Lung Cancer 154 (2021) 51–61

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

KRAS G12C-mutated advanced non-small cell lung cancer: A real-world cohort from the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315)

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ARTICLE INFO

Keywords:
Non-small cell lung cancer
Cohort studies
PD-L1 expression
KRAS mutations
KRAS G12C mutation

ABSTRACT

Objectives: After decades of unsuccessful efforts in inhibiting *KRAS,* promising clinical data targeting the mutation subtype G12C emerge. Since little is known about outcome with standard treatment of patients with G12C mutated non-small cell lung cancer (NSCLC), we analyzed a large, representative, real-world cohort from Germany.

Patients and methods: A total of 1039 patients with advanced *KRAS*-mutant or -wildtype NSCLC without druggable alterations have been recruited in the prospective, observational registry CRISP from 12/2015 to 06/2019

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https://doi.org/10.1016/j.lungcan.2021.02.005
Received 5 November 2020; Received in revised form 1 February 2021; Accepted 5 February 2021
Available online 13 February 2021

by 98 centers in Germany. Details on treatment, best response, and outcome were analyzed for patients with *KRAS* wildtype, G12C, and non-G12C mutations.

Results: Within the study population, 160 (15.4 %) patients presented with *KRAS* G12C, 251 (24.2 %) with non-G12C mutations, 628 (60.4 %) with *KRAS* wildtype. High PD-L1 expression (Tumor Proportion Score, TPS > 50 %) was documented for 28.0 %, 43.5 %, and 28.9 % (wildtype, G12C, non-G12C) of the tested patients; 68.8 %, 89.3 %, and 87.7 % of the patients received first-line treatment combined with an immune checkpoint-inhibitor in 2019. TPS > 50 % vs. TPS < 1 % was associated with a significantly decreased risk of mortality in a multivariate Cox model (HR 0.39, 95 % CI 0.26−0.60, p=<0.001). There were no differences in clinical outcome between *KRAS* wildtype, G12C or non-G12C mutations and *KRAS* mutational status was not prognostic in the model.

Conclusion: Here we describe the so far largest prospectively recruited cohort of patients with advanced NSCLC and *KRAS* mutations, with special focus on the G12C mutation. These data constitute an extremely valuable historical control for upcoming clinical studies that employ *KRAS* inhibitors.

1. Introduction

With an incidence of 2.09 million new cases in 2018, lung cancer remains the most common cancer worldwide, and non-small cell lung cancer (NSCLC) accounts for 85 % of the cases [1,2]. Despite advancements in personalized treatment and precision medicine, the overall five-year survival rate of patients with advanced NSCLC in Germany remains low at 15–21 % [3,4]. The most frequent oncogenic driver mutations are found in the *KRAS* gene, occurring in 20–40 % of the NSCLC cases in Western populations [5–7]. *KRAS* mutations are more prevalent in Western than in Asian populations, and more frequently found in smokers than in non-smokers [reviewed in 8].

Although *KRAS* mutations in NSCLC tumors have been identified more than 30 years ago, they have long been perceived as "undruggable" and there is still no approved targeted therapy [9,10]. *KRAS* mutations most frequently occur in codons 12, 13 and 61 [11]. In NSCLC, the vast majority (87 %) of these point mutations are substitutions of glycine in codon 12: G12C (42 %), G12 V (21 %), G12D (17 %) and G12A (7%) [8]. Thus, the *KRAS* G12C mutation alone is found in approximately 11 % of all mutated NSCLC cases [12]. The transversion mutations G12C and G12 V (substituting a pyrimidine for a purine or vice versa) are more prevalent in smokers, while the transition mutations G12D and G12S (substituting purine for purine or pyrimidine for pyrimidine) are more prevalent in never-smokers [reviewed in 8,13]. Contradictory results on the prognostic value of *KRAS* mutations in NSCLC have been published [8,14,15] and similarly, the association of different *KRAS* mutation subtypes with clinical outcomes remains unclear [16].

The published results on the prognostic value of *KRAS* G12C mutations also vary greatly, probably due to different inclusion criteria and methodologies: a small, retrospective study in routine care in China reported better progression-free-survival (PFS) for patients with advanced NSCLC and *KRAS* G12C mutations, compared to non-G12C mutations [17]. A larger study in the United States (US) reported similar clinical courses for patients with G12C and non-G12C mutations in any stage lung adenocarcinoma, but poorer prognosis for patients with G12C mutation and concurrent PD-L1 expression (Tumor Proportion Score, TPS ≥ 1%) [18]. A retrospective study in the US among patients with primary resected lung adenocarcinoma and a small study in the Czech Republic on advanced NSCLC both reported worse survival for patients with G12C mutations compared to those with non-G12C mutations [19,20].

Recently, five *KRAS* inhibitors have entered Phase I/II clinical trials in advanced solid tumors [reviewed in 12], among them three small molecule inhibitors specific for the cysteine of the G12C mutation with promising preliminary clinical data: AMG510 in August 2018, MRTX849 in January 2019, and JNJ-74699157 in July 2019 [21,22].

In light of these recent developments, and especially as these clinical trials are primarily designed for treatment and have no control arm, prospectively collected molecularly stratified outcome data from large cohorts in routine care are of high relevance. Such data not only show treatment reality before and after approval of new drugs but can also be used to estimate the number of patients currently tested for the mutation of interest and thus being potentially eligible for the respective new agent.

Here we present comprehensive, nationwide real-world data on a large cohort of patients from Germany with advanced NSCLC tested for *KRAS* mutations and without other druggable alterations, recruited into the CRISP-registry. We analyzed the current treatment status, the treatment regimen, the PD-L1 expression level and the outcome of patients with *KRAS* wildtype, *KRAS* G12C, and *KRAS* non-G12C mutations.

2. Patients and methods

2.1. Study design

CRISP is an open, non-interventional, prospective, multi-center registry. The registry was reviewed by the responsible ethics committees and is registered at ClinicalTrials.gov (NCT02622581). For this analysis, eligible patients are aged ≥18 years with histologically confirmed NSCLC, stage IV (IVA and IVB, UICC7) or stage IIIB (UICC 7), if ineligible for curative surgery and/or radiochemotherapy. The patients must be able to understand and willing to sign written informed consent and to complete patient-reported-outcome assessment instruments. A maximum of four weeks' time difference is allowed between start of palliative first-line systemic therapy and signed informed consent. Patients are followed until death or end of the project. In order to collect data representative for routine systemic treatment in Germany, over 150 certified lung cancer centers, comprehensive cancer centers, hospitals and office-based oncology practices located all over Germany participate in CRISP. Study sites are encouraged to recruit patients consecutively. Further details on the data collection in the CRISP registry have been published previously [7].

The first patient was recruited into CRISP on December 17, 2015; data cut for this interim analysis was June 30, 2019. In this analysis, all patients with metastatic or locally advanced, inoperable NSCLC (here collectively referred to as "advanced") were included. Patients harboring *KRAS* mutations were identified by the documented nucleotide or protein sequence, as extracted from the molecular pathology reports; for those patients with insufficient information on the protein sequence (n = 67), the nucleotide sequence was transformed to the protein sequence when this information was at hand (n = 11). The majority of *KRAS* mutations had been detected by next generation sequencing (NGS, about 75 %). PD-L1 expression status was also extracted from the pathology reports. PD-L1 expression as assessed by immunohistochemistry was reported as PD-L1 tumor proportion scores (TPS) for all patients.

Within the CRISP registry, every participating center/physician decides for themselves to which pathology lab the samples are sent, which test methods (e.g. NGS or standard sequencing) and which markers are requested. Each pathology lab follows their own methodology of testing and then reports the results back to the practice. The majority of pathologists in Germany running molecular diagnostics follow the strict

quality assurance guidelines given by the German Accreditation Body (DAkkS, ISO17020).

2.2. Statistical analysis

Descriptive statistical analyses were performed by *KRAS* mutational status (wildtype, G12C, non-G12C). Time to events were estimated using the Kaplan-Meier method [23]. All survival analyses were calculated for the outcome cohort: all patients, who have been observed for at least one year (i.e. recruited until June 30, 2018). PFS was defined as the interval between start of first-line treatment and the date of progression or death. Patients without such an event before start of second-line treatment were censored at start of second-line treatment or at last contact. OS was defined as the interval between start of first-line treatment and the date of death from any cause. Patients alive or lost to follow-up at data cut (June 30, 2019) were censored at last contact. First-line treatment was defined as any systemic palliative treatment, e.g. chemotherapy, or immunotherapy/checkpoint-inhibitors.

For the outcome cohort, a Cox proportional hazards model was used to identify potential independent prognostic factors for survival. The following independent variables were examined for the model: age at start of first-line treatment, body mass index (BMI) at enrollment, sex, Charlson comorbidity index (CCI) [24] at diagnosis, ECOG performance status, *KRAS* mutational status, and PD-L1 expression status at start of first-line treatment. Confidence intervals (CI) for the regression coefficients were based on the Wald statistics. All presented P values are two-sided, 5% will be interpreted as significant. There were no multiplicity adjustments to the level of significance.

All analyses were calculated using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2002–2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

3. Results

3.1. Patient and tumor characteristics

Until data cut for this interim analysis on June 30, 2019, a total of 4032 patients with advanced NSCLC have been recruited into the CRISP-registry (flow chart see Fig. 1). Patients with missing documentation on birth year, sex, tumor histology (squamous or non-squamous), molecular testing (yes/no), and missing start date of first-line therapy were excluded). Of the 3717 evaluable patients, 1434 have been tested for *KRAS* mutations. The exact type of *KRAS* mutation was not specified for 56 patients, these patients were excluded from the present analysis as they could not be classified into the *KRAS* mutation subgroups. Furthermore, patients with documented alterations in *EGFR*, *ALK*, *ROS1*, or *BRAF* (n = 306), or treatment with a tyrosine kinase inhibitor, but not (yet) documented targetable mutation (n = 4) were excluded, resulting in the study cohort of 1039 patients with advanced NSCLC with *KRAS* wildtype (n = 628) or known *KRAS* mutation (n = 411). Patients have been recruited by 98 centers. Of all patients with *KRAS* mutations, 160 (38.9 %) presented with a G12C mutation, and 251 (61.1 %) with another (non-G12C) mutation in the *KRAS* gene (Fig. 1).

Patient and tumor characteristics for the study cohort are shown in Table 1. Median age at start of first-line treatment was 66 years in patients with *KRAS* wildtype, 65.5 years with G12C mutations, and 64 years with non-G12C mutations. The proportion of female patients was 32.8 % (wildtype), 44.4 % (G12C), and 48.2 % (non-G12C). Current smoking was documented for 24.7 %, 40.6 %, and 31.1 % (wildtype, G12C, non-G12C, respectively); one of the most frequent metastatic sites were the bones with 26.8 %, 34.4 %, and 27.1 %, respectively (Table 1).

Of all 411 patients with *KRAS* mutations, the majority (69.6 %) harbored transversion mutations (38.9 % G12C, 21.2 % G12V, 9.5 % G12A), and 14.9 % of the patients presented with transition mutations (13.9 % G12D, 1.0 % G12S, Fig. 2A). In total, 90.3 % of the *KRAS* mutations were in codon 12, another 6.3 % in codon 13 (including three G13X mutations among the rare cases), and 3.4 % of the patients had *KRAS* Q61H mutations (Fig. 2A).

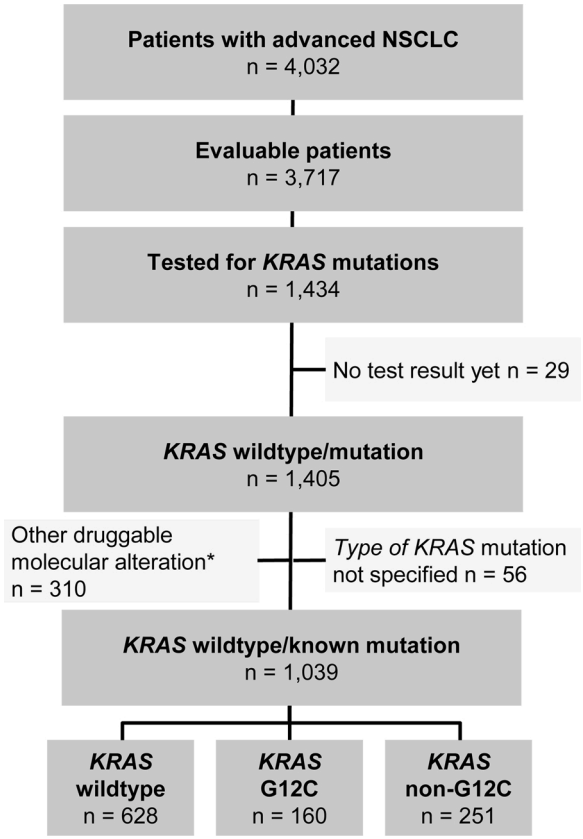


Fig. 1. Flow chart.
Patient flow chart of all patients with advanced NSCLC included in this analysis, starting from the total number of patients recruited into the CRISP registry from December 2015 until June 2019. *All patients with alterations in *EGFR*, *ALK*, *ROS1*, or *BRAF* (n = 306), or treatment with a tyrosine kinase inhibitor, but not (yet) documented targetable mutation (n = 4) have been excluded.

With respect to PD-L1 expression, TPS > 50 % was documented for 20.4 %, 33.8 %, and 22.7 % of the patients (wildtype, G12C, non-G12C), corresponding to 28.0 %, 43.5 %, and 28.9 % of the patients tested for PD-L1 expression in the respective subgroup; TPS < 1 % was documented for 11.1 %, 6.3 %, 11.6 % (wildtype, G12C, non-G12C), corresponding to 15.3 %, 8.1 %, and 14.7 % of the patients tested for PD-L1 expression in the respective subgroup (Table 1, Fig. 2B).

3.2. Treatment

The current treatment status of all patients is shown in Fig. 2C–E. Of all patients with first-line treatment, start of second-line treatment was already documented for 32.0 % (wildtype, n = 201), 26.3 % (G12C, n = 42), and 35.5 % (non-G12C, n = 89); start of third-line treatment for 7.3 % (wildtype, n = 46), 7.5 % (G12C, n = 12), and 10.8 % (non-G12C, n = 27). Of note, these percentages will increase over time, since treatment was still ongoing for a large portion of patients at the time of this analysis. The percentage of patients (wildtype, G12C, non-G12C), who died during or after first-line treatment was 24.2 % (n = 152), 30.0 % (n = 48), and 23.5 % (n = 59), respectively (Fig. 2C–E). These percentages will also increase since follow-up is ongoing. At the time of analysis, the proportion of patients currently on first-line therapy was 27.9 % (n = 175), 28.8 % (n = 46), and 29.9 % (n = 75); and the proportion currently on second-line therapy was 7.8 % (n = 49), 5.6 % (n = 9), and 6.0 % (n = 15), respectively (Fig. 2C–E).

Table 1
Patient and tumor characteristics.

Characteristic at start of first-line treatment	*KRAS* wild type* n = 628	*KRAS* G12C mutation n = 160	*KRAS* non-G12C mutation n = 251
Age in years, median (25–75 % quartile)	66.0 (59.0–73.0)	65.5 (58.0–71.0)	64.0 (58.0–72.0)
<65 years	276 (43.9 %)	79 (49.4 %)	131 (52.2 %)
≥65 years	352 (56.1 %)	81 (50.6 %)	120 (47.8 %)
Sex			
Female	206 (32.8 %)	71 (44.4 %)	121 (48.2 %)
Male	422 (67.2 %)	89 (55.6 %)	130 (51.8 %)
Patients with any comorbidity	538 (85.7 %)	139 (86.9 %)	221 (88.0 %)
Comorbidities according to the CCI [a]			
CCI = 0 [a]	338 (53.8 %)	89 (55.6 %)	155 (61.8 %)
CCI ≥1 [a]	281 (44.7 %)	71 (44.4 %)	96 (38.2 %)
Other comorbidities [b]			
Diabetes without end organ damage	86 (13.7 %)	18 (11.3 %)	30 (12.0 %)
Arterial hypertension	286 (45.5 %)	62 (38.8 %)	128 (51.0 %)
Vasosclerosis	109 (17.4 %)	19 (11.9 %)	39 (15.5 %)
Performance Status			
ECOG 0	166 (26.4 %)	60 (37.5 %)	86 (34.3 %)
ECOG 1	279 (44.4 %)	69 (43.1 %)	114 (45.4 %)
ECOG ≥2	68 (10.8 %)	14 (8.8 %)	17 (6.8 %)
Unknown	105 (16.7 %)	15 (9.4 %)	32 (12.7 %)
Missing	10 (1.6 %)	2 (1.3 %)	2 (0.8 %)
Smoking status			
Current smoker	155 (24.7 %)	65 (40.6 %)	78 (31.1 %)
Former smoker (heavy)	298 (47.5 %)	57 (35.6 %)	98 (39.0 %)
Former smoker (intensity unknown)	32 (5.1 %)	11 (6.9 %)	11 (4.4 %)
Former smoker (light)	59 (9.4 %)	16 (10.0 %)	24 (9.6 %)
Never smoker	38 (6.1 %)	4 (2.5 %)	16 (6.4 %)
Unknown	46 (7.3 %)	7 (4.4 %)	24 (9.6 %)
Missing	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Histology			
Non-squamous	524 (83.4 %)	159 (99.4 %)	247 (98.4 %)
Squamous	104 (16.6 %)	1 (0.6 %)	4 (1.6 %)
Metastasis			
Yes	555 (88.4 %)	151 (94.4 %)	228 (90.8 %)
No	43 (6.8 %)	8 (5.0 %)	14 (5.6 %)
Not derivable (MX or missing)	30 (4.8 %)	1 (0.6 %)	9 (3.6 %)
Selected metastatic sites [b]			
Adrenal gland	129 (20.5 %)	28 (17.5 %)	50 (19.9 %)
Bones	168 (26.8 %)	55 (34.4 %)	68 (27.1 %)
Brain	149 (23.7 %)	43 (26.9 %)	60 (23.9 %)
Extrathoracic lymph nodes	81 (12.9 %)	23 (14.4 %)	20 (8.0 %)
Liver	95 (15.1 %)	25 (15.6 %)	21 (8.4 %)
Lung (contralateral)	121 (19.3 %)	46 (28.8 %)	67 (26.7 %)
Pleura	96 (15.3 %)	21 (13.1 %)	45 (17.9 %)
PD-L1 expression			
TPS ≥ 50 %	128 (20.4 %)	54 (33.8 %)	57 (22.7 %)
1 %≤ TPS > 50 %	152 (24.2 %)	46 (28.8 %)	70 (27.9 %)
TPS < 1 %	70 (11.1 %)	10 (6.3 %)	29 (11.6 %)
TPS unknown, documented positive	18 (2.9 %)	4 (2.5 %)	11 (4.4 %)
TPS unknown, documented negative	89 (14.2 %)	10 (6.3 %)	30 (12.0 %)
No PD-L1 testing	171 (27.2 %)	36 (22.5 %)	54 (21.5 %)

Data are number (%), unless indicated otherwise.
Abbreviations: CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group, TPS, tumor proportion score.
* All patients without *KRAS* mutation. Patients with mutations in *EGFR*, *ALK*, *ROS1*, or *BRAF* were excluded (see flow chart).
[a] Charlson Comorbidity Index (CCI) according to Quan [43].
[b] Multiple answers possible.

In first line of treatment, a checkpoint inhibitor (CPI) was received by 36.0 % (wildtype), 50.1 % (G12C), and 41.8 % (non-G12C) of the patients, either as monotherapy (21.2 %/31.3 %/21.1 %), or in combination with chemotherapy (CPI + CT, 14.8 %/18.8 %/20.7 %) (Fig. 3A). A total of 47.1 % of the patients with *KRAS* wildtype, 38.2 % patients with G12C mutations, and 47.0 % patients with non-G12C mutations received platinum-combination therapies (Fig. 3A).

The type of first-line treatments changed considerably since 2016: while 57.1 % of the patients with G12C (40.0 % non-G12C) mutations were treated with a combination chemotherapy of a platinum and a taxane in 2016, none of the patients with G12C (4.1 % non-G12C) mutations were treated with this combination in 2019 (Fig. 3B). These

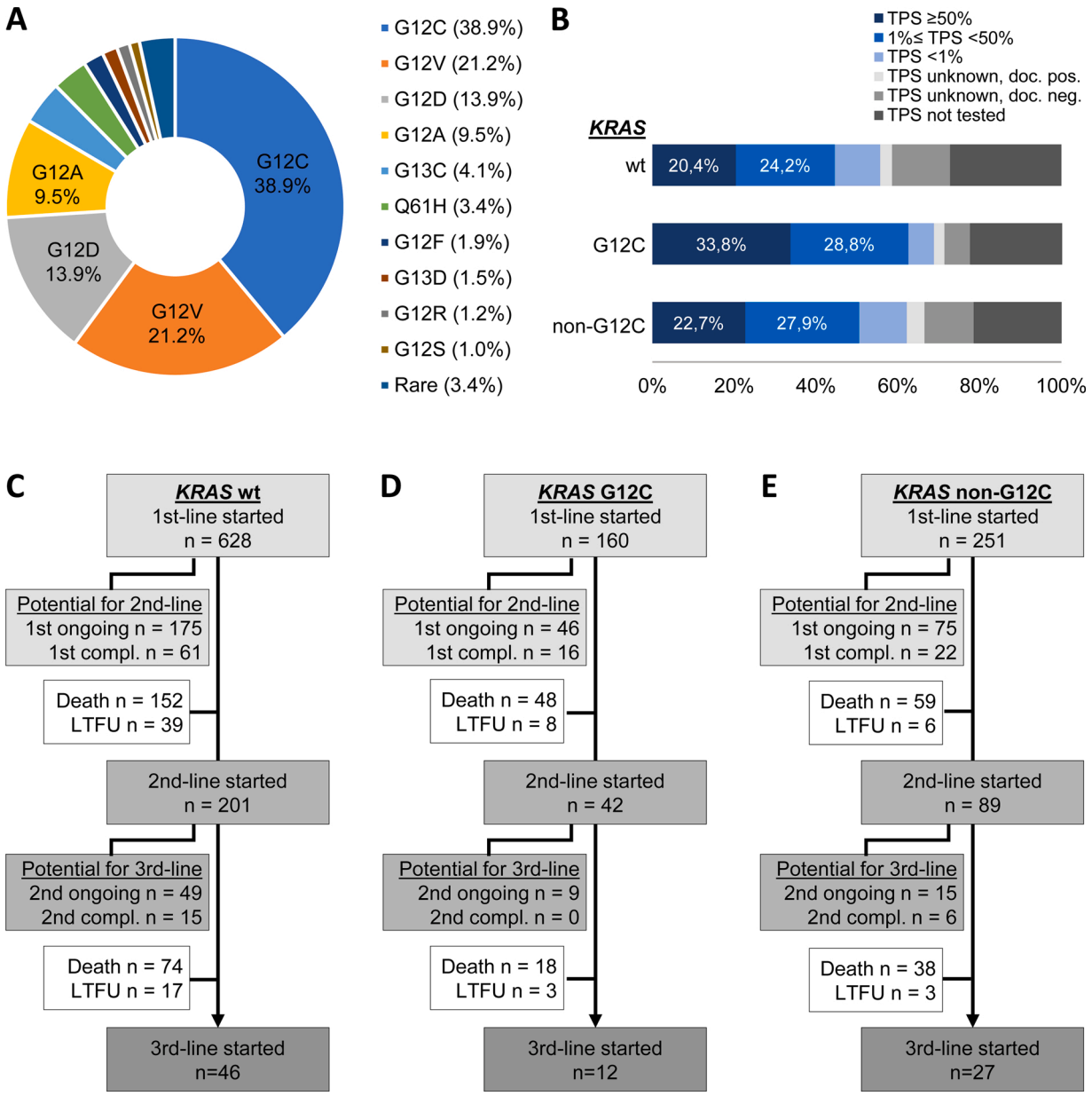


Fig. 2. Details on KRAS mutational status, TPS score and treatment status.
(A) Subtypes of *KRAS* mutations present of all patients with *KRAS* mutations in the study cohort. Rare: further mutations with very few cases each. **(B)** Proportion of PD-L1 TPS expression levels in patients with *KRAS* wt, *KRAS* G12C, or *KRAS* non-G12C tumors. **(C)-(E)**: Shown is the current treatment status of all patients with advanced NSCLC and known *KRAS* mutation status at data cut on June 30, 2019, split up according to the type of *KRAS* mutation for **(C)** patients with *KRAS* wt, **(D)** *KRAS* G12C mutation or **(E)** patients with other, non-G12C *KRAS* mutations. Of note, the patients with potential for a second-line treatment may also receive a third-line treatment afterwards. **Abbreviations:** compl., completed; doc., documented; LTFU, lost to follow-up; neg., negative; pos., positive; TPS, tumor proportion score.

changes mirror the approval of pembrolizumab for PD-L1-positive NSCLC in February 2017 and as combination with chemotherapy in September 2018, as well as the approval of atezolizumab plus bevacizumab and chemotherapy for all patients with advanced NSCLC in March 2019. Thereupon, 24.4 % (wildtype), 51.1 % (G12C) and 27.4 % (non-G12C) of the patients received pembrolizumab monotherapy in 2017, mirroring the higher percentage of patients with *KRAS* G12C mutation and high PD-L1 expression, and 54.2 % (wildtype), 75.0 % (G12C) and 65.3 % (non-G12C) of the patients receiving a CPI-combination therapy in 2019 (Table 1, Fig. 2B). A total of 68.8 % (wildtype), 89.3 % (G12C) and 87.7 % (non-G12C) of the patients received a first-line treatment based on a CPI in 2019 (Fig. 3B).

We grouped the first-line treatments into either chemotherapy (CT) or checkpoint inhibitor with or without combination chemotherapy (CPI ± CT) and present the current sequential second-line treatment regimen (Fig. 3C), showing that most patients with first-line chemotherapy received a CPI in their second-line of treatment: 54.7 % (wildtype), 59.5 % (G12C), and 61.8 % (non-G12C). Since many patients had not completed first-line treatment at the time of analysis, patients with early disease progressions might be slightly over-represented in the current second-line treatments, which should be considered when interpreting the data.

3.3. Clinical outcome of patients with KRAS mutations

Survival estimates were calculated for the outcome sample, all patients with at least one-year follow-up (recruited until June 30, 2018). The patient and tumor characteristics of the outcome sample are listed in

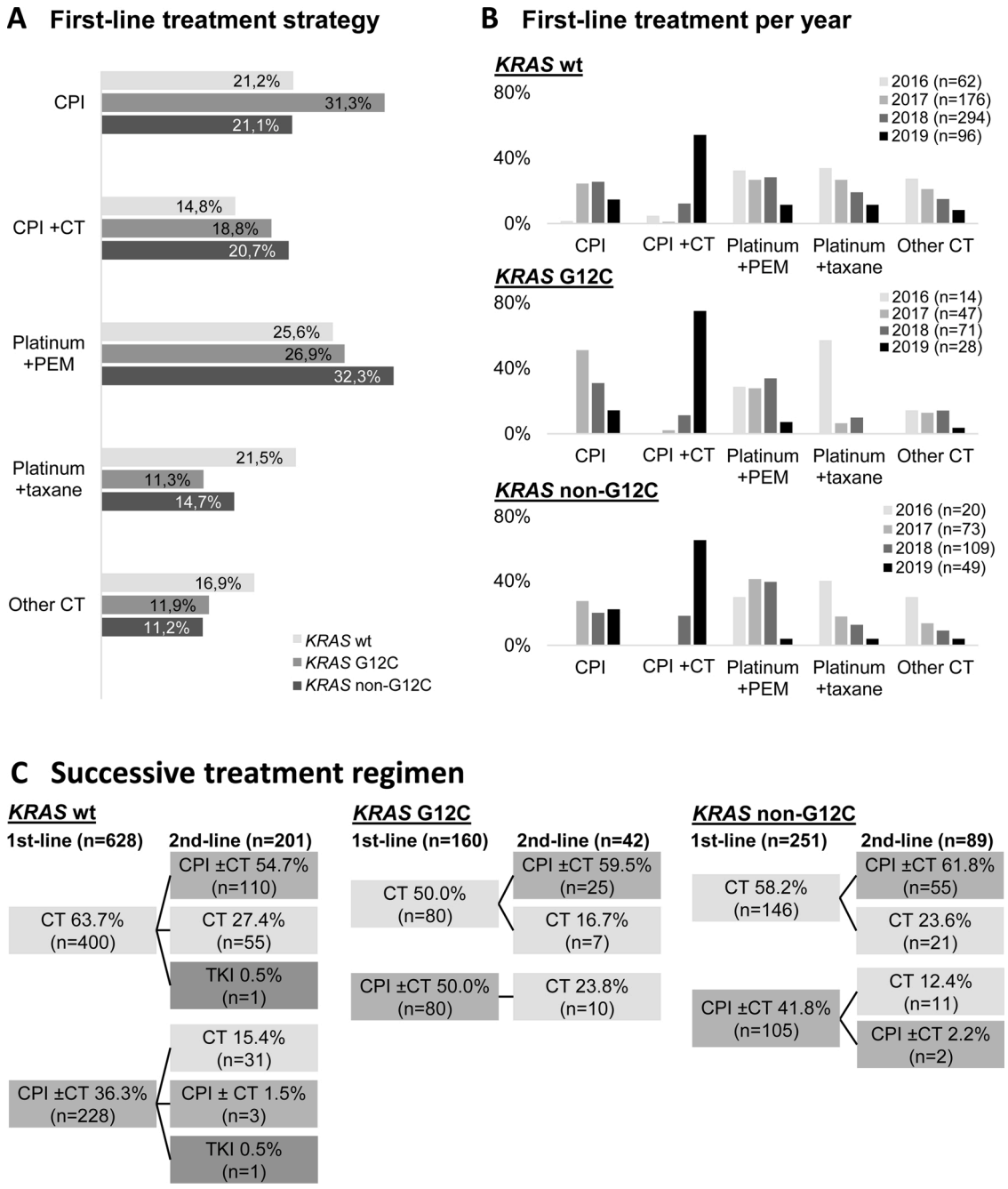


Fig. 3. Treatment.
(A) Top first-line treatment regimen split up for patients with *KRAS* wildtype, *KRAS* G12C mutations and *KRAS* non-G12C mutations. **(B)** First-line treatments over time for patients with *KRAS* wt, *KRAS* G12C mutations, and patients with *KRAS* non-G12C mutations. Checkpoint inhibitors: pembrolizumab, atezolizumab, or nivolumab; platinum agents: carboplatin or cisplatin; taxanes: *nab*-paclitaxel or paclitaxel; X: any substance combined with a checkpoint inhibitor. **(C)** Successive treatment regimen in patients who already started a second line of treatment for patients with *KRAS* wt, *KRAS* G12C mutations, and patients with non-G12C mutations. Proportions given for the second-line treatment refer to all patients with a documented second-line treatment. **Abbreviations:** CPI, checkpoint inhibitor; CT, chemotherapy; PEM, Pemetrexed; TKI, tyrosine kinase inhibitor; wt, wildtype.

supplementary Table S1. *KRAS* wildtype patients were split up according to non-squamous and squamous tumor histology. Median first-line treatment duration of patients with completed first-line therapy was 79 days (wildtype non-squamous), 86 days (wildtype squamous), 75 days (G12C), and 94 days (non-G12C); the most common reason for end of treatment was disease progression (Table 2). A (registry-) complete response was documented for 3 (1.1 %) patients with wildtype non-squamous, 2 (3.2 %) patients with wildtype squamous, 2 (2.3 %) patients with G12C mutations and none with other *KRAS* mutations; while 20.9 %, 19.0 %, 20.9 %, and 27.2 % (wildtype non-squamous, wildtype squamous, G12C, non-G12C) of the patients experienced a partial response (Table 2).

No differences in clinical outcome could be seen between patients with *KRAS* wildtype, G12C and non-G12C mutations, with a median PFS of 5.7 months (95 % CI 4.9–6.6) for wildtype non-squamous, 6.0 months (95 % CI 3.2–8.4) for wildtype 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 (Fig. 4A). Median OS was 11.6 months (95 % CI 9.5–13.4) in *KRAS* wildtype non-squamous, 15.8 months (95 % CI 10.5–20.4) in wildtype squamous, 11.6 months (95 % CI 9.0–18.1) in G12C, and 10.4 months

Table 2
Characteristics of the patients in the outcome sample (recruited until June 30, 2018).

Characteristic at start of first-line treatment	*KRAS* wildtype non-squamous n = 318	*KRAS* wildtype squamous n = 67	*KRAS* G12C mutation n = 101	*KRAS* non-G12C mutation n = 146
Age in years, median (25–75% quartile)	65.0 (58.0–72.0)	69.0 (63.0–77.0)	64.0 (58.0–71.0)	64.0 (58.0–72.0)
ECOG 0	90 (28.3 %)	13 (19.4 %)	44 (43.6 %)	51 (34.9 %)
Patients with completed 1st-line treatments	278 (87.4 %)	63 (94.0 %)	86 (85.1 %)	136 (93.2 %)
Treatment duration [days], median (25–75% quartile)	78.5 (43.0–134.0)	86.0 (43.0–137.0)	75.0 (38.0–129.0)	94.0 (43.5–160.5)
Reason for end of treatment				
Toxicity	21 (7.6 %)	3 (4.8 %)	8 (9.3 %)	10 (7.4 %)
Progression	99 (35.6 %)	19 (30.2 %)	36 (41.9 %)	53 (39.0 %)
According to protocol/guidelines	69 (24.8 %)	19 (30.2 %)	10 (11.6 %)	21 (15.4 %)
Other	85 (30.6 %)	22 (34.9 %)	32 (37.2 %)	51 (37.5 %)
Missing	4 (1.4 %)	0 (0.0 %)	0 (0.0 %)	1 (0.7 %)
Time to next treatment (TTNT)				
Events	226 (71.1 %)	44 (65.7 %)	70 (69.3 %)	119 (81.5 %)
TTNT [months], median (95 % CI)	6.1 (5.4–6.8)	6.4 (4.6–8.8)	5.7 (4.4–8.3)	5.6 (4.6–6.5)
Registry best response **	276 (99.3 %)	63 (100.0 %)	86 (100.0 %)	134 (98.5 %)
CR	3 (1.1 %)	2 (3.2 %)	2 (2.3 %)	0 (0.0 %)
PR	58 (20.9 %)	12 (19.0 %)	18 (20.9 %)	37 (27.2 %)
SD	86 (30.9 %)	20 (31.7 %)	22 (25.6 %)	43 (31.6 %)
PD	69 (24.8 %)	17 (27.0 %)	20 (23.3 %)	27 (19.9 %)
Unknown	60 (21.6 %)	12 (19.0 %)	24 (27.9 %)	27 (19.9 %)
Missing	2 (0.7 %)	0 (0.0 %)	0 (0.0 %)	2 (1.5 %)

Data are number (%), unless indicated otherwise. **Abbreviations:** CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TTNT, time to next treatment.

** There are no specifications as to the timing, frequency or criteria of tumor assessment, thus registry response data should be considered as the best clinical approximation and might not be identical to the response determined in clinical trials.

(95 % CI 8.4–14.0) in non-G12C (Fig. 4B). Notably, patients with G12C mutation on average had a slightly better performance status (43.6 % ECOG 0 vs. 26.8 % wildtype, and 34.9 % non-G12C, Tables 2 and S1).

It would be very interesting to analyze the outcome data of all patients with TPS ≥ 50 % and treatment with a checkpoint-inhibitor, however, these data are still too preliminary with too few events. We will present these data in future publications.

To look more closely into factors associated with survival, a multivariate regression analysis was calculated. The results show that a poor ECOG performance status (ECOG ≥ 2 vs. ECOG = 0) was associated with a significantly increased risk of overall mortality: HR 1.97, 95 % CI 1.31–2.97, $p = .001$ (Fig. 4C). Age, BMI, sex, Charlson Comorbidity Index and *KRAS* mutation status were not associated with survival. Due to the higher proportion of patients with TPS ≥ 50 % in the G12C group (Fig. 2B), the PD-L1 expression level was also included in the model. Compared with low PD-L1 expression (TPS < 1 %), higher PD-L1 expression was associated with a significantly lower risk of mortality: for 1 %≤ TPS < 50 %: HR 0.61, 95 % CI 0.41–0.90, $p = .012$, for TPS ≥50 %: HR 0.39, 95 % CI 0.26–0.60, $p = <.001$ (Fig. 4C). Of note, there were no adjustments made for multiple testing.

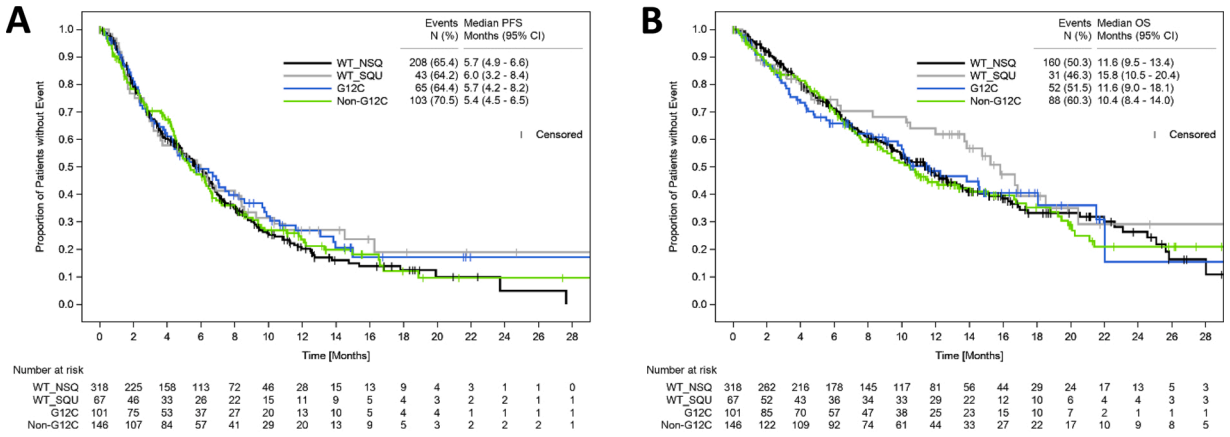
Additional outcome analyses are shown in supplemental Fig. S1: neither PFS nor OS differed significantly between the main *KRAS* mutation subtypes G12C, G12 V, G12D, G12A, and all other subtypes (Fig. S1A and B). Likewise, the first-line treatment strategy (checkpoint-inhibitor ± chemotherapy, platinum + pemetrexed, platinum + taxanes, or other chemotherapy) was not associated with differences in OS in patients with *KRAS* wildtype, G12C or non-G12C mutations (Fig. S1C–F). Of note, there are only few patients in some subgroups, therefore, these results need to be interpreted with caution.

4. Discussion

Here we describe the, so far, largest prospectively recruited cohort of patients with advanced NSCLC and *KRAS* mutations. In light of recent developments regarding a targeted therapy specific for the *KRAS* G12C mutation subtype, we set a special focus on this patient subgroup, showing a poor outcome and no significant association of the *KRAS* mutational status with survival. Data from routine care on the current frequency of diagnoses of NSCLC with *KRAS* G12C mutation and data on the conventional treatment are of high interest as “historical control”.

The proportion of patients with the specific *KRAS* mutation subtype G12C was 38.9 % of patients with any *KRAS* mutation in our cohort, which is in line with previously published numbers, ranging between 42.9 % in Germany [25], 34.9 % in the US [26], and 28–33 % in China [17,27,28].

The clinical outcome of patients with *KRAS* mutations or *KRAS* wildtype was similar and a Cox regression analysis revealed no clear association of the *KRAS* mutation status with mortality. This result is in line with a recent study on any stage lung adenocarcinoma with *KRAS* G12C mutations in the US, reporting similar clinical courses for 117 patients with G12C mutation compared to 137 patients with non-G12C mutations [18]. Likewise, a very recent study in a real-world setting on 137 patients with *KRAS* wildtype, 65 patients with G12C mutations, and 144 patients with non-G12C mutations showed similar clinical features, treatment and survival for patients with *KRAS* mutant vs. wildtype and patients with G12C vs. non-G12C mutations [29]. A German study reported an association of *KRAS* G12C mutations in NSCLC with an intermediate prognosis [25]. A retrospective survival analysis on 1456 patients with any stage NSCLC from the Guangdong Lung Cancer Institute in China reported shorter survival for *KRAS*-G12C-mutated tumors (n = 42) compared to *KRAS* wildtype tumors (n = 304) with a median OS of 18.3 vs. 26.7 months, but the *KRAS* mutation status did not reach significance in a Cox regression analysis [28]. Likewise, a study on surgically resected stage I lung adenocarcinoma samples from Shanghai reported worse OS for *KRAS*-mutated (n = 54) compared to *KRAS*--wildtype patients (n = 585), and the *KRAS*-mutations status was also identified as independent risk factor for OS in a Cox regression analysis in this patient subgroup [30]. Further published survival analyses on the *KRAS* G12C subtype reported contrary findings, but are hampered by small patient samples, different treatment settings, methodological issues and a remarkably low proportion of female patients [17,19,20,31]. Interestingly, the patients with G12C mutations in our cohort tended to have better ECOG performance status, a higher probability of high PD-L1 expression and were more often treated with



C

Cox proportional hazards model

Variable		Hazard Ratio (95% CI)	HR	95% CI	p
Age			0.99	0.98-1.01	0.335
BMI			0.98	0.96-1.01	0.189
Sex					
Male vs female	n=398 vs n=234		1.14	0.90-1.44	0.277
Charlson score					
≥1 vs 0	n=267 vs n=365		0.95	0.75-1.20	0.665
ECOG performance status					
1 vs 0	n=279 vs n=198		1.16	0.88-1.51	0.288
≥2 vs 0	n=64 vs n=198		1.97	1.31-2.97	0.001**
Missing vs 0	n=91 vs n=198		1.24	0.88-1.76	0.224
KRAS mutation status					
G12C vs WT	n=101 vs n=385		1.24	0.90-1.70	0.189
Non-G12C vs WT	n=146 vs n=385		1.20	0.92-1.56	0.177
PD-L1 expression					
TPS ≥50% vs TPS <1%	n=138 vs n=55		0.39	0.26-0.60	<0.001***
1% ≤ TPS <50% vs TPS <1%	n=149 vs n=55		0.61	0.41-0.90	0.012*
TPS ukn (pos) vs TPS <1%	n=24 vs n=55		0.44	0.22-0.90	0.023*
TPS ukn (neg) vs TPS <1%	n=81 vs n=55		0.71	0.46-1.09	0.113
No PD-L1 testing vs TPS <1%	n=185 vs n=55		0.68	0.47-0.98	0.040*

Fig. 4. Survival and regression analysis.
(A) First-line Registry PFS and (B) first-line OS in patients with advanced NSCLC, wildtype sample split up according to the histology (NSQ, non-squamous, SQU, squamous). Analysis is based on all patients observed for at least one year, e.g. starting first-line treatment until June 30, 2018. For patient characteristics of this outcome sample, see Table S1. (C) Cox proportional hazards model for overall survival for the outcome sample. TPS ukn (pos): TPS unknown, but documented as PD-L1 positive, TPS ukn (neg): TPS unknown, but documented as PD-L1 negative. **Abbreviations:** BMI, body mass index; CI, confidence interval; HR, hazard ratio; neg., negative; NSQ, non-squamous; PFS, progression-free survival; pos., positive; SQU, squamous; ukn, unknown, WT, wildtype.

checkpoint-inhibitors than patients with non-G12C mutations or *KRAS* wildtype, yet still no significant differences in survival could be seen.

In a wider context, it has been shown that *KRAS* codon 12 vs. codon 13 mutations are not associated with differing clinical outcome in advanced NSCLC [32,33]. Conversely, it has been published that co-occurring genomic alterations define distinct subgroups of *KRAS*--mutated patients, and the co-mutation of *KRAS* and *KEAP/NFE2L2* has been shown to be an independent prognostic factor for shorter survival [34,35]. In summary, no clear association of the *KRAS* G12C mutation with inferior or superior clinical outcome could be seen - neither in comparison to other *KRAS* mutations nor to the *KRAS* wildtype population.

Besides molecular markers, the other important biomarker in NSCLC is PD-L1. It has been shown before, that *KRAS* G12C mutations are associated with positive, yet low PD-L1 expression (TPS 1–49 %) [26]. In our cohort, more patients with G12C mutations presented with high PD-L1 expression (TPS > 50 %). In the Cox model, positive PD-L1 expression (TPS ≥ 1 %) was associated with a significantly decreased risk of mortality compared to low PD-L1 expression (TPS < 1 %), with high PD-L1 expression (TPS ≥ 50 %) showing the greatest risk

reduction. In concordance with these results, Falk and colleagues published an association of high PD-L1 expression with improved OS in *KRAS* mutant patients [36], while Tao and colleagues report an association of PD-L1 expression (TPS > 1 %) in *KRAS* G12C mutant patients with significantly shorter median OS compared to no PD-L1 expression (5.7 vs. 12.8 months) [18]. A French cohort of patients with advanced NSCLC receiving checkpoint-inhibitors in first-line treatment showed similar proportions of PD-L1 expression in *KRAS* wildtype and mutant tumors, and no significant differences in response rate, PFS, or OS between these patient subgroups [37]. Future analyses on larger cohorts of patients split up according to their respective treatment will help to definitely elucidate the prognostic role of PD-L1 in *KRAS* G12C mutant NSCLC.

Given the poor prognosis of advanced NSCLC, with a relative 5-year overall survival rate of only 5.2 % [38], a median PFS of 5.8 months (95 % CI 5.4–6.2), and a median OS of 11.4 months (95 % CI 10.6–12.7) in patients without druggable molecular alterations in Germany [39], novel therapeutic options for patients with *KRAS* mutations is of increasing importance for all medical oncologists [40]. The preliminary clinical data are promising: the phase I/II first-in-human trial evaluating the safety and tolerability of AMG510 (NCT03600883) has so far enrolled 14 patients with NSCLC, and reported as yet no dose-limiting toxicities; the best response data for 10 of these 14 patients showed partial response for 5, stable disease for 4 and progressive disease for 1 patient(s) [21, presented on ESMO 2019]. Based on these results, the FDA granted a fast track designation to AMG510 for the treatment of patients with previously treated metastatic NSCLC harboring a *KRAS* G12C mutation [41]. In the first results of the phase I/II trial of MRTX849 (NCT03785249), 3 of 6 patients with NSCLC achieved a partial response across all dose levels [22,42, presented on AACR 2019]. The first-in-human trial on JNJ-74699157 (NCT04006301) has just started recruiting. The validation of the promising early clinical results and the durability of responses over time are eagerly awaited.

4.1. Limitations

The non-interventional design is both a strength and a limitation of this study. It represents a strength, because it allows presentation of real-world data on patients not selected by restrictive inclusion criteria and on test rates in routine care. And it is a limitation, because it precludes causal conclusions on differences between subgroups, and data on molecular alterations were not readily available for the entire cohort. Because not all patients had been tested for *KRAS* mutations, overall incidence in our sample might vary from other published cohorts. There are no specifications as to the timing, frequency or criteria of tumor assessment and thus registry-PFS and -response data should be considered as the best clinical approximation and might not be identical to the PFS/response determined in clinical trials. This study was designed for patients receiving systemic therapy; therefore, results may not be generalized to the small group of patients not receiving any systemic treatment. Strengths of this project are the prospective data collection and the participation of both hospitals and (office-based) oncologists in private practice all over Germany, recruiting a large, representative study cohort.

5. Conclusion

The promising results of specific *KRAS* G12C inhibitors have raised expectations to overcome the “undruggable” *KRAS* mutations. Our data show that, up to now, outcome for *KRAS*-mutant tumors under current standard therapy is poor and therefore, patients will presumably benefit greatly from a targeted treatment option improving survival. The present data on 160 patients with *KRAS* G12C mutations recruited by the CRISP registry in routine care might be of major importance for the lung cancer therapists as well as historical controls on treatment and outcome of this patient subgroup.

Declarations

All experiments comply with the current laws in Germany, where they were performed.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments.

CRediT authorship contribution statement

Martin Sebastian: Conceptualization, Investigation, Resources, Writing - original draft, Supervision, Funding acquisition. **Wilfried E.E. Eberhardt:** Conceptualization, Investigation, Resources, Writing - original draft, Supervision, Funding acquisition. **Petra Hoffknecht:** Investigation, Resources, Writing - review & editing. **Martin Metzenmacher:** Investigation, Resources, Writing - review & editing. **Thomas Wehler:** Investigation, Resources, Writing - review & editing. **Konrad Kokowski:** Investigation, Resources, Writing - review & editing. **Jürgen Alt:** Investigation, Resources, Writing - review & editing. **Wolfgang Schütte:** Investigation, Resources, Writing - review & editing. **Reinhard Büttner:** Resources, Writing - review & editing. **Lukas C. Heukamp:** Resources, Writing - review & editing. **Albrecht Stenzinger:** Resources, Writing - review & editing. **Martina Jänicke:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Visualization, Supervision. **Annette Fleitz:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Visualization, Project administration. **Stefan Zacharias:** Validation, Formal analysis, Data curation, Writing - review & editing. **Stephanie Dille:** Conceptualization, Methodology, Visualization, Writing - original draft. **Annette Hipper:** Funding acquisition, Project administration, Supervision, Writing - original draft. **Marlen Sandberg:** Project administration, Supervision, Writing - review & editing. **Wilko Weichert:** Resources, Writing - review & editing. **Matthias Groschek:** Investigation, Resources, Writing - review & editing. **Eyck von der Heyde:** Investigation, Resources, Writing - review & editing. **Jacqueline Rauh:** Investigation, Resources, Writing - review & editing. **Tobias Dechow:** Investigation, Resources, Writing - review & editing. **Michael Thomas:** Conceptualization, Investigation, Resources, Writing - original draft, Supervision, Funding acquisition. **Frank Griesinger:** Conceptualization, Investigation, Resources, Writing - original draft, Supervision, Funding acquisition.

Declaration of Competing Interest

All authors declare no conflict of interest concerning the topic of this publication.

Outside of the published work, the institutions of M. Sebastian, W. Eberhardt, M. Thomas, P. Hoffknecht, M. Metzenmacher, T. Wehler, K. Kokowski, J. Alt, W. Schütte, M. Groschek, E. von der Heyde, J. Rauh, T. Dechow, and F. Griesinger received remuneration for the documentation of patient data.

R. Büttner has received honoraria for lectures and advisory boards from AbbVie, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Illumina, Lilly, MSD, Novartis, Qiagen, Pfizer, and Roche; he is co-founder and scientific advisor for Targos Mol. Pathology Inc and has served as testifying advisor for MSD in GBA-assessment for pembrolizumab. W. E. E. Eberhardt has received research funding (to the institution) from Eli Lilly, AstraZeneca, and BMS; he has received honoraria for advisory boards and lectures from Amgen, AstraZeneca, BMS, Merck/MSD, Roche, Pfizer, Novartis, Takeda, Boehringer Ingelheim, and Abbvie; honoraria for advisory boards from Amgen, Bayer, Daichi Sankyo, and Janssen Cilag; honoraria for lectures from Amgen and Baumgart Consult. F. Griesinger has received grants, personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, Bristol Myer Squibb, Celgene, MSD, Novartis, Pfizer, Roche, Takeda, and Lilly. M. Groschek

has received grants from Roche, BMS, Novartis, Pfizer, Pierre Fabre, Celgene, Amgen, AstraZeneca, Sanofi, Medac, Octapharma, Gilead, TEVA, and Merck; honoraria from Roche, BMS, Novartis, Pfizer, Amgen, Merck, and Celgene; travel expenses from Roche, Celgene, Ipsen, Onkovis, Medac, and Gilead, and has attended advisory boards for Roche, BMS, Novartis, and Pfizer. L. Heukamp has received personal fees for an advisory role from Roche, NEO NewOncology, Pfizer, Bayer, BMS, and AstraZeneca. A. Hipper and M. Sandberg report grants from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, MSD Sharp & Dohme, Lilly, Novartis, Pfizer, Roche, and Takeda to their employer (AIO-Studien-gGmbH). M. Metzenmacher has received personal honoraria for advisory boards from Boehringer Ingelheim, Takeda, MSD, BMS und Roche. W. Schütte has received research grants from Lilly, Abbvie, Merck, Boehringer Ingelheim, Roche, AstraZeneca, GlaxoSmithKline, Ose Pharma, BMS, and Novartis; honoraria and travel expenses for advisory boards/lectures from AstraZeneca, Roche, MSD, Boehringer Ingelheim, and BMS. M. Sebastian has received grants and personal fees from Roche, BMS, and AstraZeneca; personal fees from Abbvie, Takeda, MSD, Pfizer, Boehringer Ingelheim, Celgene, Biontech, CureVac, Novartis, Janssen, and Tesaro. A. Stenzinger has received grants from Bayer, BMS, and Chugai; personal fees for advisory boards from AstraZeneca, Bayer, BMS, Eli Lilly, Illumina, Janssen, Novartis, Seattle Genetics, and Thermo Fisher; personal fees from Pfizer and Roche. M. Thomas has received grants, personal fees and non-financial support from AstraZeneca, Bristol-Myers Squibb, Roche, and Takeda; personal fees and non-financial support from Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Novartis, and Pfizer. W. Weichert has received research funding from Roche, MSD, BMS and Bruker, and has attended advisory boards/served as speaker for Roche, MSD, BMS, AstraZeneca, Pfizer, Merck, Lilly, Boehringer, Novartis, Takeda, Amgen, Janssen and Astellas.

Acknowledgements

The authors thank all patients, physicians and study teams participating in the CRISP registry. CRISP is a project of the German Working Group of Medical Oncologists (AIO, project number AIO-TRK-0315), and is conducted by the AIO-Studien-gGmbH (sponsor oversight) in collaboration with iOMEDICO (conception, project management, analyses) under medical guidance of the executive steering board (FG, MT, MS, WE). The CRISP project is supported by grants from AstraZeneca GmbH, Amgen Ltd, Boehringer Ingelheim Pharma GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Celgene GmbH, MSD Sharp & Dohme GmbH, Lilly Deutschland GmbH, Novartis Pharma GmbH, Pfizer Pharma GmbH, Roche Pharma AG, and Takeda Pharma Vertriebs GmbH & Co. KG. None of the funders had any role in study design, data collection and analysis, interpretation of results, decision to publish, or preparation of the manuscript.

Appendix A. Collaborators

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2021.02.005.

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