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Large-scale clinico-genomic profile of non-small cell lung cancer with *KRAS* G12C: Results from LC-SCRUM-Asia study

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ABSTRACT

Introduction: *KRAS* G12C is an oncogenic driver mutation, accounting for approximately 14% of Caucasian patients with non-small cell lung cancer (NSCLC). Recently, several KRAS G12C-targeted drugs have been developed; however, the clinico-genomic characteristics of NSCLC patients with *KRAS* G12C remain unclear.

Materials and Methods: Based on the large-scale prospective lung cancer genomic screening project (LC-SCRUM-Asia) database, the clinico-genomic characteristics and therapeutic outcomes of NSCLC patients with *KRAS* G12C were evaluated.

Results: From March 2015 to March 2021, 10,023 NSCLC patients were enrolled in LC-SCRUM-Asia. *KRAS* mutations were detected in 1258 patients (14 %), including G12C in 376 (4.0 %), G12D in 289 (3.1 %) and G12V in 251 (2.7 %). The proportions of males and smokers were higher in patients with *KRAS* G12C than in those with *KRAS* non-G12C mutations (males: 73 % vs 63 %, $p < 0.001$; smokers: 89 % vs 76 %, $p < 0.001$). *KRAS* G12C-positive tumors showed a higher tumor mutation burden (TMB) (mean, 8.1 mut/Mb, $p < 0.001$) and a higher percentage of tumors with programmed cell death ligand-1 (PD-L1) expression ≥50 % (52 %, $p = 0.08$). The overall survival in patients with *KRAS* G12C (median, 24.6 months) was not different between patients with other mutation subtypes (G12V: 18.2 months, $p = 0.23$; G12D: 20.6 months, $p = 0.65$; other *KRAS* mutations: 18.3 months, $p = 0.20$). Among *KRAS*-mutated patients who received immune checkpoint inhibitors (ICIs), the progression-free survival in G12C-positive patients (median, 3.4 months) was similar to that in G12V-positive patients (4.2 months, $p = 0.90$), but significantly longer than that in G12D- (2.0 months, $p = 0.02$) and other *KRAS* mutation-positive patients (2.5 months, $p = 0.02$).

Conclusions: The frequencies of *KRAS* G12C were lower in Asian than in Caucasian NSCLC patients. Among the *KRAS*-mutated NSCLC patients, G12C-positive tumors showed increased immunogenicity, such as high TMB and high PD-L1 expression, and potential sensitivity to ICIs.

Abbreviations: CI, confidence intervals; CLIA, Clinical Laboratory Improvement Amendments; ECOG, Eastern Cooperative Oncology Group; EDC, electronic data capture; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; KRAS, Kristen rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; OCA, Oncomine Comprehensive Assay; OPA, Oncomine Precision Assay; OMLA, Oncomine Tumor Mutation Load Assay; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TMB, tumor mutation burden.

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1. Introduction

Mutations of the Kristen rat sarcoma viral oncogene homolog (*KRAS*) gene are one of the most common oncogene drivers in non-small cell lung cancer (NSCLC). *KRAS* mutations are reported to be present in 20 %–30 % of Caucasian patients with NSCLC [1–3], and *KRAS* G12C, one of the major subtypes of *KRAS* mutations, has been identified in approximately 14 % [4]. For nearly four decades since the discovery of *KRAS* mutations, no effective targeted therapies for *KRAS*-mutated NSCLC had emerged despite various approaches for the drug development. Since many subtypes of *KRAS* mutations have been identified in NSCLC, one of the reasons for the difficulty in drug development could be the differences in the mechanisms of oncogenesis or biological features of the tumors depending on the *KRAS* mutation subtypes. Recently, a covalent small-molecule inhibitor, sotorasib (AMG510), was the first drug to be approved for NSCLC patients with *KRAS* G12C by the Food and Drug Administration (FDA), based on the favorable results of a phase 2 study [5]. Another KRAS G12C-targted drug, adagrasib (MRTX849), has also been reported to show promising efficacy *KRAS* G12C-positive NSCLC [6,7]. However, the therapeutic efficacies of currently available chemotherapies and immune-checkpoint inhibitor (ICI) monotherapy in *KRAS* G12C-positive NSCLC patients still remain unclear.

We analyzed a large number of NSCLC using the integrated clinical and genomic data of a large-scale prospective lung cancer genomic screening project (LC-SCRUM-Asia), to evaluate the clinico-genomic characteristics and treatment outcomes of NSCLC patients with *KRAS* G12C. We consider these data are highly informative for the development of therapeutic strategies for *KRAS* G12C-positive NSCLC.

2. Material and methods

2.1. LC-SCRUM-Asia

The large-scale, prospective, multi-institutional lung cancer genomic screening project, LC-SCRUM-Asia, was initiated in February 2013, to identify lung cancer patients with targetable gene alterations and establish lung cancer precision medicine (UMIN000010234). The eligibility criteria for inclusion in this project are patients with stage II to IV or postoperative recurrence of lung cancer aged ≥16 years old, with an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0–2 and adequate organ functions. The protocol for this study was approved by the institutional review board of each of the participant institutions. To date, more than 14,000 patients are already enrolled in the LC-SCRUM-Asia.

2.2. Molecular analyses in LC-SCRUM-Asia

Fresh frozen tumor samples or malignant pleural fluid specimens are submitted and all molecular analyses are performed at the Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratory, SRL, Inc., Japan. From March 2015, targeted next-generation sequencing (NGS) systems (Oncomine Comprehensive Assay [OCA] ver.1 or 3 between March 2015 and January 2021, and Oncomine Precision Assay [OPA] [Thermo Fisher Scientific, MA, USA] between January 2021 to March 2021) has been used for the genomic screening. In addition, between June 2019 and January 2021, a multi-gene quantitative PCR assay (Pan Lung Cancer PCR Panel [Amoy Diagnostics Co., Xiamen, China]) was also implemented as a rapid multi-gene testing tool, and another NGS assay, Oncomine Tumor Mutation Load Assay (OMLA) (Thermo Fisher Scientific), was performed to detect the tumor mutation burden (TMB). Tumor programmed cell death ligand-1 (PD-L1) expression was also evaluated using anti-PD-L1 antibody, 22C3 (Dako Agilent, Santa Clara, CA, USA) between February 2017 and March 2018.

2.3. Clinical data collection from the LC-SCRUM-Asia database

Clinical data, including the baseline patient characteristics, treatment regimens used, therapeutic efficacies and survivals, are collected using an electronic data capture (EDC) system of the LC-SCRUM-Asia and updated each year. Based on these clinical and genomic screening data, a large-scale clinico-genomic database of lung cancer has been developed.

2.4. Patients

In this study, the data of NSCLC patients enrolled in the LC-SCRUM-Asia from March 2015 to March 2021 were analyzed. Patients whose samples were not available were excluded. The treatment outcomes of platinum-based chemotherapy at 1st line, pembrolizumab at 1st line and ICI monotherapy (pembrolizumab, nivolumab and atezolizumab) at any line during 2nd to 4th line were collected. The patient characteristics were analyzed in all the patients enrolled until March 31, 2021. Survival analyses were performed in patients with advanced NSCLC who received systemic chemotherapy and enrolled until January 7, 2020, and the cutoff date was July 2, 2020.

2.5. Statistical analyses

To summarize and compare the frequencies, Fisher's exact test was used. For continuous variables, Wilcoxon's rank sum test or Kruskal-Wallis test was used. Overall survival (OS) was defined as the period from the start of first-line systemic treatment to death from any cause or until censoring at the last follow-up. Progression-free survival (PFS) was defined as the period from the start of each treatment to disease progression or death from any cause, whichever occurred first. PFS was censored at the earliest date of any of the following: date of confirmation without disease progression, date of treatment completion, or the last recorded date of survival for patients who discontinued treatment, or the earliest date of confirmation without disease progression or the last recorded date of survival for those who continued treatment. Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. The hazard ratios and 95 % confidence intervals (CI) for the OS and PFS were estimated using the Cox regression model. All statistical tests were 2-sided, and $p < 0.05$ was considered as being indicative of statistical significance.

Statistical analyses were performed using SAS version 9.4 and JMP version 14.0.0 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Prevalence of KRAS mutation subtypes

A total of 10,023 NSCLC patients from 253 institutions in Japan were enrolled in LC-SCRUM-Asia between March 2015 and March 2021. Of the 10,023 NSCLC patients, tumor specimens from 9205 patients (92 %) were successfully analyzed by targeted NGS. *KRAS* mutations were detected in 1258 of the 9205 patients (14 %) (Fig. 1A). Among the 7947 *KRAS* wild-type NSCLC patients, 2775 patients (30 %) with other oncogene drivers (mutations of *EGFR, HER2, MET, NRAS, HRAS, BRAF, RAF1, MAP2K1* or *AKT1*, or fusions of *ALK, ROS1, RET, NTRK1-3*) were excluded, and the remaining 5172 patients (56 %) were defined as the "Non-Driver" group for this study. Among the 1258 *KRAS*-mutated NSCLC patients, the most frequent mutation subtype was G12C (n = 376, 30 %), accounting for 4.0 % of all NSCLC patients. The other *KRAS* mutation types detected were G12D (n = 289, 23 %), G12V (n = 251, 20 %), G12A (n = 100, 8 %), mutations in codon 13 (G13X) (n = 87, 7 %), Q61H (n = 67, 5 %), and others (n = 88, 7 %) (Fig. 1B).

3.2. Clinico-genomic characteristics

The patient characteristics are summarized in Table 1. The median age of the 1258 *KRAS*-mutated NSCLC patients was 69 years (range 25–91 years), and the majority of patients were males (66 %) and smokers (80 %), and were histologically diagnosed as adenocarcinoma (89 %). Among the *KRAS*-mutated NSCLC patients, the proportions of males and smokers were higher in patients with *KRAS* G12C than in those with *KRAS* non-G12C mutations (males: 73 % vs 63 %, $p < 0.001$: smokers: 89 % vs 76 %, $p < 0.001$), and lower in patients with *KRAS* G12D than in those with *KRAS* non-G12D mutations (males: 55 % vs 69 %, $p < 0.001$: smokers, 67 % vs 83 %, $p < 0.001$).

Frequently mutated genes concomitantly with *KRAS* G12C were *TP53* (32 %), *STK11* (6 %) and *KEAP1* (6 %). There were no differences in the frequencies of these mutations between tumors with *KRAS* G12C and those with *KRAS* non-G12C mutations (*TP53*: $p = 0.89$; *STK11*: $p = 0.26$; *KEAP1*: $p = 0.84$). The patient characteristics of all *KRAS*-mutated patients and *KRAS* G12C-positive patients according to the *TP53*, *STK11* and *KEAP1* mutation statuses are summarized in Supplementary Table 1 and Table 2, respectively. There were no differences in the clinical and pathological characteristics of the patients with *KRAS* G12C-positive tumors depending on the concomitant mutation status of *TP53*, *STK11* and *KEAP1*.

3.3. Analysis of the TMB

Evaluation of the TMB was conducted in 465 *KRAS*-mutated tumors and 1937 Non-Driver tumors. *KRAS*-mutated tumors were associated with a lower TMB than Non-Driver tumors (mean TMB: 6.6 vs 8.5 mut/Mb, $p < 0.01$) (Fig. 2A). Comparison of *KRAS*-mutated tumors among mutation subtypes revealed that *KRAS* G12C-positive tumors had a higher TMB than tumors with *KRAS* non-G12C mutations (mean TMB, 8.1 vs 5.9 mut/Mb, $p < 0.01$), as well as tumors with *KRAS* G12V, G12D and "others" (G12V 5.8 mut/Mb, G12D 5.1 mut/Mb, "others" 6.9 mut/

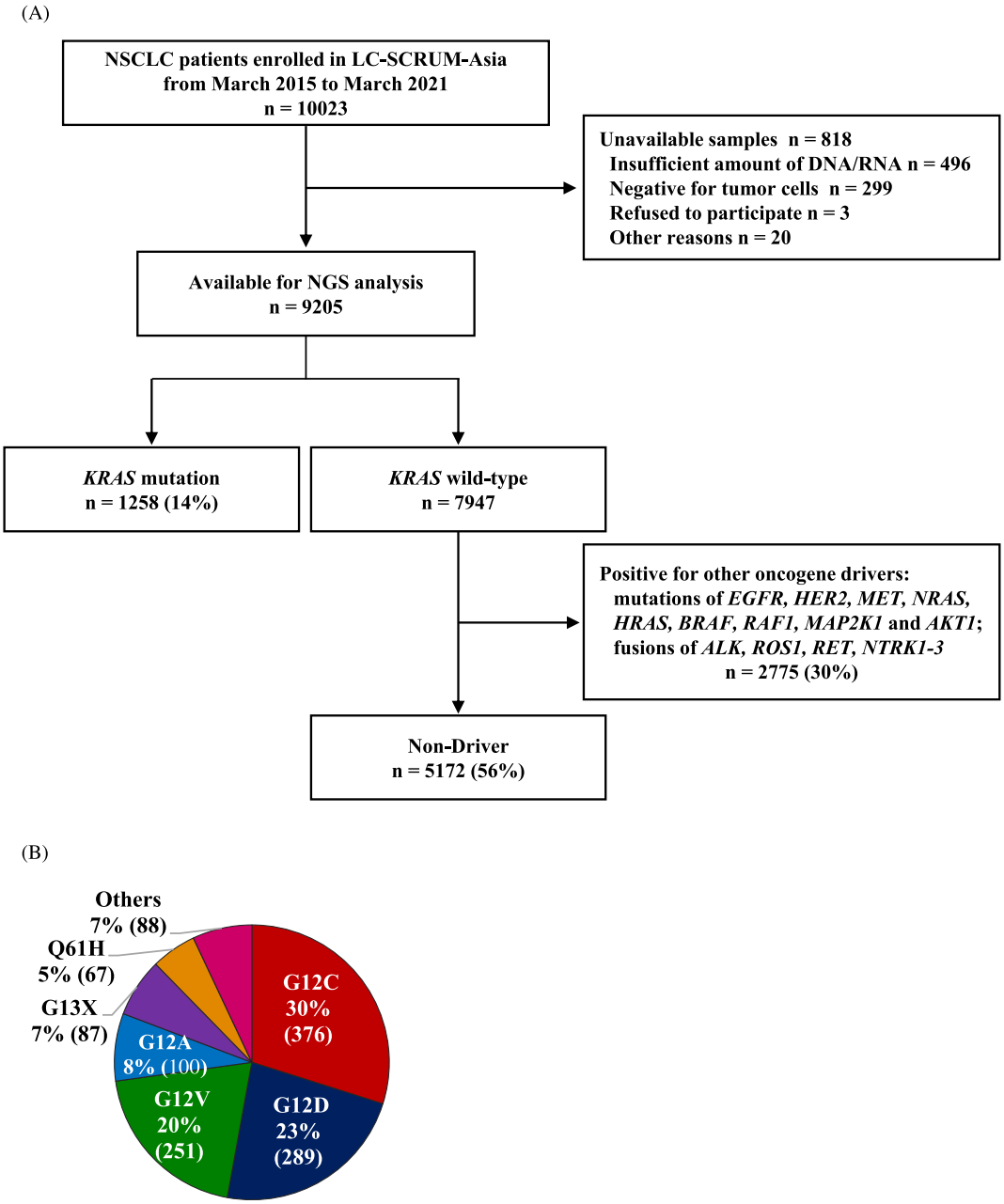

Fig. 1. (A) Consort diagram, (B) Distribution of *KRAS* mutation subtypes, NSCLC, non-small cell lung cancer; NGS, next-generation sequencing.

Table 1
Patient characteristics.

	KRAS mutations, n = 1258								Non-Driver * n = 5172 (%)
	Total n = 1258 (%)	G12C n = 376 (%)	G12D n = 289 (%)	G12V n = 251 (%)	G12A n = 100 (%)	G13X n = 87 (%)	Q61H n = 67 (%)	Others n = 88 (%)	
Age, years									
Median (range)	69 (25–91)	69 (36–91)	69 (25–86)	69 (29–89)	69 (43–88)	68 (44–89)	69 (45–86)	69 (45–86)	68 (16–94)
Sex									
Male	826 (66)	273 (73) †	160 (55) ‡	156 (62)	69 (69)	64 (74)	46 (69)	58 (66)	4004 (77)
Female	432 (34)	103 (27)	129 (45)	95 (38)	31 (31)	23 (26)	21 (31)	30 (34)	1168 (23)
Smoking status									
Ever	1003 (80)	336 (89) †	195 (67) ‡	196 (78)	81 (81)	76 (87)	52 (78)	67 (76)	4371 (84)
Never	245 (19)	31 (8)	94 (33)	54 (22)	19 (19)	11 (13)	15 (22)	21 (24)	762 (15)
Unknown	10 (1)	9 (2)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	39 (1)
Histology									
ADC	1114 (89)	324 (86)	263 (91)	221 (88)	91 (91)	79 (91)	59 (88)	72 (88)	3226 (62)
SCC	51 (4)	16 (4)	8 (4)	14 (5)	3 (3)	3 (3)	1 (1)	5 (6)	1387 (27)
Pleom	24 (2)	13 (3)	4 (1)	3 (1)	1 (1)	1 (1)	2 (3)	0 (0)	52 (1)
LCC	14 (1)	5 (1)	5 (2)	1 (0.4)	0 (0)	2 (2)	0 (0)	1 (1)	92 (2)
Others	55 (4)	18 (5)	9 (3)	12 (5)	5 (5)	2 (2)	5 (7)	4 (5)	415 (8)
Stage									
II	48 (4)	11 (3)	3 (3)	14 (5)	4 (4)	3 (3)	2 (3)	5 (6)	197 (4)
III	185 (15)	63 (17)	40 (14)	39 (16)	11 (11)	14 (16)	6 (9)	12 (13)	1186 (23)
IV	858 (68)	256 (68)	195 (67)	165 (66)	71 (71)	61 (70)	51 (76)	59 (67)	3287 (63)
Recurrence	167 (13)	46 (12)	45 (16)	33 (13)	14 (14)	9 (10)	8 (12)	12 (14)	502 (10)
Brain metastasis									
Positive	229 (18)	75 (20)	45 (16)	47 (19)	17 (17)	20 (23)	12 (18)	13 (15)	800 (15)
Negative	1029 (82)	301 (80)	244 (84)	204 (81)	83 (83)	67 (77)	55 (82)	75 (85)	4372 (85)
Concomitant mutation									
TP53	336/1159 (29)	108/344 (32)	69/269 (21)	68/233 (29)	21/92 (23)	21/77 (27)	18/62 (29)	31/82 (38)	NA
KEAP1	31/465 (7)	9/146 (6)	9/125 (7)	7/83 (8)	1/35 (3)	2/25 (8)	1/24 (4)	2/27 (7)	NA
STK11	72/1159 (6)	22/344 (6)	11/269 (4)	15/233 (6)	8/92 (9)	7/77 (9)	3/62 (5)	6/82 (7)	NA
TP53/KEAP1/ STK11	166/465 (36)	63/146 (43) †	42/125 (34)	26/83 (31)	8/35 (23)	8/25 (32)	9/24 (38)	10/27 (37)	NA

ADC, adenocarcinoma; SCC, squamous cell carcinoma; Pleom, pleomorphic carcinoma; LCC, large cell carcinoma; NA, not available.

* . Negative for oncogene drivers: mutations of *KRAS, EGFR, HER2, NRAS, HRAS, BRAF, RAF1, MAP2K1* and *AKT1*; fusions of *ALK, ROS1, RET, NTRK1-3* and *MET exon14 skipping*.

† . G12C vs G12D / G12V / G12A / G13X / Q61H / Others; $p < 0.01$.

‡ . G12D vs G12C / G12V / G12A / G13X / Q61H / Others; $p < 0.01$.

Table 2
Clinicopathological characteristics of *KRAS* G12C-positive non-small cell lung cancer (NSCLC) patients according to the *TP53*, *STK11* and *KEAP1* status.

	TP53			*STK11*			*KEAP1*		
	mt n = 108 (%)	WT n = 236 (%)	p	mt n = 22 (%)	WT n = 322 (%)	p	mt n = 9 (%)	WT n = 137 (%)	p
Age, years									
Median (range)	68 (41–91)	68 (36–83)	0.49	68 (57–81)	68 (36–91)	0.46	65 (49–75)	69 (39–91)	0.21
Sex									
Male	78 (72)	171 (72)	1.00	18 (82)	231 (72)	0.46	7 (78)	102 (74)	1.00
Female	30 (28)	65 (28)		4 (18)	91 (28)		2 (22)	35 (26)	
Smoking status									
Ever	99 (92)	210 (89)	0.74	21 (95)	288 (89)	0.47	8 (89)	126 (92)	0.62
Never	7 (6)	20 (8)		1 (5)	26 (8)		1 (11)	7 (5)	
Unknown	2 (2)	6 (3)		0	8 (2)		0	4 (3)	
Histology									
ADC	88 (82)	211 (89)	0.21	21 (95)	278 (86)	0.40	8 (89)	116 (85)	0.74
SCC	6 (6)	6 (3)		0	12 (4)		0	5 (4)	
Pleom	6 (6)	6 (3)		0	12 (4)		0	5 (4)	
LCC	3 (3)	2 (1)		0	5 (2)		0	3 (2)	
Others	5 (5)	11 (5)		1 (5)	15 (5)		1 (11)	8 (6)	
Brain metastasis									
Positive	25 (23)	45 (19)	0.39	6 (27)	64 (20)	0.41	3 (33)	29 (21)	0.41
Negative	83 (77)	191 (81)		16 (73)	258 (80)		6 (67)	108 (79)	

mt, mutation; WT, wild type; ADC, adenocarcinoma; SCC, squamous cell carcinoma; Pleom, pleomorphic carcinoma; LCC, large cell carcinoma.

Mb, respectively, p < 0.01) (Fig. 2B).

In the evaluation according to the concomitant mutation status of *STK11* (Fig. 2C), *TP53* (Fig. 2D) and *KEAP1* (Fig. 2E) in the *KRAS*-mutated tumors, concomitant presence of *TP53* mutations or *KEAP1*-mutations, as compared to their wild-type, was associated with a higher TMB (*TP53*, 9.6 vs 5.4 mut/Mb, p < 0.01; *KEAP1*, 9.7 vs 6.4 mut/Mb, p < 0.01); no such this association with a higher TMB was observed for the concomitant presence of *STK11* mutations (7.0 vs 6.6 mut/Mb, p = 0.13). Similar results were observed when high and low TMB were analyzed with a cutoff value of 10 mut/Mb (Supplementary Fig. 1).

3.4. Analysis of PD-L1 expression

The PD-L1 expression status was evaluated in 95 *KRAS*-mutated tumors and 453 Non-Driver tumors. The frequency of PD-L1-high expression (≥50 %) tended to be higher in *KRAS* mutated tumors than in Non-Driver tumors (39 % vs 30 %, p = 0.09) (Fig. 3A). When the PD-L1 expression was evaluated according to the *KRAS* mutation subtypes, *KRAS* G12C-positive tumors showed the highest frequency of PD-L1-high expression (52 %), followed by *KRAS* G12V (43 %), G12D (28 %), and "others" (26 %) (Fig. 3B). The frequency of PD-L1-high expression in the *KRAS* G12C-positive tumors tended to be higher than that in *KRAS* non-G12C tumors (52 % vs 32 %, p = 0.08).

In the evaluation of *KRAS*-mutated tumors according to the concomitant gene mutation status, the PD-L1- high expression tended to be less frequent in patients with concomitant *SKT11* mutations than in those with *STK11* wild-type (16 % vs 42 %, p = 0.12) (Fig. 3C). In contrast, concomitant *TP53* mutations were associated with a higher frequency of PD-L1-high expression than *TP53* wild-type (51 % vs 24 %, p = 0.01) (Fig. 3D).

3.5. Treatment outcomes

We investigated the impact of the presence of *KRAS* mutations in the tumors on the survival and treatment outcomes of NSCLC patients. The median duration of follow-up was 16.9 months. There were no differences in the OS between *KRAS*-mutated NSCLC patients and Non-Driver patients (median OS [mOS]; 20.3 vs 21.0 months, p = 0.84)

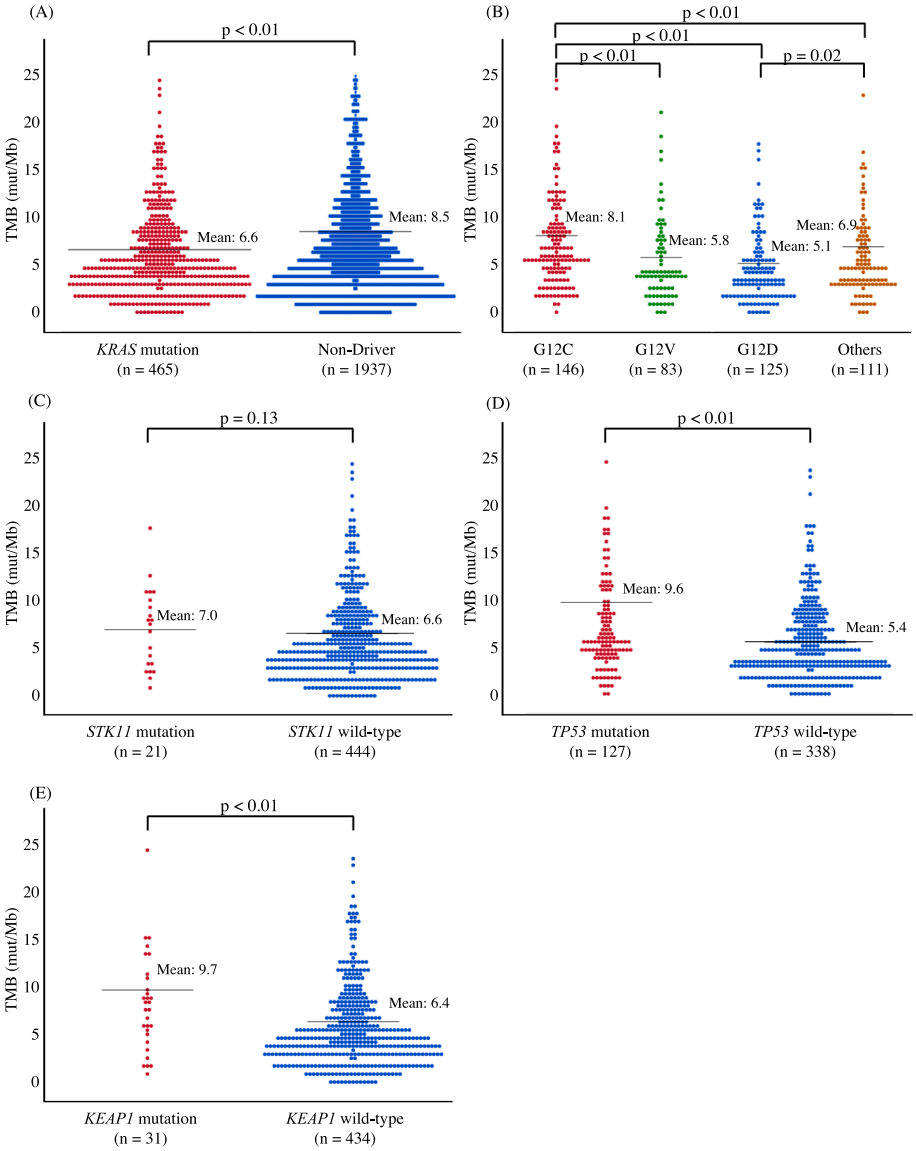

Fig. 2. (A) Tumor mutation burden (TMB) in non-small cell lung cancer (NSCLC) with *KRAS* mutations (n = 465) vs Non-Driver (n = 1937). (B) TMB in *KRAS*-mutated NSCLC according to the *KRAS* mutation subtype. (C, D, E) TMB in *KRAS*-mutated NSCLC according to the concomitant *STK11*, *TP53* and *KEAP1* mutation status. mut/Mb, mutations per megabase.

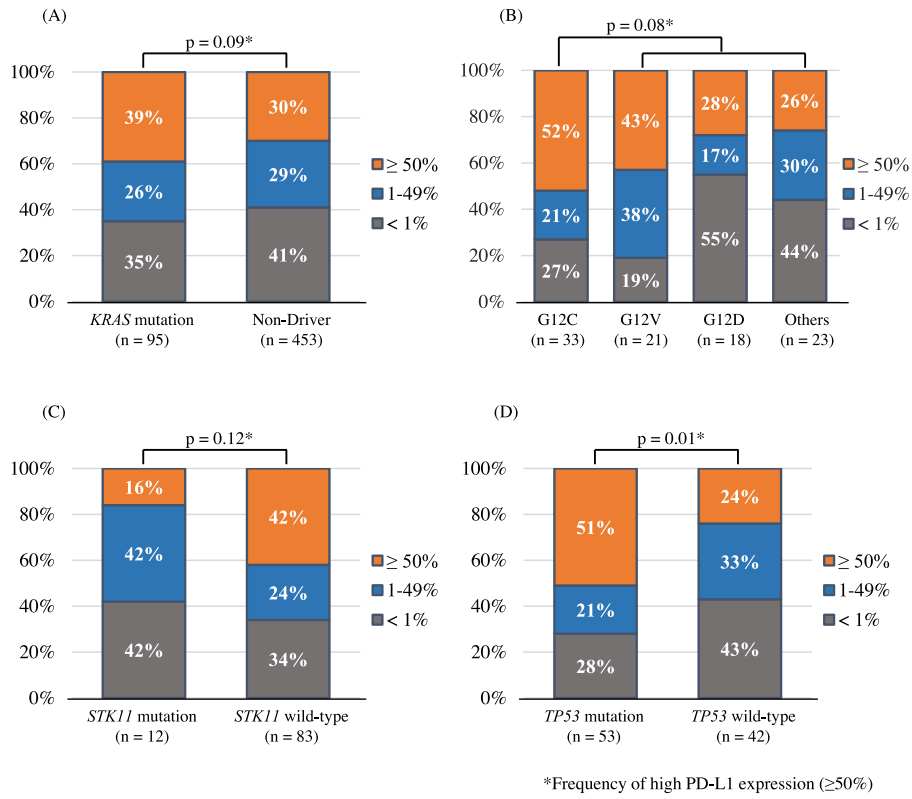

Fig. 3. Programmed cell death ligand-1 (PD-L1) expression in non-small cell lung cancer (NSCLC) with *KRAS* mutations (n = 95) vs Non-Driver (n = 453). PD-L1 expression in *KRAS*-mutated NSCLC according to the *KRAS* mutation subtype. (C, D) PD-L1 expression in *KRAS*-mutated NSCLC according to the concomitant *STK11* and *TP53* mutation status.

(Supplementary Fig. 2A). Similarly, there were also no differences in the PFS between *KRAS*-mutated NSCLC patients and Non-Driver patients who received 1st-line platinum-based chemotherapy (Supplementary Fig. 2B), 1st-line pembrolizumab therapy (Supplementary Fig. 2C), or 2nd- to 4th-line ICI monotherapy (Supplementary Fig. 2D) (median PFS [mPFS], 1st-line platinum-based chemotherapy: 5.4 vs 5.3 months, p = 0.29; 1st-line pembrolizumab therapy: 7.2 vs 7.4 months, p = 0.87; 2nd- to 4th-line ICI monotherapy: 2.8 vs 3.2 months, p = 0.58). In regard to the influence of the *KRAS* mutation subtype, the OS in patients with *KRAS* G12C was similar to that in patients with *KRAS* non-G12C mutations (mOS: 24.6 vs 19.3 months, p = 0.20) (Supplementary Fig. 3A), as well as in subgroups of patients with other mutation subtypes (G12V: 18.2 months, p = 0.23; G12D: 20.6 months, p = 0.65; "others": 18.3 months, p = 0.18) (Fig. 4A). The PFS in NSCLC patients with *KRAS* G12C was also similar to that in NSCLC patients with *KRAS* non-G12C mutations, among patients who received 1st-line platinum-based chemotherapy (Supplementary Fig. 3B) or pembrolizumab therapy (Supplementary Fig. 3C) (mPFS, 1st-line platinum-based chemotherapy: 5.3 vs 5.6 months, p = 0.64; 1st-line pembrolizumab therapy; 5.8 vs 8.2 months, p = 0.20), as well as in subgroups of patients with other mutation subtypes (1st-line platinum-based chemotherapy: p = 0.35; 1st-line pembrolizumab therapy: p = 0.38) (Fig. 4B, C). We also analyzed patients who received ICI monotherapy as 2nd- to 4th-line treatment. The patients who received prior ICI therapy were excluded in this cohort. Patient characteristics of this cohort were not different from those of the entire cohort in this study, and numbers of patient according to treatment lines (2nd, 3rd or 4th) were well-balanced (Supplementary Table 2). The PFS in NSCLC patients with *KRAS* G12C tended to be longer than that in patients with *KRAS* non-G12C mutations (mPFS: 3.4 vs 2.5 months, p = 0.06) (Supplementary Fig. 3D), and significantly longer than that in patients with *KRAS* G12D (2.0 months, p = 0.02) and "others" (2.5 months, p = 0.02) (Fig. 4D); however, not different from that in patients with *KRAS* G12V (4.2 months, p = 0.09).

Furthermore, we assessed the impact of concomitant *STK11* or *TP53* mutations on the PFS in *KRAS*-mutated NSCLC patients who received 2nd- to 4th-line ICI monotherapy. The results revealed no differences in the PFS between *KRAS*-mutated NSCLC patients with and without *STK11* mutations (mPFS, 1.7 vs 2.9 months, p = 0.16) (Supplementary Fig. 4A). On the other hand, in patients with *KRAS* G12C or *KRAS* G12V, concomitant presence of *STK11* mutations, was associated with a shorter PFS (mPFS, 1.7 vs 3.6 months, p = 0.01) (Supplementary Fig. 4B). This association was not observed in patients with or without *TP53* mutations (Supplementary Fig. 4C, 4D).

4. Discussion

This study is the largest scale study of the clinical and genomic characteristics and treatment outcomes of *KRAS*-mutated NSCLC patients, in which subgroup analyses were performed among patients with NSCLC harboring different *KRAS* mutation subtypes and other concomitant gene mutations.

In this study, *KRAS* mutations were identified in 14 % of Asian NSCLC patients. This frequency was similar to that reported in East Asian patients [8,9], but lower than that reported in Caucasian patients (20–30 %) [1–3]. The frequency of *KRAS* G12C was also lower in Asian (4 %) than in Caucasian NSCLC patients (14 %) [4]. In addition, *KRAS* G12C was identified more frequently in male than in female patients, which was consistent with a previous report of *KRAS* G12C being found more frequently in males among Asian patients, but in females among Caucasian patients [4]. These results demonstrated the racial differences in the characteristics of *KRAS*-mutated and *KRAS* G12C-positive NSCLC patients. Genomic screening for this study was performed by a multigene quantitative PCR assay and targeted NGS. We previously performed concordance study for oncogenic driver detection by these assays, and overall percent agreement (%)/positive percent agreement (%)/negative percent agreement (%) of the PCR assay compared with

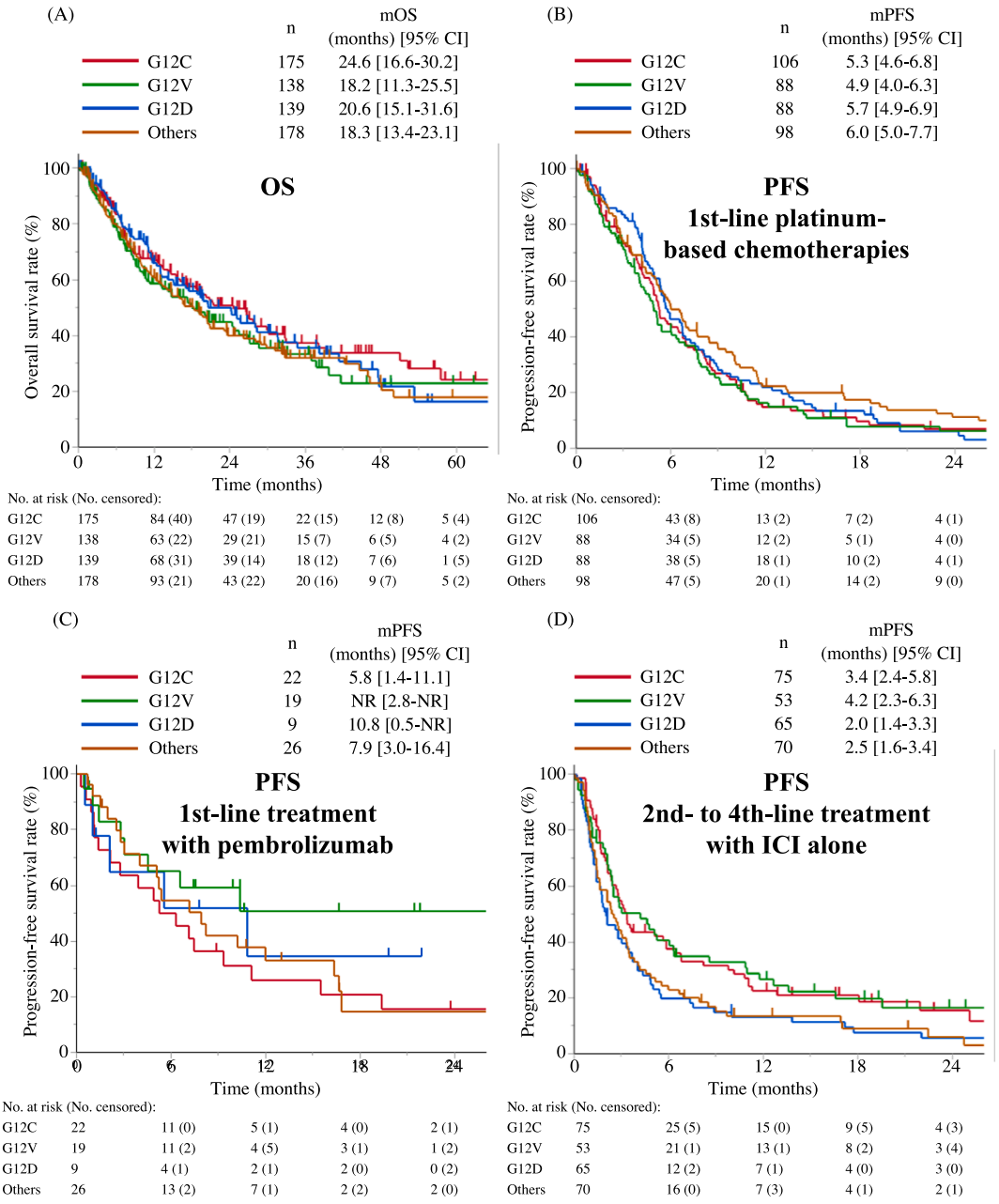

Fig. 4. (A) Overall survival (OS) in *KRAS*-mutated non-small cell lung cancer (NSCLC) patients according to the *KRAS* mutation subtype. (B) Progression-free survival (PFS) in *KRAS*-mutated NSCLC patients who received 1st-line platinum-based chemotherapy, according to the *KRAS* mutation subtype. (C) PFS in *KRAS*-mutated NSCLC patients who received 1st-line pembrolizumab therapy, according to the *KRAS* mutation subtype. (D) PFS in *KRAS*-mutated NSCLC patients who received 2nd- to 4th-line immune checkpoint inhibitor (ICI) therapy, according to the *KRAS* mutation subtype.

NGS were 99.6/98.9/99.7 for *KRAS* mutations and 99.8/99.1/99.8 for *KRAS* G12C [10]. These results showed a high concordance between these assays, suggesting that the possible bias due to the change in testing for *KRAS* subgroups is extremely limited.

Our results indicated that the frequencies of concomitant mutations, such as *STK11*, *TP53* and *KEAP1*, were lower in Asian patients than in Caucasian NSCLC patients, but not different between NSCLC patients harboring *KRAS* G12C and other *KRAS* non-G12C mutations [11]. KEAP1 is a negative regulator of transcription of the nuclear factor erythroid-2-related factor (NRF2) and dysregulate oxidative stress pathway [12,13]. Previous studies demonstrated that *KEAP1* mutations were negative biomarker of ICI treatment [14,15]. In contrast, some studies suggested that *KEAP1* mutations are associated with high TMB and high PD-L1 expression, and improve the response to ICI [16,17]. In our study, *KEAP1* mutations in *KRAS*-mutated NSCLC were also associated with high TMB. However, we were not able to evaluate the association between *KEAP1* mutations and treatment outcomes in *KRAS* G12C-positive NSCLC due to the small number of *KEAP1* mutation-positive samples. Further studies are needed to clarify this association. It has been reported that concomitant *STK11* mutations in *KRAS*-mutated NSCLC promote the production of inflammatory cytokines, contributing to neutrophil accumulation and decrease of *T*-cell infiltration [18]. In addition, tumors harboring *STK11* mutations have been shown to be characterized by low PD-L1 expression levels and primary resistance to ICIs [18,19]. In our study also, *STK11* mutations were negatively associated with the tumor PD-L1 expression level and with shorter PFS of patients with *KRAS* G12C or *KRAS* G12V who received 2nd- to 4th-line ICI monotherapy. On the other hand, the PFS in all

KRAS-mutated NSCLC patients who received 2nd- to 4th-line ICI monotherapy did not statistically differ according to the *STK11* mutation status. This could probably be explained by the higher proportion of patients with *KRAS* G12D-positive tumors in our study, as compared to previous studies in Caucasians (23 % vs 15 %) [11], with a negative impact on the treatment responses to 2nd- to 4th-line ICI monotherapy in our study.

In this study, *KRAS* G12C was identified more frequently in smokers. According to previous reports, transversion mutations of *KRAS,* such as *KRAS* G12C and *KRAS* G12V, are more frequent in smokers than transition mutations, such as *KRAS* G12D [20,21]. Furthermore, *KRAS* G12C-positive tumors also showed a high TMB and high PD-L1 expression. These results are consistent with those of recent smaller studies [11,22] and might indicate the enhanced immunogenicity of *KRAS* G12C tumors. In our study, among *KRAS*-mutated NSCLC patients who received 1st-line pembrolizumab therapy, the PFS was not different between patients with *KRAS* G12C and those with non-G12C mutations, but the small sample size of this cohort (n = 76) could not be enough for the statistical analysis. On the other hand, in a larger cohort of patients who received 2nd- to 4th-line ICI monotherapy (n = 380), the PFS in patients with *KRAS* G12C tended to be longer than that in patients with *KRAS* non-G12C mutations, and was significantly longer than that in patients with *KRAS* G12D. These results might be explained by the high immunogenicity of *KRAS* G12C-positive tumors, as indicated by the high TMB and high PD-L1 expression in these tumors, and indicate that the *KRAS* G12C-positive NSCLCs could have potential sensitivity to ICIs.

In recent years, *KRAS* G12C has become a “druggable” oncogene driver. The covalent KRAS G12C inhibitors, sotorasib and adagrasib, have been shown to block KRAS signaling, and their efficacy has been demonstrated in early-phase clinical trials [5–7,23]. In a phase 2 study, sotorasib showed objective response rate of 37.1 % and a median PFS of 6.8 months in *KRAS* G12C-positive NSCLC patients [5]. However, these results are unfavorable as compared to other targeted therapies for NSCLC [24–27], and more effective regimens for the treatment of *KRAS* G12C-positive NSCLC are needed. Furthermore, NSCLC patients with *KRAS* non-G12C mutations also showed poor treatment outcomes, similar to those with *KRAS* G12C, and efforts to develop effective targeted therapies for NSCLC tumors with other *KRAS* mutations than G12C are also ongoing. Our findings in regard to the clinico-genomic characteristics and treatment outcomes of *KRAS*-mutated NSCLC patients who received standard therapies (platinum-based chemotherapies and ICI monotherapy) according to the *KRAS* mutation subtypes might be helpful to develop new therapeutic strategies for patients with *KRAS*-mutated NSCLC.

This study had several limitations. First, our study was a real-world observational study with no specifications in regard to the timing or frequency of radiological assessments of the treatment responses. Second, we did not perform multiplicity adjustment. Due to an observational nature of the present study, a statistical significance based on p-value can lead to misinterpretation of the results because p-value gets smaller when sample size and/or the number of events increase. In addition, our primary interest was to assess an impact of *KRAS* mutation subtypes on the clinical and genomic characteristics and treatment outcomes in an exploratory manner. Third, although the PD-L1 expression status and TMB were evaluated in consecutive patients, they were assessed only in a limited number of patients. Finally, we did not evaluate the efficacies of combined ICI plus cytotoxic chemotherapy, which is one of the standards of care for NSCLC, regardless of the presence/absence of *KRAS* mutations.

In conclusion, *KRAS* mutations and *KRAS* G12C were less frequent in Asian patients than in Caucasian patients with NSCLC. Although among the *KRAS*-mutated NSCLC patients, *KRAS* G12C-positive NSCLC patients showed potentially improved sensitivity to ICI monotherapy, their responses to current standard therapies were poor. Development of more effective regimens is needed for the treatment of *KRAS* G12C-positive NSCLC.

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CRediT authorship contribution statement

Yutaro Tamiya: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. **Shingo Matsumoto:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Yoshitaka Zenke:** Investigation, Resources, Writing – review & editing. **Kiyotaka Yoh:** Investigation, Resources, Writing – review & editing. **Takaya Ikeda:** Data curation, Investigation, Resources, Writing – review & editing. **Yuji Shibata:** Data curation, Investigation, Resources, Writing – review & editing. **Terufumi Kato:** Investigation, Resources, Writing – review & editing. **Kazumi Nishino:** Investigation, Resources, Writing – review & editing. **Atsushi Nakamura:** Investigation, Resources, Writing – review & editing. **Naoki Furuya:** Investigation, Resources, Writing – review & editing. **Shingo Miyamoto:** Investigation, Resources, Writing – review & editing. **Shoichi Kuyama:** Investigation, Resources, Writing – review & editing. **Shogo Nomura:** Data curation, Formal analysis, Writing – review & editing. **Takashi Ikeno:** Data curation, Formal analysis, Writing – review & editing. **Hibiki Udagawa:** Investigation, Resources, Writing – review & editing. **Eri Sugiyama:** Investigation, Resources, Writing – review & editing. **Kaname Nosaki:** Investigation, Resources, Writing – review & editing. **Hiroki Izumi:** Investigation, Resources, Writing – review & editing. **Tetsuya Sakai:** Investigation, Resources, Writing – review & editing. **Naozumi Hashimoto:** Investigation, Resources, Writing – review & editing. **Koichi Goto:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] F. Griesinger, W. Eberhardt, A. Nusch, M. Reiser, M.O. Zahn, C. Maintz, C. Bernhardt, C. Losem, A. Stenzinger, L.C. Heukamp, R. Buttner, N. Marschner, M. Janicke, A. Fleitz, L. Spring, J. Sahlmann, A. Karatas, A. Hipper, W. Weichert, M. Heilmann, P. Sadjadian, W. Gleiber, C. Grah, C.F. Waller, M. Reck, A. Rittmeyer, P. Christopoulos, M. Sebastian, M. Thomas, C.R. Group, Biomarker testing in non-small cell lung cancer in routine care: Analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315), Lung Cancer 152 (2021) 174–184.

[2] F. Barlesi, J. Mazieres, J.-P. Merlio, D. Debieuvre, J. Mosser, H. Lena, L.H. Ouafik, B. Besse, I. Rouquette, V. Westeel, F. Escande, I. Monnet, A. Lemoine, R. Veillon, H. Blons, C. Audigier-Valette, P.-P. Bringuier, R. Lamy, M. Beau-Faller, J.-L. Pujol, J.-C. Sabourin, F. Penault-Llorca, M.G. Denis, S. Lantuejoul, F. Morin, Q. Tran, P. Missy, A. Langlais, B. Milleron, J. Cadranel, J.-C. Soria, G. Zalcman, Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT), Lancet 387 (10026) (2016) 1415–1426.

[3] P.J. Roberts, T.E. Stinchcombe, C.J. Der, M.A. Socinski, Personalized medicine in non-small-cell lung cancer: is KRAS a useful marker in selecting patients for epidermal growth factor receptor-targeted therapy? J. Clin. Oncol. 28 (31) (2010) 4769–4777.

[4] A.H. Nassar, Distribution of KRASG12C somatic mutations across race, sex and cancer type, N. Engl. J. Med. 384 (2021) 185–187.

[5] F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, R. Govindan, Sotorasib for lung cancers with KRAS p. G12C mutation, N. Engl. J. Med. 384 (25) (2021) 2371–2381.

[6] D.S. Hong, M.G. Fakih, J.H. Strickler, J. Desai, G.A. Durm, G.I. Shapiro, G. S. Falchook, T.J. Price, A. Sacher, C.S. Denlinger, Y.J. Bang, G.K. Dy, J.C. Krauss, Y. Kuboki, J.C. Kuo, A.L. Coveler, K. Park, T.W. Kim, F. Barlesi, P.N. Munster, S. S. Ramalingam, T.F. Burns, F. Meric-Bernstam, H. Henary, J. Ngang, G. Ngarmchamnanrith, J. Kim, B.E. Houk, J. Canon, J.R. Lipford, G. Friberg, P. Lito, R. Govindan, B.T. Li, KRAS(G12C) inhibition with sotorasib in advanced solid tumors, N. Engl. J. Med. 383 (13) (2020) 1207–1217.

[7] J. Hallin, L.D. Engstrom, L. Hargis, A. Calinisan, R. Aranda, D.M. Briere, N. Sudhakar, V. Bowcut, B.R. Baer, J.A. Ballard, M.R. Burkard, J.B. Fell, J. P. Fischer, G.P. Vigers, Y. Xue, S. Gatto, J. Fernandez-Banet, A. Pavlicek, K. Velastagui, R.C. Chao, J. Barton, M. Pierobon, E. Baldelli, E.F. Patricoin 3rd, D. P. Cassidy, M.A. Marx, M.L. Rybkin II, S.I. Johnson, P. Ou, K.P. Lito, P. A. Papadopoulos, P. Janne, J.G.C. Olson, The KRAS(G12C) inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients, Cancer Discov. 10 (1) (2020) 54–71.

[8] Y. Jia, T. Jiang, X. Li, C. Zhao, L. Zhang, S. Zhao, X. Liu, M. Qiao, J. Luo, J. Shi, H. Yang, Y. Wang, L. Xi, S. Zhang, G. Gao, C. Su, S. Ren, C. Zhou, Characterization of distinct types of KRAS mutation and its impact on first-line platinum-based chemotherapy in Chinese patients with advanced non-small cell lung cancer, Oncol. Lett. 14 (6) (2017) 6525–6532.

[9] A.C. Tan, G.G.Y. Lai, G.S. Tan, S.Y. Poon, B. Doble, T.H. Lim, Z.W. Aung, A. Takano, W.L. Tan, M.K. Ang, B.S. Tan, A. Devanand, C.W. Too, A. Gogna, B. H. Ong, T.P.T. Koh, R. Kanesvaran, Q.S. Ng, A. Jain, T. Rajasekaran, A.S.T. Lim, W. T. Lim, C.K. Toh, E.H. Tan, T.K.H. Lim, D.S.W. Tan, Utility of incorporating next-generation sequencing (NGS) in an Asian non-small cell lung cancer (NSCLC) population: incremental yield of actionable alterations and cost-effectiveness analysis, Lung Cancer 139 (2020) 207–215.

[10] S. Matsumoto, T. Ikeda, Y. Zenke, T. Kato, S. Sugawara, K. Nishino, I. Nakachi, H. Daga, N. Furuya, M. Morise, J. Sakakibara-Konishi, K. Yoh, K. Goto, Prospective concordance study of a multi-gene PCR assay and NGS for the detection of targetable gene alterations in lung cancer, J. Thoracic Oncol. 16 (3_Suppl) (2021) S690.

[11] K.C. Arbour, H. Rizvi, A.J. Plodkowski, M.D. Hellmann, A. Knezevic, G. Heller, H. A. Yu, M. Ladanyi, M.G. Kris, M.E. Arcila, C.M. Rudin, P. Lito, G.J. Riely, Treatment outcomes and clinical characteristics of patients with KRAS-G12C-mutant non-small cell lung cancer, Clin. Cancer Res. 27 (2021) 2209–2215.

[12] A. Galan-Cobo, P. Sitthideatphaiboon, X. Qu, A. Poteete, M.A. Pisegna, P. Tong, P. H. Chen, L.K. Boroughs, M.L.M. Rodriguez, W. Zhang, F. Parlati, J. Wang, V. Gandhi, F. Skoulidis, R.J. DeBerardinis, J.D. Minna, J.V. Heymach, LKB1 and KEAP1/NRF2 pathways cooperatively promote metabolic reprogramming with enhanced glutamine dependence in KRAS-mutant lung adenocarcinoma, Cancer Res. 79 (13) (2019) 3251–3267.

[13] J.A. Hellyer, S.K. Padda, M. Diehn, H.A. Wakelee, Clinical implications of KEAP1-NFE2L2 mutations in NSCLC, J. Thorac. Oncol. (2020).

[14] K.C. Arbour, E. Jordan, H.R. Kim, J. Dienstag, H.A. Yu, F. Sanchez-Vega, P. Lito, M. Berger, D.B. Solit, M. Hellmann, M.G. Kris, C.M. Rudin, A. Ni, M. Arcila, M. Ladanyi, G.J. Riely, Effects of co-occurring genomic alterations on outcomes in patients with KRAS-mutant non-small cell lung cancer, Clin. Cancer Res. 24 (2) (2018) 334–340.

[15] X. Chen, C. Su, S. Ren, C. Zhou, T. Jiang, Pan-cancer analysis of KEAP1 mutations as biomarkers for immunotherapy outcomes, Ann. Transl. Med. 8 (4) (2020) 141.

[16] X. Xu, Y. Yang, X. Liu, N. Cao, P. Zhang, S. Zhao, D. Chen, L. Li, Y. He, X. Dong, K. Wang, H. Lin, N. Mao, L. Liu, NFE2L2/KEAP1 mutations correlate with higher tumor mutational burden value/PD-L1 expression and potentiate improved clinical outcome with immunotherapy, Oncologist 25 (6) (2020) e955–e963.

[17] V.C. Cordeiro de Lima, M. Corassa, E. Saldanha, H. Freitas, O. Arrieta, L. Raez, S. Samtani, M. Ramos, C. Rojas, M. Burotto, D.F. Chamorro, G. Recondo, A. Ruiz-Patino, L. Mas, L. Zatarain-Barron, S. Mejia, J. Nicolas Minata, C. Martin, J. Bautista Blaquier, R. Motta Guerrero, C. Aliaga-Macha, C. Carracedo, C. Ordonez-Reyes, J.E. Garcia-Robledo, L. Corrales, C. Sotelo, L. Ricaurte, N. Santoyo, M. Cuello, E. Jaller, J. Rodriguez, P. Archila, M. Bermudez, T. Gamez, A. Russo, L. Viola, U. Malapelle, D. de Miguel Perez, C. Rolfo, R. Rosell, A. F. Cardona, STK11 and KEAP1 mutations in non-small cell lung cancer patients: descriptive analysis and prognostic value among Hispanics (STRIKE registry-CLICaP), Lung Cancer 170 (2022) 114–121.

[18] S. Koyama, E.A. Akbay, Y.Y. Li, A.R. Aref, F. Skoulidis, G.S. Herter-Sprie, K. A. Buczkowski, Y. Liu, M.M. Awad, W.L. Denning, L. Diao, J. Wang, E.R. Parra-Cuentas, M. Wistuba II, T. Soucheray, H. Thai, S. Asahina, A. Kitajima, J.D. Altabef, K. Cavanaugh, P. Rhee, H. Gao, P.E. Zhang, T. Fecci, M.D. Shimamura, J. V. Hellmann, F.S. Heymach, G.J. Hodi, D.A. Freeman, G. Barbie, P.S. Dranoff, K.K. W. Hammerman, STK11/LKB1 deficiency promotes neutrophil recruitment and proinflammatory cytokine production to suppress T-cell activity in the lung tumor microenvironment, Cancer Res. 76 (5) (2016) 999–1008.

[19] F. Skoulidis, M.E. Goldberg, D.M. Greenawalt, M.D. Hellmann, M.M. Awad, J. F. Gainor, A.B. Schrock, R.J. Hartmaier, S.E. Trabucco, L. Gay, S.M. Ali, J.A. Elvin, G. Singal, J.S. Ross, D. Fabrizio, P.M. Szabo, H. Chang, A. Sasson, S. Srinivasan, S. Kirov, J. Szustakowski, P. Vitazka, R. Edwards, J.A. Bufill, N. Sharma, S.I. Ou, N. Peled, D.R. Spigel, H. Rizvi, E.J. Aguilar, B.W. Carter, J. Erasmus, D. F. Halpenny, A.J. Plodkowski, N.M. Long, M. Nishino, W.L. Denning, A. Galan-Cobo, H. Hamdi, T. Hirz, P. Tong, J. Wang, J. Rodriguez-Canales, P.A. Villalobos, E.R. Parra, N. Kalhor, L.M. Sholl, J.L. Sauter, A.A. Jungbluth, M. Mino-Kenudson, R. Azimi, Y.Y. Elamin, J. Zhang, G.C. Leonardi, F. Jiang, K.K. Wong, J.J. Lee, V. A. Papadimitrakopoulou, V.A. Wistuba II, G.M. Miller, J.D. Frampton, A. T. Wolchok, P.A. Shaw, P.J. Janne, C.M. Stephens, W.J. Rudin, L.A. Geese, J.V. H. Albacker, STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma, Cancer Discov. 8 (7) (2018) 822–835.

[20] G.J. Riely, M.G. Kris, D. Rosenbaum, J. Marks, A. Li, D.A. Chitale, K. Nafa, E. R. Riedel, M. Hsu, W. Pao, V.A. Miller, M. Ladanyi, Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma, Clin. Cancer Res. 14 (18) (2008) 5731–5734.

[21] T.L. Ng, Y. Liu, A. Dimou, T. Patil, D.L. Aisner, Z. Dong, T. Jiang, C. Su, C. Wu, S. Ren, C. Zhou, D.R. Camidge, Predictive value of oncogenic driver subtype, programmed death-1 ligand (PD-L1) score, and smoking status on the efficacy of PD-1/PD-L1 inhibitors in patients with oncogene-driven non-small cell lung cancer, Cancer 125 (7) (2019) 1038–1049.

[22] M. Sebastian, 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), Lung Cancer 154 (2021) 51–61.

[23] J. Canon, K. Rex, A.Y. Saiki, C. Mohr, K. Cooke, D. Bagal, K. Gaida, T. Holt, C. G. Knutson, N. Koppada, B.A. Lanman, J. Werner, A.S. Rapaport, T. San Miguel, R. Ortiz, T. Osgood, J.R. Sun, X. Zhu, J.D. McCarter, L.P. Volak, B.E. Houk, M. G. Fakih, B.H. O'Neil, T.J. Price, G.S. Falchook, J. Desai, J. Kuo, R. Govindan, D. S. Hong, W. Ouyang, H. Henary, T. Arvedson, V.J. Cee, J.R. Lipford, The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity, Nature 575 (7781) (2019) 217–223.

[24] A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C. E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P. A. Cassier, L. Bazhenova, F. De Braud, E. Garralda, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S. M. Rothenberg, K. Goto, V. Subbiah, Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer, N. Engl. J. Med. 383 (9) (2020) 813–824.

[25] J.C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K. H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.C. Su, J.E. Gray, S.M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, S.S. Ramalingam, F. Investigators, Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer, N. Engl. J. Med. 378 (2) (2018) 113–125.

[26] S. Peters, D.R. Camidge, A.T. Shaw, S. Gadgeel, J.S. Ahn, D.W. Kim, S.I. Ou, M. Perol, R. Dziadziuszko, R. Rosell, A. Zeaiter, E. Mitry, S. Golding, B. Balas, J. Noe, P.N. Morcos, T. Mok, A.T. Investigators, Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer, N. Engl. J. Med. 377 (9) (2017) 829–838.

[27] A.T. Shaw, S.H. Ou, Y.J. Bang, D.R. Camidge, B.J. Solomon, R. Salgia, G.J. Riely, M. Varella-Garcia, G.I. Shapiro, D.B. Costa, R.C. Doebele, L.P. Le, Z. Zheng, W. Tan, P. Stephenson, S.M. Shreeve, L.M. Tye, J.G. Christensen, K.D. Wilner, J.W. Clark, A. J. Iafrate, Crizotinib in ROS1-rearranged non-small-cell lung cancer, N. Engl. J. Med. 371 (21) (2014) 1963–1971.