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Noordhof, A L; Damhuis, R A M; Hendriks, L E L; de Langen, A J; Timens, W; Venmans, B J W; van Geffen, W H

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Prognostic impact of KRAS mutation status for patients with stage IV adenocarcinoma of the lung treated with first-line pembrolizumab monotherapy

A.L. Noordhof^a, R.A.M. Damhuis^b, L.E.L. Hendriks^c, A.J. de Langen^d, W. Timens^e, B.J. W. Venmans^a, W.H. van Geffen^{a,*}

^a Department of Respiratory Medicine, Medical Center Leeuwarden, Henri Dunantweg 2, 8934 AD, Leeuwarden, the Netherlands

^b Department of Research, Comprehensive Cancer Organization, Plesmanlaan 121, 1066 CX, Utrecht, the Netherlands

^c Department of Respiratory Medicine, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX, Maastricht, the Netherlands

^d Department of Thoracic Oncology, Netherlands Cancer Institute, NA 1007 MB, Amsterdam, the Netherlands

^e Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Hanzplein 1, 9713 GZ, Groningen, the Netherlands

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ABSTRACT

Objectives: Monotherapy with pembrolizumab is the preferred first-line treatment for metastatic non-small cell lung cancer with programmed death-ligand 1 (PD-L1) expression $\geq 50\%$, without targetable oncogenic drivers. Although targeted therapies are in development for patients with specific Kirsten rat sarcoma (*KRAS*) mutations, these are not available in daily care yet. It is not clear whether there is a difference in survival on first-line pembrolizumab for patients with a high PD-L1 status with or without a *KRAS* mutation. We aim to compare this survival based on real-world data.

Materials and methods: This is a real-world retrospective population-based study using data from the Netherlands Cancer Registry. We selected patients with stage IV lung adenocarcinoma with PD-L1 expression $\geq 50\%$ diagnosed between January 2017 and December 2018, treated with first-line pembrolizumab. Patients with *EGFR* mutations, *ALK* translocations or *ROS1* rearrangements were excluded. The primary outcome parameter was overall survival.

Results: 388 (57 %) of 595 patients had a *KRAS* mutation. *KRAS* was seen more frequently in women than in men (65 % versus 49 % respectively, $p < 0.001$). The median overall survival was 19.2 months versus 16.8 months for patients with and without *KRAS* mutation, respectively ($p = 0.86$). Multivariable analysis revealed WHO performance score, number of organs with metastases and PD-L1 percentage as independent prognostic factors. *KRAS* mutation status had no prognostic influence (hazard ratio = 1.03, 95 % CI 0.83–1.29).

Conclusion: The survival of *KRAS* mutated versus *KRAS* wild-type lung adenocarcinoma patients, treated with first-line pembrolizumab monotherapy, is similar, suggesting that *KRAS* has no prognostic value with respect to treatment with pembrolizumab.

Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B; CCMO, central committee on research involving human subjects; CD8+, cluster of differentiation 8+; CDKN2A, cyclin-dependent kinase inhibitor 2A; CI, confidence interval; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2 gene; HR, hazard ratio; ICI, immune checkpoint inhibitors; KRAS, Kirsten rat sarcoma; MEC, medical ethics committee; MET, mesenchymal-epithelial transition factor; NCR, Netherlands cancer registry; NSCLC, metastatic non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PS, performance score; ROS1, ROS1 proto-oncogene receptor tyrosine kinase; SKT11, serine/threonine kinase 11; TP53, tumor protein p53; TPS, tumor proportion score; WHO, world health organization.

* Corresponding author at: Medical Center Leeuwarden, Henri Dunantweg 2, 8934 AD, Leeuwarden, the Netherlands.

E-mail address: wouter.van.geffen@mcl.nl (W.H. van Geffen).

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1. Introduction

In the past decade the treatment and prognosis of patients with metastatic non-small cell lung cancer (NSCLC) has significantly improved. This progress has been attributed to the introduction of immunotherapy with immune checkpoint inhibitors (ICI) and targeted therapy [1–4]. Since the introduction in 2017, monotherapy with the ICI pembrolizumab became the preferred first line of treatment for metastatic NSCLC for those with a tumor programmed death-ligand 1 (PD-L1) expression ≥ 50 % tumor proportion score (TPS) and a World Health Organization (WHO) performance score of 0–1 [5,6]. Since patients with genetic alterations in *EGFR*, *ROS*, *ALK*, *BRAF* and *MET* have a worse outcome when treated with immunotherapy, an adequate selection of patients that benefit from mono-immunotherapy remains important [7–10].

Kirsten rat sarcoma (*KRAS*) is the most common oncogenic driver mutation in NSCLC, occurring in 30 % of patients in western populations [11,12]. *KRAS* is a protein that regulates downstream signaling via different pathways, including the RAF-MEK-ERK (MAPK) pathway. When mutated it promotes cell proliferation and cell survival [13,14]. *KRAS* mutations are most often found in adenocarcinomas and occasionally in squamous cell carcinomas [15]. These mutations are associated with smoking and a higher PD-L1 expression [16,17].

Up to date there is no registered targeted therapy available for *KRAS* mutated lung adenocarcinoma, as several attempts in the past have not been successful [18,19]. However, recent preclinical and phase I-II studies are showing promising results in targeting the G12C submutation with AMG 510 (Sotorasib) and MRTX849, which are novel small molecules that keep the *KRAS* protein bound in its inactive state [20–24]. However, these targeted therapies are not available in daily care yet [18–22]. Therefore, patients with *KRAS* mutated NSCLC are being treated with standard first-line therapy. Due to inconclusive and conflictive data it remains unclear whether pembrolizumab monotherapy for those with a PD-L1 ≥ 50 % is optimal.

When assessing survival outcomes for patients with a *KRAS* mutation, trends towards improved treatment responses for patients with *KRAS* mutated NSCLC were shown by post-hoc subgroup analysis of studies comparing ICI with docetaxel, involving NSCLC patients with progression after platinum-based combination chemotherapy, compared to *KRAS* wild type patients [1,25]. Although this might be similar for patients with *KRAS* mutated lung adenocarcinoma treated with pembrolizumab, several studies regarding the effects of single-agent ICI have given different results and are biased by different chemotherapy regimens. Furthermore, this has not been studied in the first line setting where ICI treatment is currently being used predominantly [26–33].

To assess whether patients with a *KRAS* mutation should be treated differently than *KRAS* wild-type patients more data is needed. This data will become extra relevant to develop new treatment strategies and sequences when targeted therapy for *KRAS* becomes available. This will also determine how to position them in the treatment sequence, and to assess the potential for these therapies in a first-line setting especially in comparison with ICI monotherapy due to the worse outcomes for ICI monotherapy patients with other druggable driver mutations. The assessment of outcome parameters for *KRAS* mutated NSCLC treated with ICI monotherapy also is relevant in the current absence of *KRAS* targeted therapies. *KRAS* patients are now treated with the standard first-line therapy [34].

To assess the prognostic value of *KRAS* in relation to ICI monotherapy, we conducted this nationwide study. We aimed to describe the overall survival (OS) of *KRAS* mutated versus *KRAS* wild-type lung adenocarcinoma patients treated with first-line pembrolizumab monotherapy based on real world data. Based on the available incomplete data we hypothesize that for patients with PD-L1 ≥ 50 %, those with *KRAS* mutated lung adenocarcinoma have an increased OS compared to wild type *KRAS*, when treated with mono-immunotherapy. We also

Fig. 1. Patient selection using the Netherlands Cancer Registry (NCR).

evaluated for effect of further PDL1 stratification in TPS 50–89% versus >90 %.

2. Materials and methods

2.1. Data and procedures

This is a retrospective, non-interventional, population-based study from the Netherlands. All patients diagnosed with any type of cancer are registered in the Netherlands Cancer Registry (NCR) [35,36]. A standardized dataset is collected from hospital patient records consisting of basic patient and disease characteristics, including histology, TNM stage, WHO Performance Score (PS), site(s) of metastasis and type of first line treatment. PD-L1 TPS score and common driver mutations are also recorded; molecular testing method is not recorded but the national guideline recommends standard testing for *EGFR*, *ALK* and *KRAS* in patients with stage IV adenocarcinoma [37] and this is common practice, since barriers with testing capacity and costs are low in the Netherlands. In 2017, molecular testing involved multiplex sequencing techniques in more than 75 % of cases.

Information on OS is obtained by annual linkage with the population registry. The primary endpoint of this study is OS, calculated from the day of starting pembrolizumab until death from any cause, with follow up until February 1 st, 2020. Data on comorbidity, treatment response, date of progression, second line treatment and cause of death are not available in the registry.

From the NCR, we selected all patients diagnosed between January 1 st, 2017 and December 31 st, 2018, with stage IV adenocarcinoma of the lung and PD-L1 ≥ 50 %, treated with first line pembrolizumab monotherapy. To avoid confounders, we included only patients who started treatment within 90 days of diagnosis, and we excluded patients with types of NSCLC other than adenocarcinoma [Fig. 1].

Considering its retrospective and non-interventional nature, this study does not require approval from an accredited medical ethics committee (MEC) or the Central Committee on Research involving Human Subjects (CCMO) according to Dutch jurisdiction. However, the study has been reviewed and approved by the Privacy Review Board and the Scientific Review Board of the NCR (application number K20.135).

Table 1
Patient characteristics.

		Overall	KRAS _{mut}		p
		n	n	%	
Age	18–59	167	91	54	0.70
	60–69	216	127	59	
	≥70	212	120	57	
Gender	Men	296	144	49	<0.001
	Women	299	194	65	
	0	216	129	60	
WHO Performance Score	1	244	140	57	0.44
	2–3	57	28	49	
	Unknown	78	41	53	
Number of Metastatic Organs	1	266	147	55	0.72
	2	174	103	59	
	≥3	155	88	57	
PD-L1	50–89	430	239	56	0.33
	≥90	165	99	60	
	2017	172	97	56	0.90
	2018	423	241	57	

Abbreviations: KRAS_{mut}, KRAS mutational status; PD-L1, programmed death-ligand 1.

2.2. Statistical analysis

Age was stratified as a categorical variable. PS scores 2 and 3 were combined into one category, PS scores of 0 or 1 were categorized separately. Although we only included patients with high PD-L1 percentage, we decided to stratify PD-L1 score into 50–89 and 90+ to avoid potential groups differences in PD-L1 expression [38]. Categorical variables were tabulated and reported as proportions. Associations between categorical variables and KRAS mutation frequency were tested for significance with the chi-square test. The Kaplan-Meier method was used to estimate 90-day, one-year, median and two-year OS, including 95 % confidence intervals (95 % CI). Variation in survival was tested for significance with the log-rank test. Multivariable analysis was performed using Cox proportional hazards regression, including age, gender, number of metastatic organs, metastatic organ involved, WHO PS, year and PD-L1 score. Independent prognostic factors were defined using backwards analysis. In all analyses a p-value of <0.05 was considered to be significant. KRAS was added to the final model and results are reported as hazard ratios (HR) with 95 % CI. Statistical analyses were performed using Stata 16.1.

3. Results

Between January 1 st, 2017 and December 31 st, 2018, a total of 595 patients with metastatic lung adenocarcinoma and PD-L1 ≥ 50 % were treated in the Netherlands with first line pembrolizumab [Fig. 1].

The median age at diagnosis was 65 years, interquartile range 59–72. Half of the patients were women and 10 % was diagnosed with PS 2 or higher [Table 1]. The majority of patients were diagnosed in 2018. More than half of the patients (57 %) was diagnosed with a KRAS mutation (n = 338), including 12 patients with combined mutations. Other mutations recorded in this cohort treated with first-line pembrolizumab were BRAF (n = 25), MET (n = 13), HER2 (n = 5) and uncommon EGFR (n = 5). The study base did not include patients with classical activating EGFR mutations (exon 19 deletion or L858R mutation), ALK translocation or ROS1 rearrangement as they were not treated in the first-line with ICI but with targeted therapies. KRAS mutation was seen more frequently in women (65 %) than in men (49 %), p < 0.001. Other baseline characteristics were similar between KRAS mutated and wild type patients.

The median follow-up of censored cases was 19.1 months, and 317 patients (53 %) had died. OS at 90 days, 1 year and 2 year was 79 % (95 % CI 75–82), 57 % (95 % CI 53–61) and 44 % (95 % CI 39–48), respectively. The median survival was 17.2 months overall, and 19.2 months

Fig. 2. Overall survival by KRAS mutation status. Kaplan-Meier estimates of overall survival.

for patients with KRAS mutation versus 16.8 months for wild type patients [Fig. 2].

Univariable analysis suggested PS and the number of involved metastatic organs as the most significant prognostic factors [Table 2]. Two-year survival was 23 % for patients with PS 2 or higher, versus 42 % for PS 1 and 53 % for PS 0 [Fig. 3]. For patients with 1, 2, or ≥3 metastatic organs involved, two-year survival was 54 %, 43 % and 28 %, respectively [Fig. 4]. Two-year survival for patients with bone, brain, or liver metastasis was 31 %, 34 % and 32 %, respectively [Table 2].

Survival did not differ between age groups (p = 0.67).

Multivariable analysis revealed PS, number of metastatic organs and PD-L1 category as independent prognostic factors [Table 2]. For KRAS mutation status no prognostic influence was found (hazard ratio = 1.03, 95 % CI 0.83–1.29).

4. Discussion

For patients with metastatic lung adenocarcinoma treated with first-line pembrolizumab monotherapy KRAS mutation status had no prognostic influence (hazard ratio = 1.03, 95 % CI 0.83–1.29). Patients with a KRAS mutation had a median OS of 19.2 months, compared with 16.8 months for KRAS wild type patients (p = 0.86).

Recent data from ICI landmark trials in the second line and beyond setting suggested a better survival for KRAS mutated patients treated with immunotherapy compared to KRAS wild type patients [1,25]. Whether patients with KRAS mutated lung adenocarcinoma actually have a better OS compared to KRAS wild type patients, when treated with immuno-monotherapy in the first line remained unclear, as previous studies gave inconclusive results, and this has not been studied in a first line setting before [Table A1] [26–33].

Our study shows a 1-year OS of 57 %, a 2-year survival of 44 %, and a median OS of 17.2 months. KRAS mutations are more frequently seen in women than in men. Other trials and real-world studies studying the survival of patients with PD-L1 ≥ 50 % treated with first line pembrolizumab described a 1-year and 2-year OS of 59–70 % and 45–52 % respectively [3,39–41], with a median OS of 18.9–20.0 months [39,40]. The differences between our outcomes and those from previous studies could be explained by confounding effects of patient selection in the registration trials. In the studies from Reck et al., Mok et al. and Velcheti et al. only fit patients with a PS of 0–1 and few comorbidities were included and KRAS status was not used as primary comparator. Cortellini et al. showed in a multicenter retrospective study using real-world data a 1-year OS of approximately 57 %, and a median OS of 17.2 months [42]. These results are similar to ours [Table A2]. It is important to notice that in previous phase III studies not all included patients had adenocarcinoma type lung cancer [3,39,40,42]. Our observation that KRAS mutations were seen more frequently in women than in men is

Table 2
Prognostic factors for overall survival.

		n	Univariable analysis			Multivariable analysis	
			1-Year %	2-Year %	p-value	Hazard ratio	95 % CI
Age	18–59	167	54	44	0.67	–	
	60–69	216	58	47			
	≥70	212	58	40			
Gender	Men	296	56	38	0.07	–	
	Women	299	58	50			
WHO Performance Score	0	216	70	53	<0.001	1	
	1	244	53	42		1.45	1.11–1.90
	2–3	57	37	23		2.36	1.63–3.42
	Unknown	78	46	38		1.96	1.38–2.79
Number of Metastatic Organs	1	266	69	54	<0.001	1	
	2	174	56	43		1.54	1.17–2.02
	≥3	155	37	28		2.44	1.87–3.19
Metastatic Organ Involved	Bone	231	48	31	<0.001	–	
	Brain	125	46	34			
	Liver	86	35	32			
PD-L1	50–89	430	55	41	0.03	1	
	≥90	165	62	53		0.77	0.59–1.00*
Year	2017	172	60	47	0.44	–	
	2018	423	56	43			
KRAS	Mutant	338	56	43	0.86	1.03	0.83–1.29
	No	257	58	45		1	

Multivariable analysis was performed using Cox proportional hazards regression. Apart from KRAS, multivariable analysis only retained prognostic factors significant at 0.05 level. Abbreviations: PD-L1, programmed death-ligand 1; KRAS, Kirsten rat sarcoma; CI, confidence interval. *0.997 thus being statistically significant at 0.05 level.

Fig. 3. Overall survival by WHO Performance Score. Kaplan-Meier estimates of overall survival.

Fig. 4. Overall survival by number of metastatic organs involved. Kaplan-Meier estimates of overall survival.

remarkable as this is in contrast with other studies describing *KRAS* cohorts, and is probably due to the selection criteria we used [27,30,32]. Another explanation could be that there could have been a considerable presence of the *KRAS*^{G12C} submutation in this study population, as Nassar et al. described that the G12C submutation is found more frequently in white and black women, than in white and black men [43].

Strengths of the current study are that it is nationwide, with real-world data of the Netherlands Cancer Registry that represents the entire Netherlands and contains a large cohort in relation to other often much smaller studies. Since pembrolizumab monotherapy is in current guidelines the first line of therapy for fit patients with metastatic lung adenocarcinoma with a PD-L1 expression ≥50 % [5,6], there is no confounding effect of concomitant use of chemotherapy or best supportive care and only patients with a PD-L1 expression ≥50 % were included in this study. There are very limited confounding effects of other driver mutations in this study as they are treated with targeted therapy in the first line and are therefore excluded from our dataset. This could also explain the high percentage of patients with a *KRAS* mutation in this dataset (57 %), which is higher than the incidence of 20–40 % of *KRAS* mutation in unselected populations with lung adenocarcinoma described in the literature [19].

A limitation of this study is that no data concerning progression free survival, disease control, comorbidity, treatment response, side-effects, compliance to pembrolizumab or response to pembrolizumab was available in the registry. Overall survival also includes deaths from other causes, but cause of death information was not available.

3713 out of 6524 patients diagnosed with metastatic lung adenocarcinoma received systemic treatment (57 %), which is similar to other studies describing systemic treatment trends in The Netherlands [44, 45], and reflecting a high proportion of patients with a higher age and poor performance status.

KRAS mutated lung adenocarcinoma is a heterogeneous disease, with different types of submutations occurring on different alleles, each leading to different downstream signaling pathways. The most common submutation is *KRAS*^{G12C}, with a prevalence of 46 % [46]. There are also several mutations that can co-occur with *KRAS*. The most common is *TP53*, which is seen in 40 % of *KRAS* mutated lung adenocarcinomas. Co-mutations with *STK11* or *CDKN2A* are also found frequently. These occur in 32 % and 19.8 % of the *KRAS* mutated NSCLC, respectively

[19]. Data on these different types of submutations and possibly co-occurring mutations were not available in the registry and could thus be included in this study. Several other studies were performed to assess the influence of different subtypes of *KRAS* mutations and co-occurring mutations on disease control and survival. In retrospective studies there was no difference in survival between different submutations in patients treated with mainly chemotherapy, and with immunotherapy in a cohort of pretreated patients [7,47–49]. *KRAS* co-mutation with *TP53* is associated with a higher PD-L1 expression and a higher CD8+ T-cell infiltration, possibly increasing its susceptibility to immunotherapy [26]. *STK11* comutated tumors usually have lower levels of PD-L1 expression and patients with this specific comutation have a shorter progression free and OS [50,51]. It is unclear how many patients with a *KRAS/STK11* or other co-mutations were present in the now studied cohort and whether that influenced our results. Based on the mechanism of action of *KRAS*, one could hypothesize that there is prognostic value for some co-mutations, and mutation subtypes. This might be an interesting topic for future research.

4.1. Conclusion

In conclusion, this study shows no prognostic value for *KRAS* in lung adenocarcinoma patients, when treated with first-line monotherapy pembrolizumab. Further research should focus on the impact of different comutations, and mutation subtypes, as promising clinical trials aiming to target *KRAS*^{G12C} are enrolling [Table A3], and efforts are being made to also target other *KRAS* mutation subtypes. When performed in first-line, the comparator arm for randomized controlled trials should be a regular treatment schedule including immunotherapy.

CRediT authorship contribution statement

A.L. Noordhof and W.H. van Geffen contributed to the conception of the study, acquisition of data, and data analyses and wrote the first version of the manuscript. R.A.M. Damhuis contributed to the conception of the study and acquisition of data, data analyses and revised the manuscript. B.J.W. Venmans contributed to the conception of the study and revised the manuscript. L.E.L. Hendriks, A.J. de Langen and W. Timens contributed to acquisition of data and revised the manuscript. A.L. Noordhof, W.H. van Geffen, R.A.M. Damhuis, B. J.W. Venmans, L.E.L. Hendriks, A.J. de Langen and W. Timens authors approved the final version of the manuscript.

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Declaration of Competing Interest

AN has nothing to disclose. RD has nothing to disclose. LH reports other from Boehringer Ingelheim (fees for institution for advisory board), other from BMS (fees for institution for advisory board), other from Roche Genentech (travel support (self), ad board (institution)), grants from Roche Genentech, grants from Boehringer Ingelheim, other from AstraZeneca (mentorship program with key opinion leaders; funded by AstraZeneca), personal fees from Quadia, grants from AstraZeneca, other from Eli Lilly (ad board (institution)), other from Roche Genentech (ad board (institution)), other from Pfizer (ad board (institution)), other from MSD (speaker (institution), ad board (institution)), other from Takeda (ad board (institution)), non-financial support from AstraZeneca, non-financial support from Novartis, non-financial support from BMS, non-financial support from MSD/Merck, non-financial support from GSK, non-financial support from Takeda, non-financial support from Blueprint Medicines, non-financial support from Roche Genentech, other from Amgen (ad board (institution)), non-financial support from Janssen Pharmaceuticals, non-financial support from Mirati, outside the submitted work. AL reports grants from BMS, grants from MSD, grants from AstraZeneca, non-financial support from Merck, grants from Boehringer, non-financial support from Roche, outside the submitted work. WT reports personal fees from Roche Diagnostics/Ventana, personal fees from Merck Sharp Dohme, personal fees from Bristol-Myers-Squibb, personal fees from AbbVie, outside the submitted work. BV has nothing to disclose. WvG has nothing to disclose.

Appendix A

Table A1

Outcome differences between *KRAS*_{mut}- vs. *KRAS*_{wt}-patients when treated with mono-immunotherapy as described in previous literature.

Study	N, all patients	N, <i>KRAS</i> _{mut} - patients	Conclusion	HR for overall survival
Gianoncelli et al. 2020	160	43	No significant difference in OS and PFS between <i>KRAS</i> _{mut} - and <i>KRAS</i> _{wt} -patients	HR 0.81, 95 % CI 0.50–1.31
Cinausero et al. 2019	47	20	<i>KRAS</i> _{mut} -patients had a better PFS and OS compared to <i>KRAS</i> _{wt} -patients	HR 0.39, 95 % CI 0.17–0.89
Torralvo et al. 2020	38	21	<i>KRAS</i> _{wt} -patients had a DCR of 59% with 49% PR, PFS was 8.4 months and OS 16.8 months. <i>KRAS</i> _{mut} -patients had a DCR of 81% with 62% PR, PFS was 13.6 months and OS 18.5 months. No statistical analysis preformed	–
Guibert et al. 2019	97	31	No significant difference in PFS between <i>KRAS</i> _{mut} - and <i>KRAS</i> _{wt} -patients	–
Jeanson et al. 2019	282	162	No significant difference in ORR, PFS and OS between <i>KRAS</i> _{mut} - and <i>KRAS</i> _{wt} -patients	HR 0.93, 95 % CI 0.68–1.29
Passiglia et al. 2019	530	206	No significant difference in ORR, DCR, median PFS and median OS between <i>KRAS</i> _{mut} - and <i>KRAS</i> _{wt} -patients. <i>KRAS</i> _{mut} -patients did have a significant higher 3-months PFS than <i>KRAS</i> _{wt} -patients	–
Dong et al. 2017	23	8	<i>KRAS</i> _{mut} -patients had a significant better median PFS than <i>KRAS</i> _{wt} -patients	–
Karatasoglou et al. 2020	220	62	<i>KRAS</i> _{mut} -patients had a better OS than <i>KRAS</i> _{wt} -patients	–
Noordhof et al. 2021	595	338	No significant difference in OS between <i>KRAS</i> _{mut} - and <i>KRAS</i> _{wt} -patients	HR 1.03, 95 % CI 0.83–1.29

Abbreviations: *KRAS*, Kirsten rat sarcoma; *KRAS*_{mut}, *KRAS* mutational status; *KRAS*_{wt}, *KRAS* wild type status; OS, overall survival; PFS, progression free survival; DCR, disease control rate; PR, partial response; ORR, overall response rate.

Table A2

Overall survival with first-line pembrolizumab monotherapy (regardless of KRAS mutational status) as described in previous literature.

Study	N	1-year OS	Median OS (months)	2-year OS	Details
KN024 Reck (trial)	154	70,3 %	Not reached	52 %	<ul style="list-style-type: none"> • 81,2 % adenocarcinoma • PD-L1 $\geq$ 50 % • PS 0 and 1
KN042 Mok (trial)	299*	63,5 %	20,0	45 %	<ul style="list-style-type: none"> • Excluding EGFR of ALK • 64 % adenocarcinoma • PD-L1 $\geq$ 50 % • PS 0 and 1 • Excluding EGFR of ALK
Velcheti EHR cohort (real-world data)	423	59,1 %	18,9	–	<ul style="list-style-type: none"> • 71,4% adenocarcinoma • PD-L1 $\geq$ 50 % • PS 0 and 1
Velcheti SPOTLIGHT cohort (real-world data)	188	60,4 %	Not reached	–	<ul style="list-style-type: none"> • Excluding EFGR, ALK, ROS1 • 68,6 % adenocarcinoma • PD-L1 $\geq$ 50 % • PS 0 and 1
Cortellini (real-world data)	1026	–	17,2	–	<ul style="list-style-type: none"> • Excluding EGFR, ALK, ROS1 • 75,8 % adenocarcinoma • PD-L1 $\geq$ 50 % • PS 0-3
Noordhof (real-world data), this study	595	57 %	17,2	44 %	<ul style="list-style-type: none"> • 0,9% with EGFR mutation, and 0% with ALK translocation • 100 % adenocarcinoma • PD-L1 $\geq$ 50 % • PS 0-3 • No other driver mutations

Abbreviations: KRAS, Kirsten rat sarcoma; PD-L1, programmed death-ligand 1; PS, WHO performance score.

* Sub-population with PD-L1 $\geq$ 50 %.**Table A3**Single-agent inhibitors targeting KRAS^{G12C} in clinical development.

Drug	ClinicalTrials.gov registration
AMG 510	NCT03600883
AMG 510	NCT04625647
AMG 510	NCT04185883
MRTX849	NCT03785249
MRTX849	NCT04330664
JNJ-74699157	NCT04006301
LY3499446	NCT04165031
GDC-6036	NCT04449874
TNO155	NCT03114319
TAS0612	NCT04586270

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