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LETTER TO THE EDITOR

Clinical characteristics and outcomes of Chinese patients with KRAS-mutant non-small cell lung cancer after chemotherapy

Dear Editor,

The *RAS* gene is one of the most frequent oncogenes in human cancers, with significantly different mutation frequencies. The *RAS* family contains three isoforms: *KRAS*, *HRAS* and *NRAS*, with the *KRAS* mutations being more common than the other two. The *KRAS* mutation rate varies in non-small cell lung cancer (NSCLC) patients of different races: 27% in Caucasians [1] and approximately 10% in Asians [2, 3]. Recently, the U.S. Food and Drug Administration (FDA) approved sotorasib (AMG510) and adagrasib (MRTX849) for the treatment of metastatic NSCLC harboring *KRAS* G12C mutations. In the face of novel treatment choices for *KRAS*-mutated NSCLC, it is indispensable to learn more about the systemic treatment of these patients. Clinical studies have shown that Caucasian patients with *KRAS*-mutated NSCLC had poor outcomes following first-line chemotherapy [4, 5]. However, studies on treatment outcomes of Asian patients with *KRAS*-mutated NSCLC are lacking. As the overwhelming majority of cases are diagnosed with lung adenocarcinoma, the standard first-line treatment for metastatic disease is pemetrexed-based doublet chemotherapy in combination with bevacizumab and/or immunotherapy in China. Herein, we investigated the clinical characteristics of *KRAS* mutation subtypes, co-occurring genomic alterations, and efficacy of first-line pemetrexed-platinum chemotherapy in Chinese *KRAS*-mutated NSCLC patients.

The data of 5180 patients with NSCLC (either *de novo* or relapsed) who underwent genetic testing at Shandong Cancer Hospital between January 2016 and October 2020 were reviewed (Supplementary Figure S1). Data on clinical features, mutation subtypes, and co-mutations of *KRAS*-mutated lung cancer were collected. A paired study was also performed to evaluate the effect of chemotherapy in advanced-stage patients with *KRAS* mutations. The prognostic factors of advanced-stage *KRAS*-mutated patients were analyzed. Patient selection and assessment protocols are detailed in the Supplementary Material.

Of the 5180 NSCLC patients screened, 477 had *RAS* mutations, and 471 had *KRAS* mutations. Among the 1239 patients who underwent amplification refractory mutation system (ARMS)-PCR testing, 103 had *KRAS* mutations (8.3%), and two had *NRAS* mutations (Supplementary Figure S2). In the other 3941 patients who underwent next-generation sequencing (NGS) testing, 368 had *KRAS* mutations (9.3%), and one of them had *KRAS* and *NRAS* co-mutations. In addition, three patients had *NRAS* mutations, and one had an *HRAS* mutation.

The characteristics of the 1239 patients who underwent ARMS-PCR testing are shown in Supplementary Table S1. Compared with patients with *epidermal growth factor receptor (EGFR)* mutations, those with *KRAS* mutations had a higher proportion of smoking history ($n = 64$, 62.1%), males ($n = 84$, 81.6%), and were older (63.0 ± 9.2 years). The relationship between gene mutation profiles and brain metastasis at the time of diagnosis was analyzed, and we observed that T stage, N stage, pathological type, and *EGFR* mutation were predictive of brain metastasis, while *KRAS* mutation was not a risk factor ($P = 0.819$) (Supplementary Table S2).

The *RAS* mutation subtypes in 372 patients who underwent NGS testing were analyzed. The three most common *RAS* mutation sites were *KRAS* G12C ($n = 106$, 28.5%), G12D ($n = 79$, 21.1%), and G12V ($n = 75$, 20.2%) (Supplementary Table S3 and Figure 1A). Notably, 2.7% ($n = 10$) of *RAS*-mutated patients had two *RAS* mutation sites. *KRAS*-mutated NSCLC is reported to have a high frequency of co-mutations in cancer-associated pathways [6]. Co-mutation

Abbreviations: ALK, anaplastic lymphoma kinase; ARMS, amplification refractory mutation system; EGFR, epidermal growth factor receptor; MLR, monocyte-to-lymphocyte ratio; NGS, Next-Generation Sequencing; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death-1; PDL1, programmed cell death-ligand 1; PFS, progression-free survival; PLR, Platelet-to-lymphocyte ratio; STK11, serine threonine kinase 11; TP53, tumor protein p53

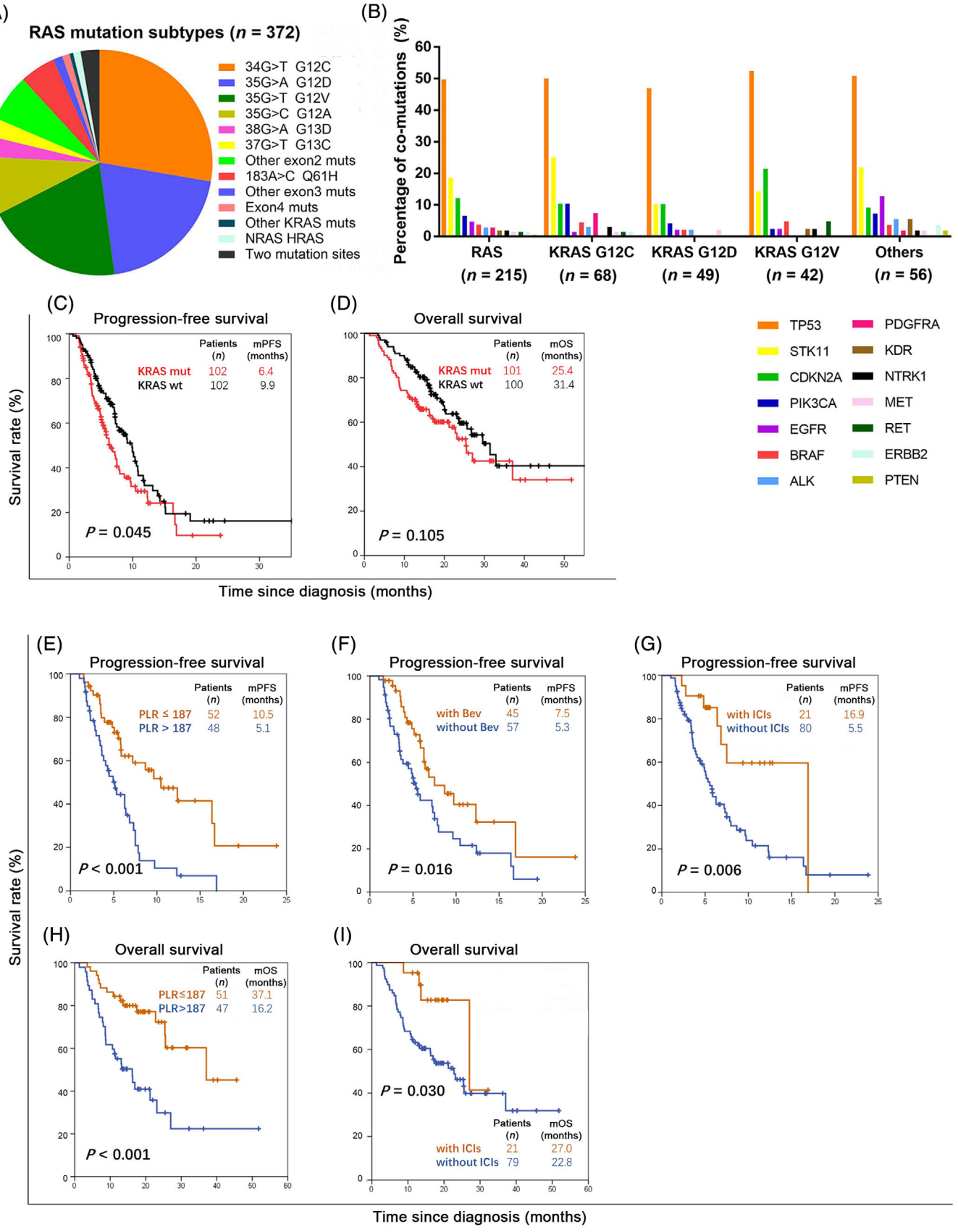

FIGURE 1 Clinical characteristics and chemotherapy outcomes in patients with *KRAS*-mutated NSCLC. A. *RAS* mutation subtypes of 372 NSCLC patients who underwent NGS. B. Co-mutations in patients with *RAS*-mutated NSCLC. C. PFS of *KRAS*-mutated and *KRAS*-wild-type patients. D. OS of *KRAS*-mutated and *KRAS*-wild-type patients. E. PFS curve of *KRAS*-mutated patients based on PLR. F. PFS

information was available for 215 patients, and *tumor protein p53* (TP53) ($n = 107$, 49.8%) and *serine threonine kinase 11* (STK11) ($n = 40$, 18.6%) were the most common mutated genes in *RAS*-mutated NSCLC (Figure 1B).

Next, *KRAS*-mutated and *KRAS*-wild-type patients who had received pemetrexed-based doublet chemotherapy as first-line therapy were selected. Patients in the two groups were matched for the shown clinical features (Supplementary Table S4). After a median follow-up period of 19.7 (95% confidence interval [CI] 17.5–21.8) months, the median progression-free survival (PFS) in the *KRAS*-mutated group and *KRAS* wild-type group was 6.4 (95% CI 5.1–7.7) and 9.9 (95% CI 7.7–12.1) months, respectively, and the difference was significant ($P = 0.045$) (Figure 1C). *KRAS*-mutated patients tended to have shorter median overall survival (OS), but the difference was not significant (25.4 vs. 31.4 months, $P = 0.105$) (Figure 1D).

The prognostic factors of *KRAS*-mutated patients who had received pemetrexed-platinum chemotherapy were further analyzed using univariate and multivariate analyses (Supplementary Table S5 and S6). The platelet-to-lymphocyte ratio (PLR) (hazard ratio [HR] = 2.38, $P = 0.019$), bevacizumab combination (HR = 0.52, $P = 0.019$), and immunotherapy combination (HR = 0.30, $P = 0.004$) were independent predictive factors for PFS (Figure 1E–G). *KRAS* mutation type was not an independent predictive factor for PFS; however, patients with *KRAS* G12C mutation had the shortest median PFS (4.5 months, 95% CI 0–9.1 months) (Supplementary Figure S3A). PLR (HR = 2.55, $P = 0.030$) and immunotherapy combination (HR = 0.31, $P = 0.025$) were independent influencing factors of OS (Figure 1H and I).

In this study, the *KRAS* mutation rate was 8.8% in patients who underwent ARMS-PCR testing and 9.3% in those who underwent NGS testing, which is in accordance with a previous study [2]. Only seven patients had NRAS or HRAS mutations. *KRAS*-mutated cancer patients tended to be male and elderly, 62.1% had a history of smoking while Caucasian patients comprised of a higher proportion of females (58%) and history of smoking (93%) [1]. Whether the *KRAS* mutation subtype is associated with survival remains controversial [7, 8]. Although the *KRAS* G12C group was associated with shortest PFS in this study, no survival difference in different *KRAS* mutation subtypes was found.

The therapeutic response and survival of lung cancer patients without *EGFR* or *anaplastic lymphoma kinase* (ALK) driver gene alterations receiving first-line chemotherapy are difficult to predict. Recently, He et al. [9] showed that molecular signatures could only provide limited information. In this study, NSCLC patients were classified into four subtypes based on genomic alteration characteristics, however, no survival difference between the subtypes were observed. Our findings showed that NSCLC patients with *KRAS* mutations had worse PFS after initial pemetrexed-based platinum doublets than those without driver genes, and the survival difference seems mainly from those receiving chemotherapy alone and those with bevacizumab combination (Supplementary Figure S3B and S3C). When comparing the PFS of those with immunotherapy combination in the two groups (Supplementary Figure S3D), the survival curves almost overlapped. In addition, immunotherapy combination was an independent influencing factor for both PFS and OS in *KRAS*-mutated NSCLC patients. Therefore, a combination of chemotherapy and immunotherapy could be recommended to improve the efficacy of these patients. PLR, neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR) are factors that reflect systemic inflammation, and studies have shown their relationship with poor prognosis in NSCLC [10]. Here, we also found that these factors were predictive in *KRAS*-mutated NSCLC, and PLR was an independent influencing factor for both PFS and OS.

The limitation of this study was that its retrospective nature, and the drugs used as anti-programmed cell death-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) immunotherapy were diverse. In addition, the ARMS-PCR test was performed in 23.9% ($n = 1239$) of NSCLC patients screened. Although paired analyses were performed to ensure comparability between the clinical characteristics of the *KRAS*-mutated and *KRAS*-wild-type groups, there could remain unavoidable risk of selection bias.

In summary, the *KRAS* mutation rate in Chinese NSCLC patients seemed lower than that in Caucasians, and the proportion of *KRAS* G12C mutation was no more than 30%. Compared with *KRAS* wild-type patients, *KRAS*-mutated

curve of *KRAS*-mutated patients based on the administration of bevacizumab combination. G. PFS curve of *KRAS*-mutated patients based on the administration of immunotherapy combination. H. OS curve of *KRAS*-mutated patients based on PLR. I. OS curve of *KRAS*-mutated patients based on the administration of immunotherapy combination.

Abbreviations: NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; KRAS, Kirsten rat sarcoma viral oncogene homolog; NRAS, Neuroblastoma rat sarcoma viral oncogene homolog; HRAS, Harvey rat sarcoma viral oncogene homolog; RAS, rat sarcoma gene; PFS, progression-free survival; OS, overall survival; mut, mutation; wt, wild-type; PLR, platelet-to-lymphocyte ratio; bev, bevacizumab; ICIs, immune checkpoint inhibitors

patients had worse PFS after pemetrexed-platinum chemotherapy. Lastly, a combination of chemotherapy and immunotherapy could improve the survival of patients with *KRAS*-mutated lung adenocarcinoma.

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AUTHORS' CONTRIBUTIONS

YWZ and LGX designed the research. YWZ, QHL, and XRS acquired the data and performed patients' selection process. YWZ and QHL analyzed the data and wrote the manuscript. XLL and HXZ reviewed the medical images. XRS and LGX revised the manuscript. All authors critically reviewed the manuscript and approved the contents.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by Shandong Cancer Hospital Shandong Cancer Hospital and Institute (No. SDTHEC2020010012).

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