Original Article

KRAS^{G12C}/TP53 co-mutations identify long-term responders to first line palliative treatment with pembrolizumab monotherapy in PD-L1 high (≥50%) lung adenocarcinoma

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Background: Pembrolizumab is a standard of care as first line palliative therapy in PD-L1 overexpressing (≥50%) non-small cell lung cancer (NSCLC). This study aimed at the identification of KRAS and TP53-defined mutational subgroups in the PD-L1 high population to distinguish long-term responders from those with limited benefit.

Methods: In this retrospective, observational study, patients from 4 certified lung cancer centers in Berlin, Germany, having received pembrolizumab monotherapy as first line palliative treatment for lung adenocarcinoma (LuAD) from 2017 to 2018, with PD-L1 expression status and targeted NGS data available, were evaluated.

Results: A total of 119 patients were included. Rates for KRAS, TP53 and combined mutations were 52.1%, 47.1% and 21.9%, respectively, with no association given between KRAS and TP53 mutations (P=0.24). By trend, PD-L1 expression was higher in KRAS-positive patients (75% *vs.* 65%, P=0.13). Objective response rate (ORR), median progression-free survival (PFS) and overall survival (OS) in the KRAS^{G12C} group (n=32, 51.6%) were 63.3%, 19.8 months (mo.) and not estimable (NE), respectively. Results in KRAS^{other} and wild type patients were similar and by far lower (42.7%, P=0.06; 6.2 mo., P<0.001; 23.4 mo., P=0.08). TP53 mutations alone had no impact on response and survival. However, KRAS^{G12C}/TP53 co-mutations (n=12) defined a subset of long-term responders (ORR 100.0%, PFS 33.3 mo., OS NE). In contrast, patients with KRAS^{other}/TP53 mutations showed a dismal prognosis (ORR 27.3%, P=0.002; PFS 3.9 mo., P=0.001, OS 9.7 mo., P=0.02).

Conclusions: A comprehensive assessment of KRAS subtypes and TP53 mutations allows a highly relevant prognostic differentiation of patients with metastatic, PD-L1 high LuAD treated upfront with pembrolizumab.

Keywords: Non-small cell lung cancer (NSCLC); checkpoint inhibitors; KRAS mutations; TP53 mutations

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Introduction

Pembrolizumab monotherapy is a highly effective standard-of-care in metastatic, programmed death ligand 1 positive (PD-L1 ≥50%) non-small cell lung cancer (NSCLC) (1,2). However, predictive biomarkers distinguishing long-term responders to immune checkpoint inhibitors (ICI) from those experiencing no or only a limited benefit are still an unmet medical need.

Assuming a positive correlation of tumor neoantigens and the respective immune host response, assessment of tumor mutational burden (TMB) may serve as a predictor to ICI treatment (3-6), but several constraints have prevented an extensive integration into daily clinical practice yet. Compared to next-generation sequencing (NGS)-based gene panel tests, TMB testing is substantially more tissue-, time- and cost-consuming and harmonization of methods and cut-offs used is lacking (5,7-10). Finally, prospective clinical trials using upfront immuno-oncologic approaches in metastatic NSCLC have not unanimously demonstrated a predictive value for TMB (11,12).

KRAS mutations account for approximately 30% of driver mutations in lung adenocarcinoma (LuAD) (13,14), but are just rarely identified in squamous carcinoma (15). No specific therapies have been established yet and prognosis, in general, is poor (16). They are clearly tobacco-related and associated to a higher PD-L1 expression (17) as well as TMB (18). As lung cancer is characterized by a high average number of somatic mutations in general (19), co-occurring mutations like TP53 became the focus of attention. In contrast to TMB, both are routinely investigated in NGS assays and, besides distinguishing distinct molecular subgroups, might identify responders to ICI (20,21). Hence, our retrospective study aimed at the identification of KRAS- and TP53-defined prognostic subsets of PD-L1 positive (≥50%) LuAD treated with pembrolizumab monotherapy as first line palliative treatment. We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-958).

Methods

Study population

For this retrospective study all patients from four certified lung cancer centers in Berlin, Germany, with relapsed or metastatic LuAD, without any actionable target mutation (ALK or ROS1 rearrangements, BRAF^{V600E} or EGFR mutations), with available results for PD-L1 testing and NGS panel diagnostics and having received first line palliative treatment with pembrolizumab in the period between January 2017 and December 2018 were included. The contributing centers were: Department of Infectious Diseases and Pulmonary Medicine at the Charité – Universitätsmedizin Berlin; Department of Pulmonary Medicine at the Evangelische Lungenklinik Berlin-Buch; Department of Pulmonary Medicine at the HELIOS Klinikum Emil-von-Behring, Lungenklinik Heckeshorn and the Department of Pulmonary Medicine at the Gemeinschaftskrankenhaus Havelhöhe.

Data collection and endpoints

Patients' baseline demographics [age, sex, performance status (PS), smoking behavior], tumor-specific data [date of diagnosis, histology, PD-L1 expression, molecular profiling (NGS), initial staging (cTNM), treatments], radiologic evaluation and outcome were collected using the respective hospital's tumor registry, site-specific clinical databases and individual charts. Follow-up data, when not documented in the respective clinical database, were obtained from the patients or their primary care physicians to minimize missing data.

Response was assessed according to national guidelines (22) using "Response Evaluation Criteria in Solid Tumors" (RECIST) version 1.1 (23). PFS was defined as the time in months from the date of first dose pembrolizumab to the first documented progression (RECIST-defined or death), OS as the time in months from the first dose pembrolizumab to death from any cause.

PD-L1 testing and targeted NGS used to characterize KRAS and TP53 mutations

PD-L1 expression was determined as the percentage of tumor cells with positive membranous staining using the E1L3N (n=80; Cell Signaling, Cambridge, UK) or QR1 antibody (n=39; Quartett Immunodiagnostics, Berlin, Germany). Scoring was determined counting ≥100 tumor cells by experienced thoracic pathologists. Multiplex PCR-based, targeted NGS assays used were the Ion AmpliSeq™ Colon and Lung Cancer Panel covering 22 genes (93 patients; Thermo Fisher Scientific, Waltham, USA) and the panel from the German Network Genomic Medicine, Cologne, Germany, covering 14 genes (26 patients) (24). Mutation status was assessed for TP53 and KRAS hotspot regions with focus on non-synonymous variants known or predicted to be pathogenic or non-functional.

Statistical analysis

Demographics and disease data were described and compared using the Pearson Chi^2-test, Fisher's exact test or Mann-Whitney U-test. The Kaplan-Meier method was used to estimate median PFS, time to treatment failure (TTF) and OS. P values comparing survival curves were calculated with log-rank tests. Hazard ratios were calculated using Cox proportional hazard regression. Analyses were performed using IBM SPSS statistics version 24 (IBM, Armonk, NY, USA). A P value <0.05 (two-tailed) was defined as statistically significant.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Charité Universitätsmedizin Berlin (approval number EA2/223/18) and individual consent for this retrospective analysis was waived (patient's written informed consent was obtained within the treatment contract as ICI were administered as standard of care).

Results

Baseline characteristics

A total of 153 patients had received pembrolizumab as first line palliative treatment from January 2017 until December 2018. One hundred and nineteen patients with available results for PD-L1 testing and targeted NGS assays and with LuAD or related histologies were included in this study. Median age at the beginning of ICI treatment was 68 years (range, 40–86) with a predominance of male patients (n=68, 57.8%). PS was 0–1 in 92 patients (77.3%), and 2 and 3 in 23 (19.4%) and 4 patients (3.4%), respectively. Ninety-eight patients were active or former smokers (91.6%), 9 patients had a history of never-smoking (8.4%). LuAD was the predominant histology in 95 patients (79.8%), adenosquamous carcinoma (ASqC), large cell carcinoma (LCC) and a not-otherwise specified (NOS) pattern were identified in 11 (9.3%), 1 (0.8) and 12 patients (10.1%), respectively. Median PD-L1 expression in the entire cohort was 75% (95% CI, 65–75%). Stage at primary diagnosis was III in 19 patients (16.0%) and IV in 100 patients (84.0%). Ten patients underwent a primary therapy with curative intent (8.4%) and received pembrolizumab after disease relapse. Rates for adrenal (ADR), brain (BRA), liver (HEP) and bone metastases (OSS) at the beginning of pembrolizumab were 16.8%, 20.2%, 10.1% and 27.7%, respectively. The main characteristics are reported in *Table 1*.

Frequency of KRAS mutations ($KRAS^{mut}$) was 52.1%, of whom 51.6% were $KRAS^{G12C}$ (*Figure 1A*). Non-synonymous TP53 mutations ($TP53^{mut}$) occurred in 47.1% of the patients, 58.9% displayed missense mutations (*Figure 1B*). No association between $KRAS^{mut}$ and $TP53^{mut}$ was observed (P=0.24). Rates of wild type patients, $KRAS^{mut}$ or $TP53^{mut}$ alone, and KRAS/TP53 co-mutations were 22.7%, 30.3%, 25.2% and 21.8%, respectively (*Figure 1C*). By trend, PD-L1 expression was higher in $KRAS^{mut}$ tumors (75 *vs.* 65%, P=0.13). Whereas no differences were observed among KRAS subgroups, $KRAS^{G12C}$/$TP53^{mut}$ tumors more frequently had a PD-L1 expression within the highest percentile (≥90%: 41.7% *vs.* 20.0%, P=0.14). Expression levels were similar among TP53 subsets. Apart from a trend to a higher rate of current/former smokers in $KRAS^{mut}$ patients (96.5% *vs.* 86.0%, P=0.08), clinical baseline characteristics were similar across all molecularly defined groups.

Treatment characteristics and RECIST-evaluation

All treatment characteristics are listed in *Tables 2,3*. Median follow-up was 26.4 months for the entire cohort. The median number of cycles administered, duration of therapy and rate of patients still on treatment were 10, 8.2 months and 19.3%, respectively. RECIST-based evaluation was

Table 1 Patients' baseline demographics for all patients, KRAS mutations, KRAS subgroups, TP53 mutations and KRAS/TP53 co–mutations

Variable	All patients (n=119)	KRAS^{mut} (n=62)	KRAS^{wt} (n=57)	P value	KRAS^{G12C} (n=32)	KRAS^{other} (n=30)	P value	TP53^{mut} (n=56)	TP53^{wt} (n=63)	P value	KRAS^{G12C}/ TP53^{mut} (n=12)	KRAS^{other}/ TP53^{mut} (n=14)	P value
Age, y (median, range)	68 [40–86]	66 [45–85]	69 [40–86]	0.53	65 [53–84]	67 [45–85]	0.75	66 [40–86]	68 [48–86]	0.25	62 [53–77]	66 [45–81]	0.90
Sex, n (%)				0.20			0.22			0.14			1.0
Female	51 (42.9)	30 (48.4)	21 (36.8)		14 (43.8)	12 (40.0)		28 (50.0)	23 (36.5)		6 (50.0)	7 (50.0)	
Male	68 (57.8)	32 (51.6)	36 (63.2)		18 (56.3)	18 (60.0)		28 (50.0)	40 (63.5)		6 (50.0)	7 (50.0)	
ECOG–PS, n (%, 0–1 *vs.* ≥2)				0.18			0.19			0.90			0.37
0–1	92 (77.3)	51 (82.3)	41 (71.9)		24 (75.0)	27 (90.0)		43 (76.8)	49 (77.8)		8 (66.7)	12 (85.7)	
2	23 (19.3)	9 (14.5)	14 (24.6)		6 (18.8)	3 (10.0)		13 (23.2)	10 (15.9)		4 (33.3)	2 (14.3)	
3	4 (3.4)	2 (3.2)	2 (3.5)		2 (6.3)	0		0	4 (6.3)		0	0	
Smoking history, n (%)				0.08			1.0			1.0			1.0
Current or former smoker	98 (91.6)	55 (96.5)	43 (86.0)		28 (96.6)	27 (96.4)		49 (92.5)	49 (90.7)		12 (100.0)	14 (100.0)	
Never smoker	9 (8.4)	2 (3.5)	7 (14.0)		1 (3.4)	1 (3.3)		4 (7.5)	5 (9.3)		0	0	
Missing data	12 (–)	5 (–)	7 (–)		1 (–)	2 (–)		3 (–)	9 (–)		0	0	
Histology, n (%, LuAD *vs.* other)				0.49			1.0			0.89			0.64
Adenocarcinoma (LuAD)	95 (79.8)	51 (82.3)	44 (77.2)		26 (81.3)	25 (83.3)		45 (80.4)	50 (79.4)		9 (75.0)	12 (85.7)	
Other	24 (20.2)	11 (17.7)	13 (22.8)		6 (18.8)	5 (16.7)		11 (19.6)	13 (20.6)		3 (25.0)	2 (14.3)	
Adenosquamous carcinoma (ASQ)	11 (9.3)	5 (8.0)	6 (10.6)		3 (9.4)	2 (6.7)		5 (8.9)	6 (9.6)		1 (8.3)	0	
Large cell carcinoma (LCC)	1 (0.8)	1 (1.6)	0(0)		0	1 (3.3)		1 (1.8)	0		1 (8.3)	1 (7.1)	
Not otherwise specified (NOS)	12 (10.1)	5 (8.1)	7 (12.3)		3 (9.4)	2 (6.7)		5 (8.9)	7 (11.1)		1 (8.3)	1 (7.1)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	All patients (n=119)	KRAS^{mut} (n=62)	KRAS^{wt} (n=57)	P value	KRAS^{G12C} (n=32)	KRAS^{other} (n=30)	P value	TP53^{mut} (n=56)	TP53^{wt} (n=63)	P value	KRAS^{G12C}/ TP53^{mut} (n=12)	KRAS^{other}/ TP53^{mut} (n=14)	P value
PD–L1 expression (%TC), median (95% CI)	75 [65–75]	75 [65–83]	65 [65–75]	0.13	75 [55–85]	75 [70–85]	0.38	73 [65–75]	75 [65–80]	0.72	75 [60–95]	70 [63–78]	0.67
50–59%, n (%)	34 (28.6)	16 (25.8)	18 (31.6)		11 (34.4)	5 (16.7)		14 (25.0)	20 (31.7)		3 (25.0)	2 (14.3)	
60–69%, n (%)	20 (16.8)	8 (12.9)	12 (21.1)		3 (9.4)	5 (16.7)		13 (23.2)	7 (11.1)		2 (16.7)	5 (35.7)	
70–79%, n (%)	23 (19.3)	12 (19.4)	11 (19.3)		6 (18.8)	6 (20.0)		11 (19.6)	12 (19.0)		2 (16.7)	3 (21.4)	
80–89%, n (%)	17 (14.3)	11 (17.7)	6 (10.5)		4 (12.5)	7 (23.3)		3 (5.4)	14 (22.2)		0	1 (7.1)	
90–100%, n (%)	25 (21.0)	15 (24.2)	10 (17.5)		8 (25.0)	7 (23.3)		15 (26.8)	10 (15.9)		5 (41.7)	3 (21.4)	
Stage at primary diagnosis				0.45			1.0			0.98			0.20
III	19 (16.0)	8 (12.9)	11 (19.3)		4 (12.5)	4 (13.3)		9 (16.1)	10 (15.9)		2 (16.7)	0	
IV	100 (84.0)	54 (87.1)	46 (80.7)		28 (87.5)	26 (86.7)		47 (83.9)	53 (84.1)		10 (83.3)	14 (100.0)	
Prior treatment with curative intent, n (%)	10 (8.4)	4 (6.5)	6 (10.5)	0.52	1 (3.1)	3 (10.0)	0.35	5 (8.9)	5 (7.9)	0.85	0	1 (7.1)	1.0
Metastatic sites at the begin of IO, n (%)													
ADR	20 (16.8)	8 (12.9)	12 (21.1)	0.33	4 (12.5)	4 (13.3)	1.0	11 (19.6)	9 (14.3)	0.47	1 (8.3)	2 (14.3)	1.0
BRA	24 (20.2)	13 (21.0)	11 (19.3)	0.82	7 (21.9)	6 (20.0)	1.0	15 (26.8)	9 (14.3)	0.11	5 (41.7)	5 (35.7)	1.0
HEP	12 (10.1)	4 (6.5)	8 (14.0)	0.23	1 (3.1)	3 (10.0)	0.35	7 (12.5)	5 (7.9)	0.55	1 (8.3)	1 (7.1)	1.0
OSS	33 (27.7)	17 (27.4)	16 (28.1)	0.94	9 (28.1)	8 (26.7)	1.0	15 (26.8)	18 (28.6)	0.84	4 (33.3)	3 (21.4)	0.67

*, P<0.05; CI, confidence interval; ECOG–PS, Eastern Co–operative Oncology Group Performance Status; %TC, percentage of positive tumor cells; ADR, adrenal metastases; BRA, brain metastases; HEP, liver metastases; OSS, bone metastases; KRAS^{mut}, KRAS mutation; KRAS^{wt}, KRAS wildtype; KRAS^{other}, KRAS mutation other than KRAS^{G12C}; TP53^{mut}, TP53 mutation; TP53^{wt}, TP53 wildtype.

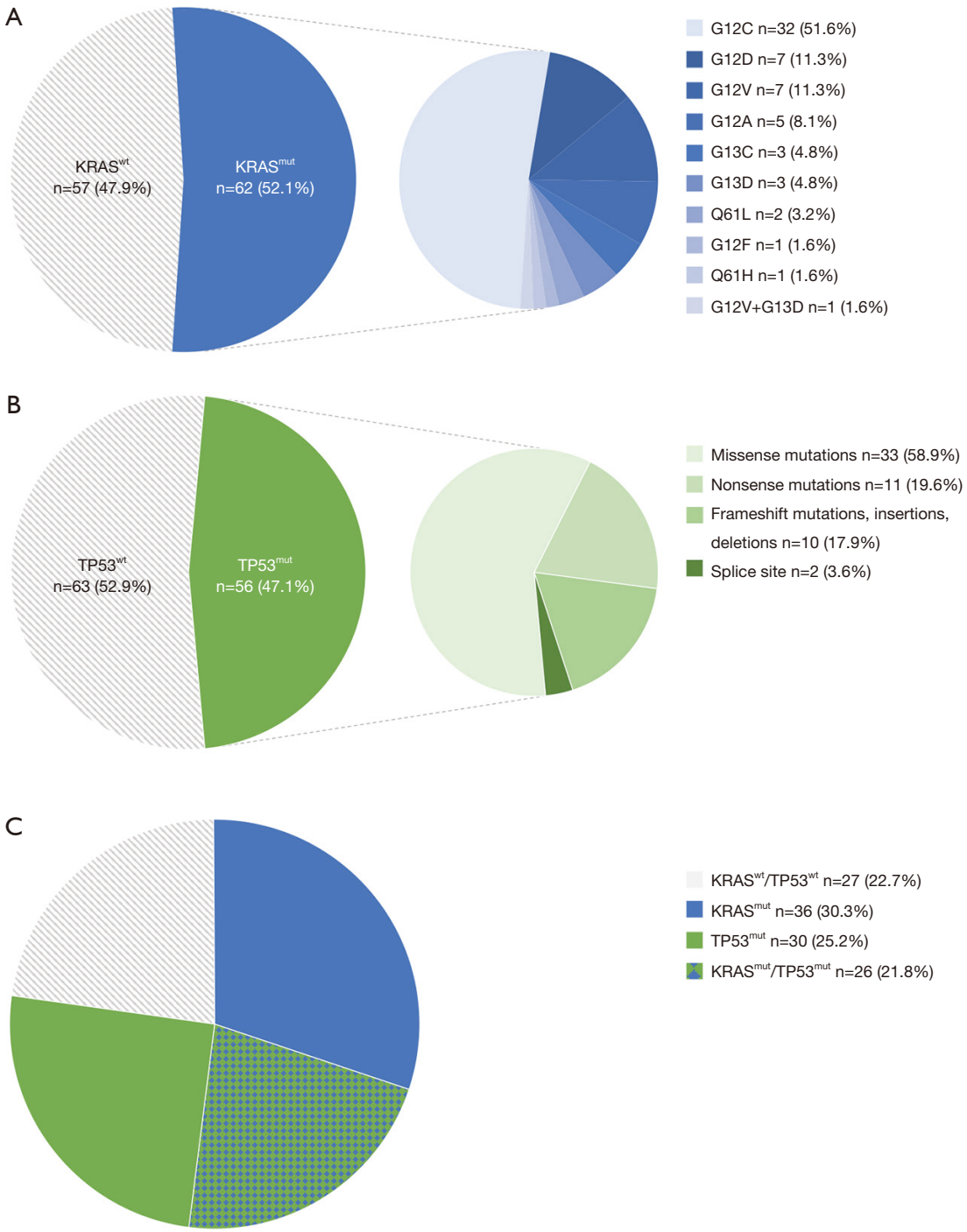

Figure 1 Distribution of KRAS mutations (A), TP53 mutations (B) and mutational pattern according to both mutations (C). KRAS^{mut}, KRAS mutation; KRAS^{wt}, KRAS wild type; TP53^{mut}, TP53 mutation; TP53^{wt}, TP 53 wild type.

Table 2 Treatment characteristics and response according to RECIST 1.1 for all patients (left column), KRAS-mutations (second column from left side), KRAS subgroups (third column from left side) and TP53 mutations (right column)

Variable	All patients (n=119)	$KRAS^{mut}$ (n=62)	$KRAS^{wt}$ (n=57)	P value	$KRAS^{G12C}$ (n=32)	$KRAS^{other}$ (n=30)	P value	$TP53^{mut}$ (n=56)	$TP53^{wt}$ (n=63)	P value
Cycles administered, n [range]	10 [1–58]	11 [1–45]	8 [1–58]	0.19	20 [1–38]	9 [1–45]	0.05*	11 [1–43]	9 [1–58]	0.95
Follow-Up, months (median, 95% CI)	26.4 (24.3–28.5)	28.9 (26.1–31.6)	23.0 (19.9–26.1)	0.05*	26.9 (23.6–30.1)	30.7 (27.3–34.2)	0.18	23.7 (9.8–27.5)	28.0 (23.8–32.1)	0.07
Duration of treatment, months (median, 95% CI)	8.2 (5.5–11.0)	11.2 (6.2–16.2)	6.2 (2.1–10.3)	0.20	20.0 (12.3–27.6)	7.6 (4.7–10.5)	0.03*	7.2 (4.8–9.6)	10.0 (3.4–16.7)	0.51
Therapy ongoing, n (%)	21 (17.6)	11 (17.7)	10 (17.5)	0.98	9 (28.1)	2 (6.7)	0.03*	14 (25.0)	7 (11.1)	0.06
RECIST-evaluation available, n (%)	105 (88.2)	55 (88.7)	50 (87.7)	1.0	30 (93.8)	25 (83.3)	0.20	50 (89.3)	55 (87.3)	0.78
ORR, % [95% CI]	48.6 [39–58]	50.9 [36–64]	46.0 [32–60]	0.62	63.3 [47–80]	36.0 [20–56]	0.05*	52.0 [38–66]	45.5 [33–58]	0.51
DCR, % [95% CI]	79.0 [71–86]	83.6 [73–93]	74.0 [62–86]	0.23	86.7 [73–97]	80.0 [64–92]	0.51	76.0 [64–88]	81.8 [71–91]	0.47

Table 3 Treatment characteristics and response according to RECIST 1.1 depending on the KRAS/TP53 co–mutational status and for $KRAS^{G12C}$/TP53, respectively

Variable	$KRAS^{wt}$/ $TP53^{wt}$ (n=27)	$KRAS^{mut}$/ $TP53^{wt}$ (n=36)	$KRAS^{wt}$/ $TP53^{mut}$ (n=30)	$KRAS^{mut}$/ $TP53^{mut}$ (n=26)	P value	$KRAS^{G12C}$/ $TP53^{mut}$ (n=12)	$KRAS^{G12C}$/ $TP53^{wt}$ (n=20)	$KRAS^{other}$/ $TP53^{mut}$ (n=14)	$KRAS^{other}$/ $TP53^{wt}$ (n=16)	P value
Cycles administered, n [range]	11 [1–45]	15 [1–45]	12 [1–43]	10 [1–38]	0.48	28 [2–37]	13 [1–38]	7 [1–38]	16 [2–45]	0.03*
Follow-up, months (median, 95% CI)	25.6 (20.9–30.4)	29.2 (24.7–33.7)	21.3 (17.5–25.2)	28.9 (19.3–38.4)	0.02*	26.9 (19.0–34.7)	28.0 (23.7–32.2)	29.3 (20.5–38.1)	30.7 (24.3–37.1)	0.33
Duration of treatment, months (median, 95% CI)	3.2 (1.2–5.3)	12.4 (9.7–15.0)	7.2 (4.6–9.7)	6.8 (3.1–10.5)	0.41	22.0 (16.7–26.4)	12.4 (0.8–24.0)	4.1 (0.1–11.8)	12.3 (9.0–15.7)	0.01*
Therapy ongoing, n (%)	11 (17.7)	4 (11.1)	7 (23.3)	7 (26.9)	0.26	6 (50.0)	3 (15.0)	1 (7.1)	1 (6.3)	0.01*
RECIST-evaluation available, n (%)	22 (81.5)	33 (91.7)	28 (93.8)	22 (84.6)	0.45	11 (91.7)	19 (95.0)	11 (78.6)	14 (87.5)	0.51
ORR, % [95% CI]	50.0 [32–73]	42.4 [24–61]	42.9 [25–61]	63.6 [41–82]	0.42	100.0 [100–100]	42.1 [21–63]	27.3 [9–55]	42.9 [14–71]	0.003*
DCR, % [95% CI]	77.3 [59–96]	84.8 [70–97]	71.4 [54–86]	81.8 [64–96]	0.62	100.0 [100–100]	78.9 [58–95]	63.6 [36–91]	92.9 [79–100]	0.09

*, P<0.05. CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; DCR, disease control rate; KRAS+, KRAS mutation; KRAS–, KRAS wildtype; $KRAS^{other}$, KRAS mutation other than $KRAS^{G12C}$; TP53+, TP53 mutation; TP53–, TP53 wildtype.

available for 105 patients (88.2%), showing an objective response rate (ORR) and disease control rate (DCR) of 48.6% and 79.0%, respectively. Treatment characteristics and responses were comparable for KRAS^{mut} and TP53^{mut} as well as wild type patients (*Table 2*). However, patients with KRAS^{G12C} as compared to KRAS^{other} were significantly longer on therapy (20.0 *vs.* 7.6 months, P=0.03) and ORR was markedly higher (63.3% *vs.* 36.0%, p=0.05). Patients with KRAS^{G12C}/TP53^{mut} (n=12) had the longest duration of therapy (22.0 months) and all patients showed a response (ORR 100.0%, *Table 3*).

Survival analyses

Median PFS was 8.8 months (92 events, 77.3% of patients, 95% CI, 4.6–12.9). KRAS^{mut} patients displayed an improved PFS (13.3 *vs.* 6.2 months; HR, 0.66, 95% CI, 0.43–1.0, P=0.05, *Figure 2A*), whereas TP53 status had no impact (8.0 *vs.* 9.7 months; HR 0.97, 95% CI, 0.64–1.46, P=0.88, *Figure 2B*). The substantial increase in KRAS^{mut} was strongly driven by KRAS^{G12C} [19.8 *vs.* 5.8 months (KRAS^{other}); HR, 0.37, 95% CI, 0.20–0.68, P=0.001, *Figure 2C*], whereas results for KRAS^{other} and wild type patients (KRAS^{wt}) were nearly identical. KRAS^{G12C}/TP53^{mut} patients experienced the by far longest PFS (33.3 months; 95% CI, not estimable (NE), 1- and 2-year PFS 83% and 67%) as compared to KRAS^{G12C}/TP53^{wt} (15.6 months; 95% CI, 10.8–20.4, HR, 0.48, 95% CI, 0.17–1.35, P=0.16), KRAS^{other}/TP53^{wt} (13.1 months; 95% CI, 10.3–15.9; HR 0.23, 95% CI, 0.08–0.72, P=0.01) and KRAS^{other}/TP53^{mut}, the latter group displaying the worst PFS (2.8 months; 95% CI, 0.0–6.2; HR, 0.18, 95% CI, 0.06–0.53, P=0.002, *Figure 2D*). Patients displaying a PD-L1 expression <70% had a 1.7-fold decreased PFS (HR, 1.72, 95% CI, 1.14–2.60, P=0.01). In multivariate analysis, smoking history and KRAS subtypes were identified as independent predictors for PFS (*Table 4*).

Patients treated beyond RECIST-defined progression (n=19, 22.9%) due to a sustained clinical benefit displayed a time-to-treatment-failure (TTF) of 14.0 months. The probability for a treatment beyond progression was higher in KRAS^{mut} patients (33.3% *vs.* 13.6%, P=0.04). However, TTF was not different according to KRAS mutational status (KRAS^{mut} *vs.* KRAS^{wt}, 9.0 *vs.* 6.2 months, P=0.27) and within KRAS subgroups, respectively.

Median OS reached 23.6 months (61 events, 51.3% of patients, 95% CI, 15.0–32.2) and was neither influenced by KRAS (HR, 0.92, 95% CI, 0.55–1.52, P=0.74, *Figure 3A*) nor TP53 mutational status (HR, 0.85, 95% CI, 0.51–1.41, 0.85, P=0.52, *Figure 3B*). Patients with KRAS^{G12C} experienced a longer OS by trend (HR, 0.50, 95% CI, 0.25–1.01, P=0.06, *Figure 3C*). Again, survival was strongly influenced by KRAS^{G12C}/TP53^{mut} (median OS not yet reached; 1- and 2-year OS 92% and 79%), as compared to KRAS^{G12C}/TP53^{wt} (17.9 months; 95% CI, 12.0–23.8; 1- and 2-year OS 79% and 41%, HR, 0.24, 95% CI, 0.05–1.07, P=0.06) and KRAS^{other}/TP53^{wt} (22.0 months; 95% CI, 13.6–30.6, 1- and 2-year OS 81% and 44%, HR, 0.23, 95% CI, 0.05–1.05, P=0.06). KRAS^{other}/TP53^{mut} patients experienced the shortest OS (9.7 months; 95% CI, 2.4–17.0; 1- and 2-year OS 48% and 30%, HR, 0.17, 95% CI, 0.04–0.76, P=0.02, *Figure 3D*). A PD-L1 expression level of <70% was associated with a reduced OS (HR, 1.93, 95% CI, 1.16–3.20, P=0.01). In multivariate analysis, the initial PS and molecular status independently predicted OS, with the best HR for KRAS^{G12C}/TP53^{mut} (0.20, P=0.03, *Table 3*).

Discussion

This investigation identified patients with KRAS^{G12C}/TP53^{mut} LuAD as long-term responders benefitting most from upfront pembrolizumab. All patients in this molecularly defined subgroup responded to ICI treatment. Our study cohort was markedly enriched by KRAS mutations, present in >50% of the patients (13), subgroups showed the normal distribution pattern of KRAS^{mut} LuAD. KRAS^{mut} patients had a higher PD-L1 expression, probably resulting from KRAS-induced stabilization of PD-L1 (25). A better response to ICI in KRAS^{mut} patients may be attributable to a "KRAS phenotype", clinico-pathologically characterized by its tobacco-association, PD-L1 positivity and an inflamed tumor microenvironment (26). However, results from prospective clinical trials and real-world data are conflicting. A meta-analysis including 509 patients from 3 second and further line studies with ICI demonstrated an OS benefit in KRAS mutations as compared to wild type patients (HR, 0.64, 95% CI, 0.43–0.96, P=0.03) (27). In contrast, real-world data with nivolumab from the Italian expanded access program analyzing 530 patients in the second and further line setting (PFS 4 *vs.* 3 months, P=0.56; OS 11.2 *vs.* 10 months, P=0.86) (28) and a French investigation with 282 patients having received ICI in all lines of therapy showed no survival differences (HR for PFS and OS 0.93) (29). Altogether, patient populations were very heterogeneous; only one study included first line patients and this to a very small degree (8.5%).

Our results suggest that looking on the KRAS mutational

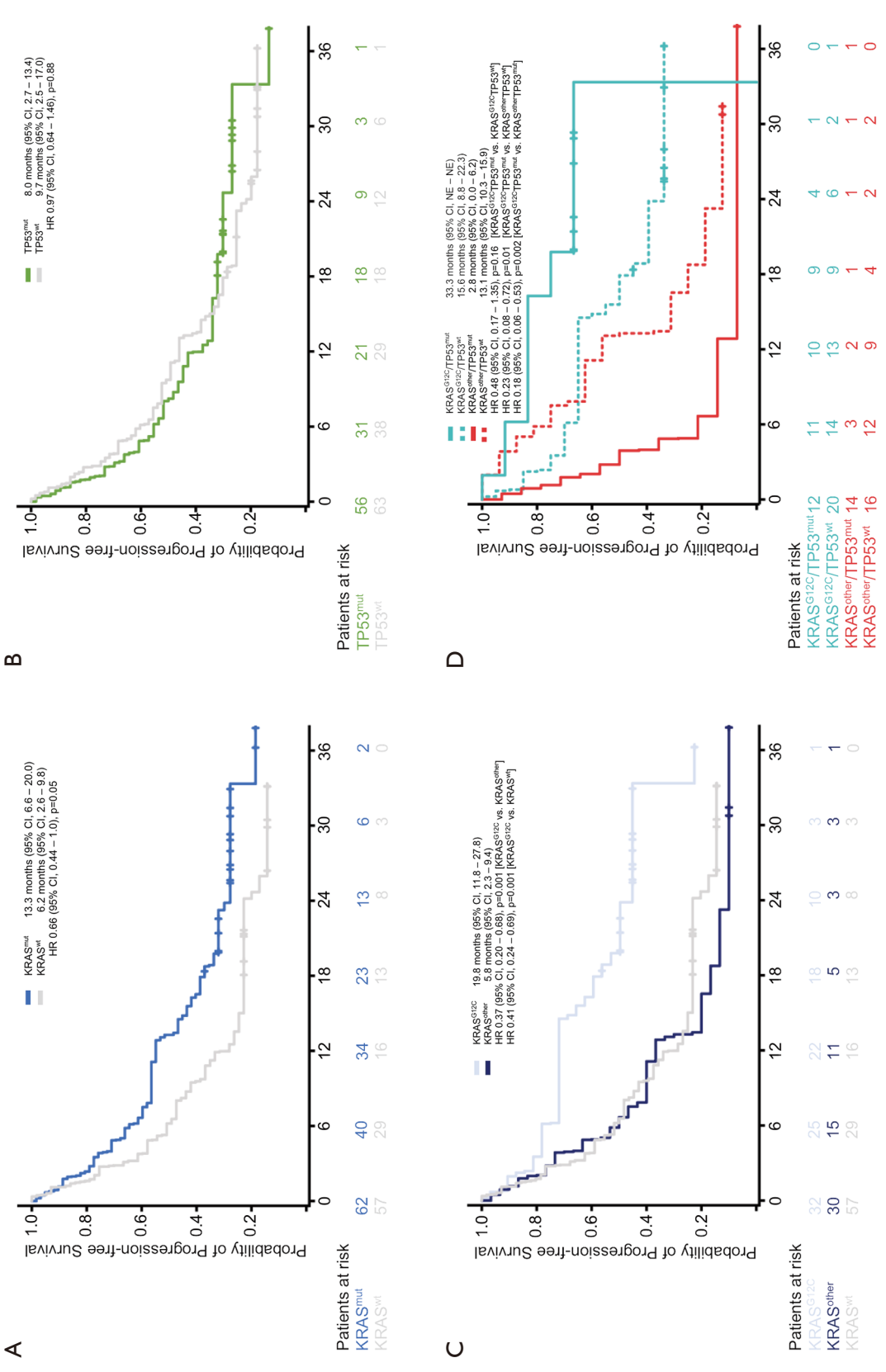

Figure 2 Kaplan-Meier curves for progression-free survival (PFS) depending on KRAS mutational status (A), TP53 mutational status (B), KRAS subgroups ($KRAS^{G12C}$ *vs.* $KRAS^{other}$) (C) and KRAS/TP53 co-mutations ($KRAS^{G12C}/TP53^{mut}$ *vs.* $KRAS^{G12C}/TP53^{wt}$ *vs.* $KRAS^{other}/TP53^{mut}$ *vs.* $KRAS^{other}/TP53^{wt}$ (D).

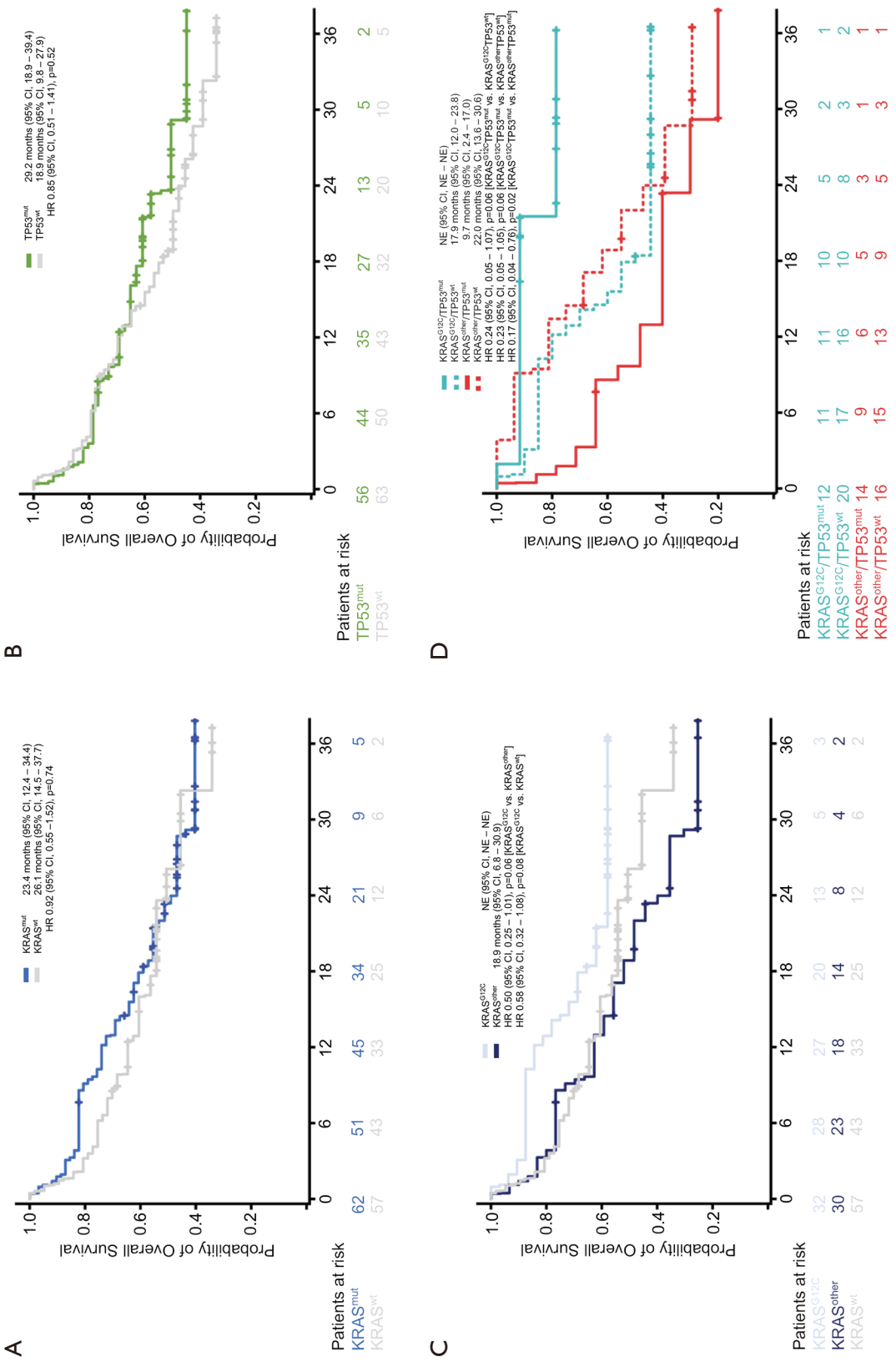

Figure 3 Kaplan-Meier curves for overall survival (OS) depending on KRAS mutational status (A), TP53 mutational status (B), KRAS subgroups (KRAS^{G12C} *vs.* KRAS^{other} mutations (C) and KRAS/TP53 co-mutations (KRAS^{G12C}/TP53^{mut} *vs.* KRAS^{G12C}/TP53^{wt} *vs.* KRAS^{other}/TP53^{mut} *vs.* KRAS^{other}/TP53^{wt} (D).

Table 4 Univariate and multivariate Cox proportional hazard regression analysis for PFS and OS

Variable	Univariate analysis (PFS)			Multivariate analysis (PFS)			Univariate analysis (OS)			Multivariate analysis (OS)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age												
<70 *vs.* ≥70 years	1.09	0.72–1.64	0.70				0.79	0.48–1.31	0.37			
Sex												
Female *vs.* male	1.08	0.71–1.64	0.72				0.94	0.56–1.56	0.80			
ECOG-PS												
0–1 *vs.* ≥2	0.71	0.43–1.17	0.18				0.43	0.25–0.74	0.003*	0.40	0.23–0.71	0.002*
Smoking history												
Current or former *vs.* never smoker	0.36	0.18–0.72	0.004*	0.43[a]	0.21–0.89	0.02*	0.45	0.19–1.06	0.07			
				0.49[b]	0.24–1.01	0.05*						
				0.43[c]	0.21–0.89	0.02*						
Histology												
Adenocarcinoma (LuAD) *vs.* other	1.14	0.68–1.91	0.62				0.82	0.46–1.46	0.50			
PD–L1 expression (%TC)												
<70 *vs.* ≥70%	1.72	1.14–2.60	0.01*	1.41[a]	0.90–2.21	0.13	1.93	1.16–3.20	0.01*	1.65	0.98–2.76	0.06
				1.51[b]	0.97–2.35	0.07						
				1.40[c]	0.90–2.19	0.13						
Molecular alteration												
KRAS (pos. *vs.* neg.)	0.66	0.44–1.00	0.05*	0.75	0.48–1.18	0.13	0.92	0.55–1.52	0.73			
$KRAS^{G12C}$ (pos. *vs.* $KRAS^{other}$/$KRAS^{wt}$)	0.41	0.24–0.69	0.001*	0.42	0.24–0.73	0.002*	0.58	0.32–1.08	0.08			
$KRAS^{G12C}$/$TP53^{mut}$ (pos. *vs.* else)	0.30	0.12–0.74	0.009*	0.32	0.13–0.80	0.02*	0.23	0.06–0.93	0.04*	0.20	0.05–0.82	0.03*
TP53 (pos. *vs.* neg.)	0.97	0.64–1.46	0.88				0.85	0.51–1.41	0.52			
Stage at primary diagnosis												
III *vs.* IV	1.09	0.63–1.90	0.76				0.78	0.37–1.65	0.78			
Metastatic sites at the begin of IO, n (%)												
ADR (Y *vs.* N)	1.26	0.74–2.14	0.39				1.34	0.71–2.51	0.37			
BRA (Y *vs.* N)	1.00	0.60–1.66	1.00				1.10	0.60–2.04	0.76			
HEP (Y *vs.* N)	0.75	0.36–1.55	0.44				0.82	0.33–2.06	0.67			
OSS (Y *vs.* N)	0.88	0.55–1.40	0.58				0.97	0.56–1.71	0.92			

*, P<0.05; [a], HR for KRAS (pos. *vs.* neg.); [b], HR for $KRAS^{G12C}$ (pos. *vs.* $KRAS^{else}$/$KRAS^{wt}$); [c], HR for $KRAS^{G12C}$/$TP53^{mut}$ (pos. *vs.* else); CI, confidence interval; ECOG-PS, Eastern Co-operative Oncology Group Performance Status; %TC, percentage of positive tumor cells; ADR, adrenal metastases; BRA, brain metastases; HEP, liver metastases; OSS, bone metastases.

status as positive or negative alone may be inadequate, as substantial differences between KRAS^{G12C} and KRAS^{other} are given for response and survival. Smoking behavior is correlated to a distinct spectrum of KRAS mutations with KRAS^{G12D} more frequently observed in never smokers and KRAS^{G12C} being the predominant mutation in smokers (30). The lower probability for a high TMB in KRAS^{G12D} mutations might provide a molecular rationale for different responses to IO, whereas KRAS^{G12C} mutations display higher shares of PD-L1 positivity (≥50%) as well as high TMB (31). A prognostic value of KRAS^{G12C} remained to be demonstrated, as KRAS subtyping, if determined, showed no survival difference in the second- and further line setting (29,32). An exploratory analysis from the Keynote-042 study recently suggested a moderate benefit in ORR (67% *vs.* 57%), PFS (15 *vs.* 12 months) and OS (not reached *vs.* 28 months) in favor of KRAS^{G12C} *vs.* KRAS^{other}, but the subgroup of patients with PD-L1 ≥50% has not been reported separately (33).

Analogous to KRAS^{mut}, TP53^{mut} are associated with an enhanced PD-L1 expression (34,35). These cancers are molecularly characterized by neoantigen accumulation-induced tumor immunogenicity, resulting from a loss of function of this transcriptional key player in cell homeostasis. In PD-L1 non-selected metastatic NSCLC, TP53^{mut} consequently increased response to ICI and improved OS (HR, 0.48, 95% CI, 0.25–0.95, P=0.04) (36). In contrast, no relationship between TP53 and response or outcome was obvious in our study, although OS was numerically also in favor of TP53^{mut}. Interestingly, a large and sustained clinical benefit was observed in KRAS^{G12C}/TP53^{mut}, associated to a higher share of highest PD-L1 expression levels (≥90%: 41.7% *vs.* 20.0% in KRAS^{other}). We identified a PD-L1 expression ≥70% as threshold for an improved survival, but observed an even more pronounced benefit in patients with a PD-L1 expression ≥90% (ORR, PFS and OS 68.0%, 13.1 months and NE *vs.* 42.5%, 6.2 and 18.9 months in PD-L1 <90%), thereby confirming recently published findings (37).

The favorable outcome observed in these co-mutated subgroups might thus result from synergistic and complementary effects on PD-L1 expression, TMB and cell cycle repair mechanisms mediated independently by KRAS^{mut} and TP53^{mut} and leading to an inflamed tumor microenvironment with adaptive immune resistance and high immunogenicity (35). In an exploratory analysis from the Keynote-001 trial, all patients with KRAS^{mut}/TP53^{mut} were also PD-L1 high (≥50%) and experienced a durable clinical benefit (35). Similar results have been reported from real life cohorts (38,39). However, as KRAS subgroups have not been investigated separately, it remains unclear, whether a "KRAS-TP53-synergy" is independent from the specific KRAS^{mut} or rather might be strongly relying on KRAS^{G12C}/TP53^{mut}.

To the best of our knowledge, our investigation is the first one demonstrating a strong prognostic value for KRAS^{G12C}/TP53^{mut} in the PD-L1 high population. Its strength is a clear focus on a well-defined, uniform patient population in contrast to studies including patients irrespective from PD-L1 strata and line of therapy. The thereby resulting heterogeneity may not only make comparisons impossible, but might also dilute an impact of KRAS and TP53 mutations, as these molecularly defined cohorts might perform differently according to the PD-L1 expression levels.

Recently and after years of discouraging research, promising results have been published for the first small molecules directly targeting specific KRAS mutations. Sotorasib and MRTX849 selectively inhibit KRAS-dependent signaling by modifying mutant cysteine 12 in GDP-bound KRAS^{G12C} (40,41) and are currently investigated in clinical trials. Comparing different modes of action, with ICI on the one hand and specific tyrosine kinase inhibitors on the other, it is tempting to speculate, which therapeutic option for patients with KRAS^{G12C}/TP53^{mut} might perform best.

This study has several limitations. Due to its retrospective design, a certain selection bias in favor of patients displaying a better PS cannot be excluded. As only patients with available PD-L1 expression and parallel NGS testing were included, those with a clinically unfavorable prognosis due to a reduced PS in whom molecular testing may have been omitted were not analyzed. Second, the use of different diagnostic antibodies (22C3 in the KEYNOTE trials, E1L3N and QR1 in our investigation) as well as the examination by different pathologists might have biased results for PD-L1 staining. However, a growing body of evidence supports the comparability of different standardized assays and laboratory-developed tests (42,43). All participating centers were certified by the quality management initiative of the German Society of Pathology (QuIP®) after having successfully passed round-robin tests for PD-L1 testing, therefore results can be regarded as comparable. Third, TMB was not evaluated. Thus, molecular groups may be unbalanced and outcome may be biased by a higher neoantigen load in KRAS^{G12C}/

TP53^{mut} patients (35,44). Forth, we did not account for additional, presumably negative predictive and prognostic KRAS-associated co-mutations like STK11 or KEAP1, as they were not included into the routine NGS assay (20). Lower frequencies of e.g., STK11 mutations leading to immunologically cold cancers might have contributed to the improved outcome in KRAS^{G12C} patients. However, recently published data in this setting are inconclusive. Whereas no differences among KRAS subgroups were observed in the LC-SCRUM-Japan study, STK11 co-mutations occurred less frequently in KRAS^{G12D} but were equally present in KRAS$^{G12A, C, V \text{ or } Q61X}$ in a large US cohort (31,44). Noteworthy, a favorable survival in KRAS^{mut}/TP53^{mut} patients may be even preserved in the presence of STK11 mutations (38). Fifth, as patients were treated within the valid standard of care outside a clinical trial, imaging intervals varied, thereby potentially biasing PFS. Additionally, RECIST assessments were not confirmed independently. Finally, given the inclusion of patients with pembrolizumab monotherapy only without a control group, this study was not designed to evaluate a predictive value of either KRAS^{G12C} alone or in combination with TP53^{mut}. However, one should keep in mind that KRAS^{mut} have consistently been associated with a worse outcome in the era of chemotherapy and no survival differences were identified according to the applied regimens. Thus, no predictive value for standard chemotherapy has been established (16,45,46).

Conclusions

A comprehensive KRAS subtyping and TP53 assessment may allow a prognostic highly relevant differentiation of patients with metastatic, PD-L1 high LuAD, treated upfront with pembrolizumab. The advantage of the proposed approach is its availability for the majority of patients with LuAD, as NGS panel testing has become the method of choice to screen for actionable genetic alterations. In contrast to large panels or whole exome sequencing needed for TMB, a small gene panel might be sufficient to provide the necessary prognostic information. Whether the constellation of PD-L1 ≥50% and KRAS^{G12C}/TP53^{mut} favors upfront ICI monotherapy *vs.* an ICI-chemotherapy combination should be addressed in further, prospective studies.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Charité Universitätsmedizin Berlin (approval number EA2/223/18) and individual consent for this retrospective analysis was waived (patient's written informed consent was obtained within the treatment contract as ICI were administered as standard of care).

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