K + R58T (1–0.6%) Codon 12 (27–16.5%): G12D (10–6.1%), G12C (8–4.9%), G12A (5–3%), G12V (2–1.2%), G12R (1–0.6%), G12S (1–0.6%) Codon 13 (8–4.9%): G13R (6–3.7%), G13D (1–0.6%), G13V (1–0.6%) Other (15–9.1%): A146S (1–0.6%), A146T (2–1.2%), C118R (1–0.6%), D119C (1–0.6%), G10A (1–0.6%), G10E (1–0.6%), G15R (1–0.6%), G60R (1–0.6%), M67V (1–0.6%), R68T (1–0.6%), S17I (1–0.6%), T58I (1–0.6%), V14G (1–0.6%), Y64C (1–0.6%).



**Fig. 2.** Overall survival (OS) from the date of metastatic disease diagnosis (n = 127). Kaplan–Meier estimate of overall survival from the time of metastatic non-small cell lung cancer. Tick marks indicate censoring of data at the last time the patient was known to be alive.



**Table 2**

Clinical efficacy of systemic therapy received for stage IV *NRAS* mutated NSCLC. (DCR: Disease Control Rate; DOR: Duration Of Response; DOT: Duration Of Treatment; ICI: Immune Checkpoint Inhibitors; IQR: Interquartil Range; n: number of patients; NR: Not Reached; ORR: Objective Response Rate; PFS: Progression-Free Survival; 95% CI: 95% Confidence Interval).

Treatment	n	Drug	n (%)	Treatment line	n (%)	ORR (95% CI)	DCR (95% CI)	Median follow up (IQR, months)	Median PFS (95% CI, months)	Median DOR (IQR, months)	Median DOT (IQR, months)
Platinum doublet	66	Platinum-pemetrexed	29 (43.9)	1L	59 (89.4)	45% (29–64)	59% (42–65)	14.9 (8.1–33.7)	5.8 (4.5–7.1)	3.4 (2.0–8.3)	3.2 (1.8–5.5)
		Platinum-paclitaxel	16 (24.2)								
		Platinum-Other*	12 (18.2)	2L	7 (10.6)						
		Platinum-pemetrexed-bevacizumab	9 (13.6)								
ICI	48	Pembrolizumab	25 (52.1)	1L	22 (45.8)	35% (22–51)	54% (39–68)	15.5 (9.3–23.4)	6.9 (4–27.6)	12.2 (5.5–18.8)	5.7 (1.8–16.5)
		Nivolumab	22 (45.8)	2L	23 (47.9)						
		Atezolizumab	1 (2.1)	3L	3 (6.3)						
Platinum doublet combined with ICI	10	Carboplatin-pemetrexed-pembrolizumab	6 (60)	1L	10 (100)	70% (35–91)	90% (54–99)	6.1 (4.6–8.4)	8.6 (8.6–NR)	4.6 (2–5.3)	5.5 (2.9–7.2)
		Cisplatin-pemetrexed-pembrolizumab	4 (40)								

\*-vinorelbine (4), -docetaxel (2), -gemcitabine (2), —5FU (1), -paclitaxel-doxorubicine (1), -paclitaxel-pemetrexed (1), unknown (1).

**Table 3**

ICI efficacy according to the PD-L1 status. (ICI: Immune Checkpoint Inhibitors; n: number of patients; NR: Not Reached; ORR: Objective Response Rate; PFS: Progression-Free Survival; 95% CI: 95% Confidence Interval).

Treatment	According to PD-L1 tumor proportion scale	n / 48 (%)	ORR (95% CI)	Median PFS (95% CI, months)
ICI	PD-L1 < 1%	6 (12.5)	16.7% (0–63)	2.9 (1.71-NR)
	PD-L1 1–49%	7 (14.6)	28.6% (5–69)	2.1 (1.74-NR)
	PD-L1 ≥ 50%	27 (56.2)	40.7% (23–61)	8.9 (6.14-NR)
	Unknown	8 (16.7)	37.5% (10–74)	6.9 (4.0-NR)