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Authors

Iams, Wade T
Yu, Hui
Shyr, Yu
et al.

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Original Study

First-line Chemotherapy Responsiveness and Patterns of Metastatic Spread Identify Clinical Syndromes Present Within Advanced KRAS Mutant Non–Small-cell Lung Cancer With Different Prognostic Significance

Wade T. Iams,[1] Hui Yu,[2] Yu Shyr,[3] Tejas Patil,[4] Leora Horn,[5] Caroline McCoach,[6] Karen Kelly,[7] Robert C. Doebele,[4] D.Ross Camidge[4]

Abstract

In the present multicenter study, we performed a retrospective medical record review of 218 patients. We identified 2 distinct clinical cohorts with *KRAS* mutant, recurrent, metastatic or de novo metastatic non–small-cell lung cancer: patients with nonscalp, soft tissue metastases with a uniquely poor prognosis and patients with disease responsive to first-line chemotherapy with a uniquely good prognosis. A deeper molecular understanding of these cohorts is needed.

Background: Unsuccessful *KRAS*-specific treatment approaches in non–small-cell lung cancer (NSCLC) might reflect underlying disease heterogeneity. We sought to define clinical "syndromes" within advanced *KRAS* mutant NSCLC to improve future clinical trials and create a clinical framework for future molecular development. **Patients and Methods:** To test a series of a priori hypotheses regarding *KRAS*-mutant NSCLC clinical syndromes, we conducted a multi-institutional retrospective medical record review. Survival probabilities were estimated using the Kaplan-Meier model. Between-group differences were assessed using the log-rank test. Multivariate Cox regression analyses and Wilcoxon rank sum testing were used to assess progression-free survival and overall survival (OS) differences. **Results:** Among 218 patients with advanced *KRAS*-mutant NSCLC, OS and progression-free survival with first-line chemotherapy did not differ by intrathoracic versus extrathoracic spread, smoking intensity, or the specific *KRAS* mutation. Metastatic disease at diagnosis resulted in significantly worse OS than recurrent, unresectable disease (median OS, 14.6 vs. 40.9 months; $P = .001$). Among the patients with metastatic disease at diagnosis, nonscalp, soft tissue metastases (syndrome X; 6% of cases; 95% confidence interval [CI], 2.5%-10.1%) signified a poor prognosis (median OS, 7.5 vs. 15.9 months for the controls; $P = .021$). The response to first-line chemotherapy (syndrome Y; 41% of cases; 95% CI, 32.3%-50.6%) signified a good prognosis (median OS, 26.7 vs. 11.9 months; $P = .002$). The overlap between these 2 syndromes was minimal (2 of 111). Multivariate analysis confirmed these observations. The hazard ratio for death for syndromes X and Y was 2.64 (95% CI, 1.13-6.14) and 0.45 (95% CI, 0.28-0.76), respectively. **Conclusion:** Chemotherapy-responsive disease and nonscalp, soft tissue spread might represent distinct clinical syndromes within *KRAS*-mutant NSCLC. The molecular biology underlying this heterogeneity warrants future studies.

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Keywords: Chemotherapy-responsive, KRAS clinical syndromes, Metastatic, NSCLC, Soft tissue metastasis

[1]Division of Hematology/Oncology, Department of Medicine, Northwestern University, Chicago, IL
[2]Department of Internal Medicine, University of New Mexico, Albuquerque, NM
[3]Department of Statistics, Vanderbilt-Ingram Cancer Center, Nashville, TN
[4]Division of Medical Oncology, Department of Medicine, University of Colorado, Denver, CO
[5]Division of Hematology/Oncology, Department of Medicine, Vanderbilt-Ingram Cancer Center, Nashville, TN
[6]Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, San Francisco, CA
[7]Department of Medical Oncology, University of California, Davis, Sacramento, CA

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Address for correspondence: D.Ross Camidge, MD, PhD, Division of Medical Oncology, Department of Medicine, University of Colorado, Anschutz Cancer Pavilion, 1665 North Aurora Court, Mail Stop F-704, Room 5237 Aurora, CO 80045
E-mail contact: ross.camidge@ucdenver.edu

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Introduction

Oncogenic mutations in *KRAS* occur in ~26% and ~11% of patients with lung adenocarcinoma in Western and Asian populations, respectively.[1-3] Despite success in therapeutically targeting mutations in other dominant oncogenes in patients with non–small-cell lung cancer (NSCLC), such as the epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*), no *KRAS* mutation-specific therapeutic approach has entered standard practice for patients with NSCLC.[4,5]

Several KRAS-directed approaches have been unsuccessful in large clinical trials, including farnesyl-transferase inhibitors and MEK inhibitors.[6-10] One explanation for the lack of success in targeting these pathways in patients with *KRAS*-mutant NSCLC is the challenge of pharmacologic inhibition of RAS. However, recognition has also been increasing that *KRAS*-mutant NSCLC might not be a single disease entity. If subgroups present within *KRAS*-mutant NSCLC are associated with different prognostic significance and are imbalanced in randomized clinical trials, efficacy results such as progression-free survival (PFS) or overall survival (OS) could be confounded.

Significant preclinical evidence to date has supported the existence of relevant *KRAS*-mutant subgroups. Both KRAS-signaling independence and variable dependence on downstream MEK/ERK, PI3K, and RAL signaling have been identified in vitro in *KRAS*-mutant cell lines.[11,12] Recently, with the introduction of routine genomic profiling platforms into the clinic, a broad range of coincident mutations in patients with *KRAS*-mutant NSCLC has been described that could have prognostic significance.[13,14]

What has been lacking has been a robust description of the different clinical manifestations of *KRAS*-mutant NSCLC. A better understanding of the different clinical behaviors coexisting within the same broad disease entity could clarify the relationship between distinct clinical phenotypes and specific *KRAS* molecular contextual groups. Our earlier work identified 1 example of potential clinically relevant heterogeneity existing within patients with *KRAS*-mutant NSCLC. In addition to identifying prolonged PFS from pemetrexed in any line of therapy among patients with *ALK*-rearranged NSCLC, we observed 2 distinct groups in relation to pemetrexed sensitivity within the *KRAS* control group.[15] In that study, nearly 50% of patients with *KRAS*-mutant NSCLC had PFS of < 4 months with pemetrexed, but nearly 30% of patients with *KRAS*-mutant NSCLC experienced PFS that was > 12 months with pemetrexed.[15]

Also, because previous reports have suggested the dominant oncogenic driver mutation in NSCLC can influence the sites of metastatic disease at diagnosis, we hypothesized that specific sites of metastatic disease among patients with *KRAS*-mutant NSCLC could be used to define the clinical phenotypes associated with different underlying molecular biology and clinical outcomes.[16] For example, 1 of us (D.R.C.), based on personal clinical observation, hypothesized that patients with nonscalp, soft tissue metastatic *KRAS*-mutant NSCLC might have a uniquely poor prognosis.

In the present study, we explored the evidence for distinct clinical phenotypes existing within patients with advanced *KRAS*-mutant NSCLC, correlating the baseline and during treatment clinical and *KRAS* mutation features with PFS and OS from the diagnosis of metastatic or recurrent, unresectable disease within a large, multisite, retrospective analysis. After seeking single variables associated with outcomes, we described the clinical features associated with each preidentified variable. We termed our final proposed clinically relevant subcategorizations clinical "syndromes."

Patients and Methods

Study Population

After institutional review board approval, the clinical and demographic data were collected from the medical records of qualifying patients treated at the Vanderbilt Ingram Cancer Center, University of Colorado Cancer Center, and University of California, Davis, Comprehensive Cancer Center. Patients with stage IV or recurrent, unresectable *KRAS*-mutant NSCLC treated from August 1, 2005 to April 2, 2015 were included. The survival and disease status information was updated through May 1, 2015. *KRAS* mutation status was determined by molecular profiling of formalin-fixed, paraffin-embedded tumor biopsy tissue conducted in accordance with each institution's standards. The responses to systemic chemotherapy (complete response [CR], partial response [PR], stable disease [SD], progressive disease) were determined using the Response Evaluation Criteria In Solid Tumors, version 1.1, as documented in the radiology reports, provider notes, and/or tumor measurement forms. All clinical data were maintained in compliance with Health Insurance Portability and Accountability Act standards.

Data Collection

Information was captured on smoking history in pack-years, specific *KRAS* mutation type (G12C, G12A, G12V, G12D, G12S, G12R, G13C, G13D, Q61H 183A>T, Q61H 183A>C, Q61L, or Q61K), and sites of metastases at the diagnosis of stage IV disease or recurrent, unresectable disease. The disease of all patients was clinically staged from the radiographic findings and clinical documentation. The sites of metastatic disease captured included lung parenchyma, thoracic lymph nodes, pleural fluid, adrenal, renal, hepatic, and abdominal lymph nodes, bone, brain, and soft tissue metastases (defined as epidermal, dermal [scalp vs. nonscalp, based on 1 a priori hypothesis], or myofascial). All soft tissue metastases were defined as occurring in nonlymphoid tissue, and the identification of soft tissue metastases was determined by the presence of any of the following: imaging findings, clinical examination documentation, or biopsy results. Biopsy was not required to identify soft tissue metastases. Myofascial involvement was defined as metastatic deposits in muscle tissue. The best response to each line of systemic chemotherapy was collected.

Therapy-responsive cohorts were defined as patients with a best response of PR or CR with the specific therapy and line of therapy assessed. We compared pemetrexed-responsive and pemetrexed nonresponsive groups according to their best response to pemetrexed with any line of therapy. In this analysis, the patients who had not received pemetrexed were excluded. Pemetrexed-responsive patients were defined as those patients with a PR or CR to pemetrexed (given as monotherapy or combination therapy). Pemetrexed nonresponsive patients were those patients exposed to pemetrexed with a best response of SD or progressive disease during pemetrexed-containing therapy.

Statistical Analysis

PFS was defined as the interval between the diagnosis of metastatic or recurrent, unresectable disease and progression (or death, if no previous progression). OS was defined as interval between the diagnosis of metastatic or recurrent, unresectable disease and death. We used the Kaplan-Meier model to estimate survival probabilities and the log-rank test to compare survival probabilities between the 2 groups. A 1-sided Wilcoxon rank-sum test was used to test whether the first-line PFS duration was similar between those responding to pemetrexed-containing therapy and those responding to non−pemetrexed-containing first-line regimens. In this analysis, PFS duration was the interval between the first-line therapy start date and disease progression or death. The data from patients who had received pemetrexed maintenance were not analyzed separately. They were included in the group of patients who had received any pemetrexed. A Wilcoxon rank-sum test was used to compare the number of metastatic sites between patient cohorts. All statistical computations were performed in the R computational environment,[17] and the R package "survival" was used to analyze the survival probabilities and graph the survival plots.[18] Because of the a priori clinical observation that patients with nonscalp, soft tissue metastases tended to have a poor prognosis, we conducted a log-rank test to assess whether the presence of a nonscalp, soft tissue metastatic site resulted in a worse prognosis. We also conducted a multivariate Cox regression analysis among the patients with metastatic *KRAS*-mutant NSCLC at diagnosis to verify the prognostic implications of the suspected syndromes with the other potentially confounding factors adjusted for (> 40 pack-year smoking history, intrathoracic-limited disease, and *KRAS* G12C mutation status).

Results

Demographic Data

In total, 218 patients with advanced *KRAS*-mutant NSCLC were included, 158 with metastatic disease at diagnosis, 57 with recurrent, unresectable disease, and 3 with unclassified advanced disease. The demographic, molecular, and treatment characteristics of the patients are listed in Table 1. Most patients were white women with stage IV disease at diagnosis and adenocarcinoma histologic type and had initially received platinum-based chemotherapy. The performance status at diagnosis or at the start of specific therapy was not captured. Overall, 70 patients (32%) had M1a disease and 148 had M1b disease (68%).

Metastatic Versus Recurrent, Unresectable Disease

When comparing patients with recurrent, unresectable disease versus metastatic disease at diagnosis, the median OS and PFS to first-line chemotherapy were both longer for patients with recurrent, unresectable disease (median OS, 40.9 months; 95% confidence interval [CI], 23.1-59.4 months vs. 14.6 months; 95% CI, 10.5-21.6 months; $P = .001$; median PFS, 10.7 months; 95% CI, 7.9-21.4 months vs. 5.9 months; 95% CI, 5.4-7.1 months; $P = .001$, respectively; Figure 1). The 3 unclassified patients were excluded from the analysis. The first-line chemotherapy regimens were similar between the 2 groups, with the exception of a greater rate of platinum plus bevacizumab (20% vs. 4%) for patients with metastatic *KRAS*-mutant NSCLC at diagnosis.

Intrathoracic Disease and Smoking History

We found no differences in OS or PFS to first-line chemotherapy in our *KRAS*-mutant NSCLC cohort when stratified by intrathoracic-limited (M1a) disease and widely metastatic (M1b) disease or the intensity of smoking history. We compared the median OS and PFS to first-line chemotherapy using a priori cutpoints of either 20 pack-years or 40 pack-years of smoking history. These 2 cutpoints were close to the 25% quantile (n = 17) and 75% quantile (n = 45) of the smoking pack number distribution, with a median of 30 pack-years in our patient population. We were not able to capture data on current versus former smoking status or the time from the cessation of smoking. In evaluations of both the full cohort (n = 218) and only patients with metastatic disease at diagnosis (n = 158), none of these comparisons of differences in outcome reached statistical significance.

KRAS *Mutation Type*

To assess other distinct clinical cohorts within our patients with advanced *KRAS*-mutant NSCLC, we compared the OS and PFS to first-line chemotherapy between patients with *KRAS* G12C mutant disease and all other *KRAS* mutations. It has been observed that patients with *KRAS* G12C mutations might have a worse prognosis than that of patients with other *KRAS* mutation types.[19] Also, the G12C mutation was the largest subgroup of *KRAS*-mutant patients in our cohort, representing 39% of the 218 patients. The median OS and PFS to first-line chemotherapy were not significantly different in the *KRAS* mutation comparison for the overall cohort (n = 218; median OS, 14.6 months for *KRAS* G12C-mutant patients vs. 19.6 months for the comparator group; $P = .433$; PFS, 6.6 months for *KRAS* G12C-mutant patients vs. 7.5 months for the comparator group; $P = .905$). The median OS and PFS to first-line chemotherapy were also not significantly different for the comparison of only patients with metastatic disease at diagnosis (n = 158; median OS, 11.9 months for *KRAS* G12C-mutant patients vs. 15.9 months for the comparator group; $P = .871$; PFS, 6.3 months for the *KRAS* G12C-mutant patients vs. 5.7 months for the comparator group; $P = .921$).

Sites of Metastasis at Diagnosis

The sites of metastasis in the study population are listed in Table 2. With the aforementioned clinical observation of potentially worse outcomes for those with soft tissue metastases, except for scalp metastases, we assessed the effect of these sites and of comparably sized subgroups of metastatic disease: specifically, soft tissue spread, nonscalp soft tissue spread (n = 15), adrenal spread (n = 33), and brain spread (n = 62). Because of the potential for initial definitive therapy among those with recurrent disease altering the pattern of subsequent spread and our previously observed differences in PFS and OS between those with recurrent, unresectable disease and those with metastatic disease at diagnosis, we limited our analyses to the 158 patients with metastatic disease at diagnosis. In these 158 patients with metastatic disease at diagnosis, the 3 sites of metastasis included 14 patients with nonscalp soft tissue, 25 with adrenal, and 46 with brain metastases.

Patients with metastatic *KRAS*-mutant NSCLC at diagnosis and soft tissue metastasis, excluding scalp metastasis (KRAS syndrome

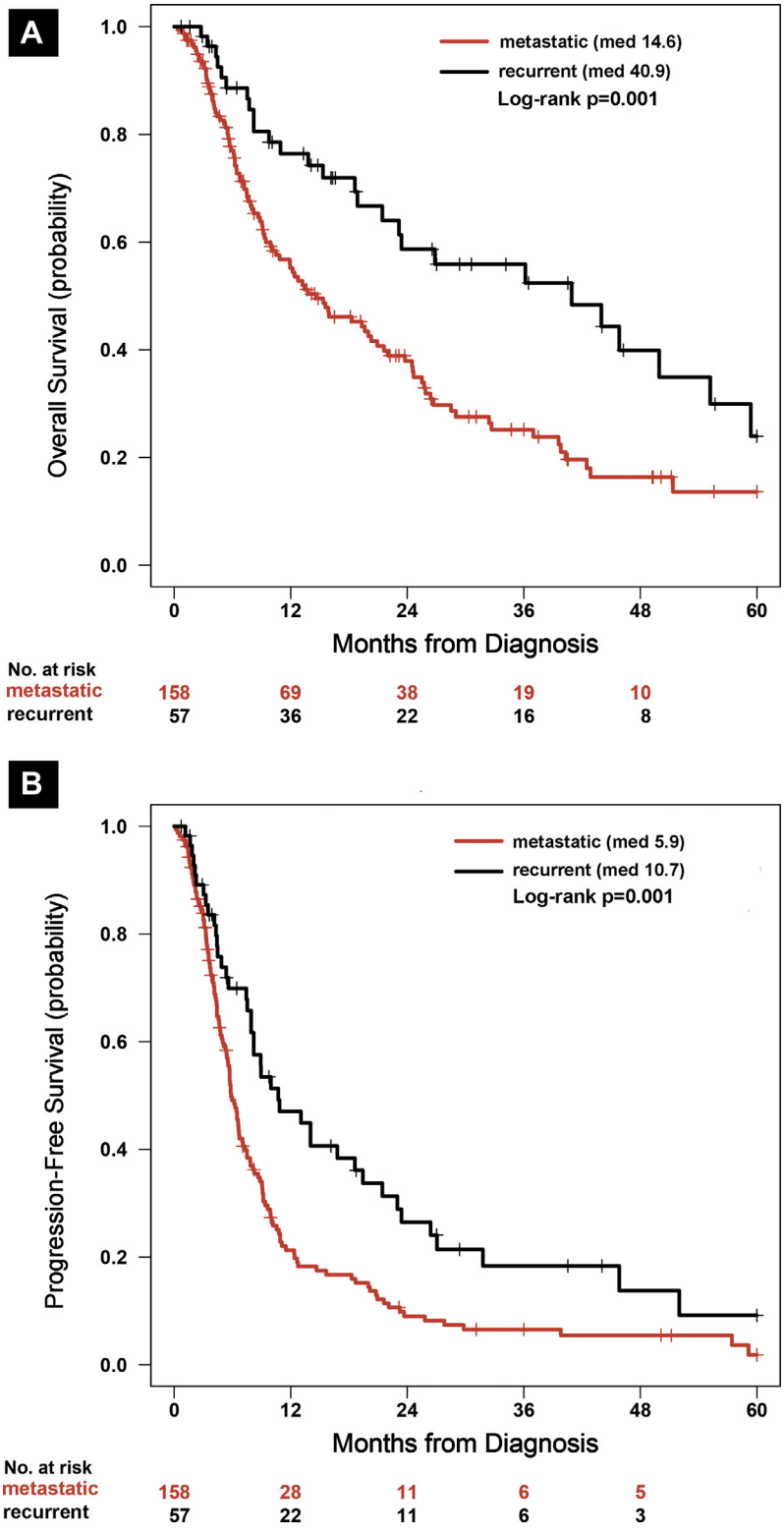
Table 1 Baseline Characteristics

Characteristic	All Patients (n = 218)	Metastasis at Diagnosis (n = 158)	Recurrent, Unresectable (n = 57)
Median age at diagnosis, y	63	62	65.5
Median tobacco use, pack-years	30	30	40
Male gender	89 (41)	73 (46)	14 (25)
Race			
White	190 (87)	139 (88)	50 (88)
African American	14 (6)	9 (6)	3 (4)
Asian	2 (1)	2 (1)	0 (0)
Hispanic	2 (1)	0 (0)	2 (4)
Unknown	10 (5)	8 (5)	2 (4)
Intrathoracic disease only	70	45	24
Histologic type			
Adenocarcinoma	189 (87)	139 (88)	48 (84)
Adenosquamous	3 (1)	2 (1)	1 (2)
Squamous	7 (3)	3 (2)	4 (7)
Poorly differentiated	9 (4)	8 (5)	1 (2)
Large cell	8 (4)	5 (3)	3 (5)
Unknown	2 (1)	1 (1)	0 (0)
First-line therapy			
Platinum based			
No pemetrexed/bevacizumab	55 (25)	42 (27)	11 (19)
Pemetrexed	56 (26)	43 (27)	13 (23)
Bevacizumab	34 (16)	32 (20)	2 (4)
Both pemetrexed/bevacizumab	10 (5)	7 (4)	3 (5)
Pemetrexed maintenance	30 (14)	19 (12)	11 (19)
None	22 (10)	14 (9)	8 (14)
Other[a]	24 (11)	7 (4)	17 (30)
Unknown	16 (7)	13 (9)	3 (5)
KRAS mutation type			
G12C	85 (39)	59 (37)	24 (42)
Q61H 183A>C	3 (1)	3 (2.5)	0 (0)
Q61H 183A>T	6 (3)	5 (3.5)	1 (2)
G12V	45 (21)	32 (20)	12 (21)
Q61L	1 (0.5)	1 (0.5)	0 (0)
G13D	8 (4)	5 (3.5)	3 (5)
G12A	16 (7)	11 (7)	5 (8)
G12D	29 (13)	21 (13)	8 (14)
G13C	5 (2)	3 (2.5)	2 (4)
G12S	7 (3.5)	7 (4)	0 (0)
Q61K	1 (0.5)	1 (0.5)	0 (0)
G12R	2 (1)	2 (1)	0 (0)
G13S	1 (0.5)	1 (0.5)	0 (0)
Other	3 (1)	2 (1)	1 (2)
Unknown	6 (3)	5 (3.5)	1 (2)

Data presented as n (%).
[a]Other first-line therapies included erlotinib monotherapy, sorafenib monotherapy, pemetrexed monotherapy, and gemcitabine monotherapy.

X), experienced inferior median OS and PFS (median OS, 7.5 months; 95% CI, 6.2 months to undefined; vs. 15.9 months, 95% CI, 11.9-23.8 months; $P = .021$; median PFS, 4.3 months; 95% CI, 3.1 months to undefined; vs. 6.4 months, 95% CI, 5.5-7.8 months; $P = .012$, respectively; Figure 2). Consistent with the a priori clinical hypothesis, when we included patients with scalp

Figure 1 Comparison of (A) Overall Survival and (B) Progression-Free Survival to First-Line Chemotherapy Between Patients With Metastatic *KRAS*-Mutant Non–Small-Cell Lung Cancer (NSCLC) at Diagnosis and Recurrent, Unresectable *KRAS*-Mutant NSCLC



Abbreviation: Med = median.

Table 2 Sites of Metastases Stratified by Cohort

Metastatic Site	All Patients (n = 218)	Metastatic (n = 158)	Recurrent (n = 57)
Lung parenchyma	96 (44)	64 (41)	32 (56)
Thoracic lymph node	44 (20)	32 (20)	11 (19)
Pleural	50 (23)	36 (23)	13 (23)
Adrenal	33 (15)	25 (16)	8 (14)
Renal	2 (1)	2 (1)	0 (0)
Liver	28 (13)	24 (15)	4 (7)
Abdominal lymph node	2 (1)	2 (1)	0 (0)
Bone	71 (33)	60 (38)	10 (18)
Brain	62 (28)	46 (29)	14 (25)
Soft tissue (including scalp)	19 (9)	14 (9)	5 (9)
Soft tissue (excluding scalp)	15 (7)	10 (6)	5 (9)
Other	31 (14)	21 (13)	10 (18)

Data presented as n (%).
No formal statistical comparison of the frequencies of metastatic sites among the groups was performed.

metastasis in the soft tissue metastasis group, the differences in median OS and PFS were no longer statistically significant (median OS, 8.6 months; 95% CI, 6.2 months to undefined; vs. 15.9 months, 95% CI, 12.2-23.8 months; $P = .14$; median PFS, 4.9 months; 95% CI, 4.3 months to undefined, vs. 6.4 months, 95% CI, 5.5-7.8 months; $P = .29$, respectively).

Patients with metastatic *KRAS*-mutant NSCLC at diagnosis with adrenal metastasis (n = 25; 4 patients with both soft tissue and adrenal metastases at diagnosis) had a statistically nonsignificant shorter median OS and shorter PFS to first-line chemotherapy compared with patients without adrenal metastasis (median OS, 8.8 months; 95% CI, 5.9-24.5 months; vs. 15.9 months, 95% CI, 12.2-24.6 months; $P = .07$; median PFS, 4.9 months; 95% CI, 4-7.8 months; vs. 6.3 months, 95% CI, 5.5-7.9 months; $P = .132$, respectively).

Patients with metastatic *KRAS*-mutant NSCLC with brain metastasis (n = 46; 3 patients with both soft tissue and brain metastases at diagnosis) showed nonstatistically significant differences in median OS and PFS to first-line chemotherapy compared with *KRAS*-mutant patients without brain metastasis at diagnosis (median OS, 12.8 months; 95% CI, 10.5-29 months; vs. 15.6 months, 95% CI, 9.2-24.5 months; $P = .348$; median PFS, 6.4 months; 95% CI, 5.5-9.9 months; vs. 5.8 months, 95% CI, 4.7-7.5 months; $P = .285$, respectively).

Pemetrexed-responsive and Other First-line Therapy-responsive Disease

Patients (n = 43) with pemetrexed-responsive disease in any treatment line exhibited significantly longer OS and PFS to first-line therapy compared with patients (n = 65) with nonresponsive disease (median OS, 37 months; 95% CI, 20.3 months to undefined; vs. 21.4 months, 95% CI, 14.6-32.4 months; $P = .037$; median PFS, 9.9 months; 95% CI, 8.9-16.8 months; vs. 5.7 months, 95% CI, 4.6-7.9 months; $P = .002$).

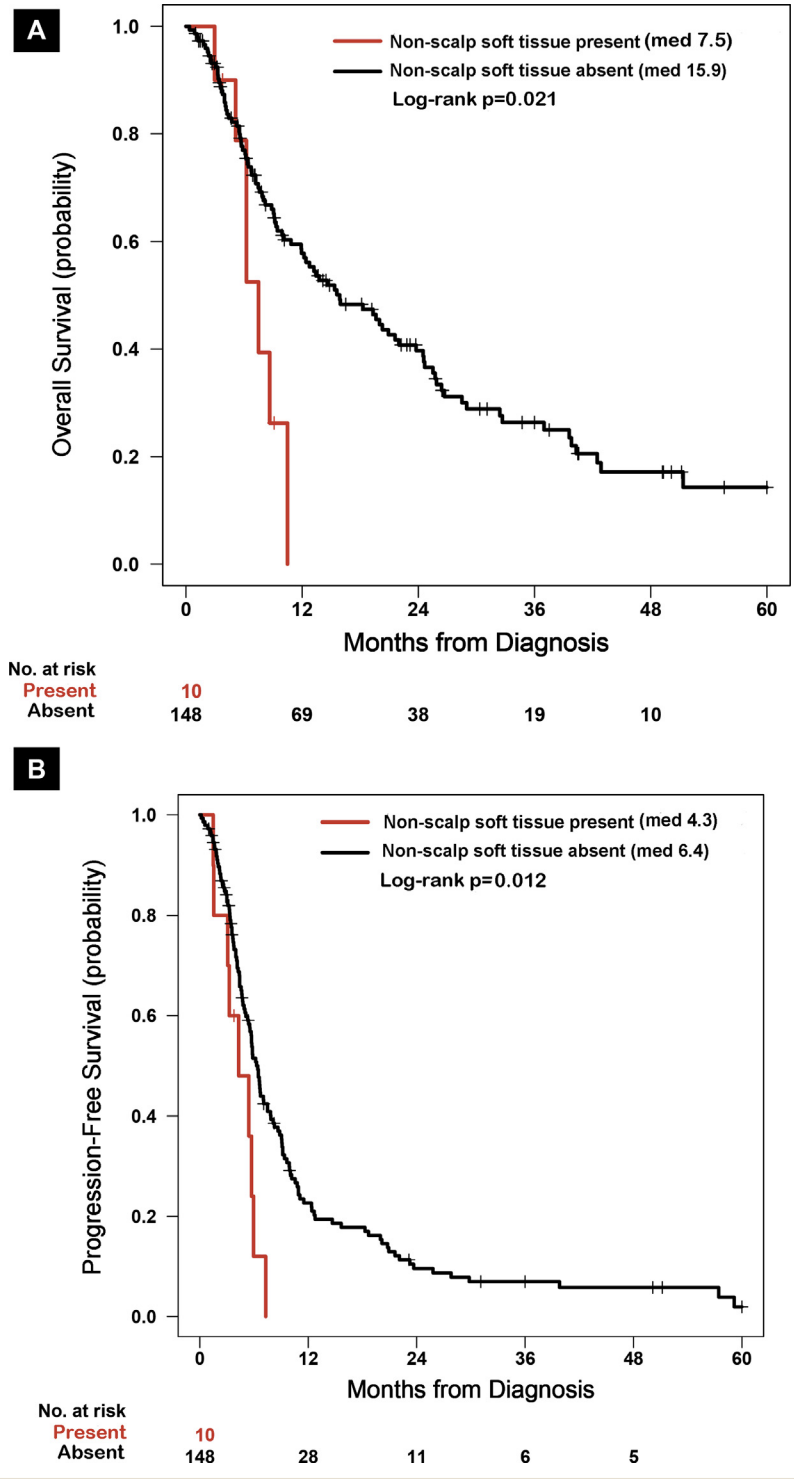
Because this finding could have been confounded by patients who lived long enough to receive pemetrexed in subsequent lines of therapy, we repeated the analysis but restricted it to patients who had received first-line pemetrexed-containing platinum doublets (n = 67). The OS and PFS differences remained statistically significant (median OS, 37; 95% CI, 18.9 months to undefined; vs. 13.8 months, 95% CI, 7.5-25.9 months; $P = .001$; median PFS, 10.7; 95% CI, 8.2-20 months; vs. 6 months, 95% CI, 3.4-7.9 months; $P = .002$; Figure 3A, B).

To validate this finding as specific to pemetrexed, we explored the differences in OS and PFS between the patients with and without a disease response to non−pemetrexed chemotherapy in any line and in first-line settings. Patients with metastatic or recurrent, unresectable *KRAS*-mutant NSCLC who responded to non−pemetrexed-containing chemotherapy in any line experienced near-significantly increased median OS and PFS compared with patients without a disease response to non−pemetrexed-containing chemotherapy in any line (median OS, 39.8 months; 95% CI, 24.6 months to undefined; vs. 19.6 months, 95% CI, 13.4-37 months; $P = .055$; median PFS, 9.9 months; 95% CI, 6.6-12.7 months; vs. 5.4 months, 95% CI, 4.5-7.1 months; $P = .053$, respectively).

When limiting the analysis to the first-line setting only, patients with metastatic or recurrent, unresectable *KRAS*-mutant NSCLC who responded to first-line non−pemetrexed-containing chemotherapy exhibited a trend toward improved median OS and significantly increased median PFS compared with patients without a disease response to first-line non−pemetrexed-containing chemotherapy (median OS, 39.6 months; 95% CI, 15.3 months to undefined; vs. 18.6 months, 95% CI, 13.4-42.5 months; $P = .278$; median PFS, 11.1 months; 95% CI, 7-25.8 months; vs. 4.7 months, 95% CI, 4.4-6.4 months; $P = .007$, respectively).

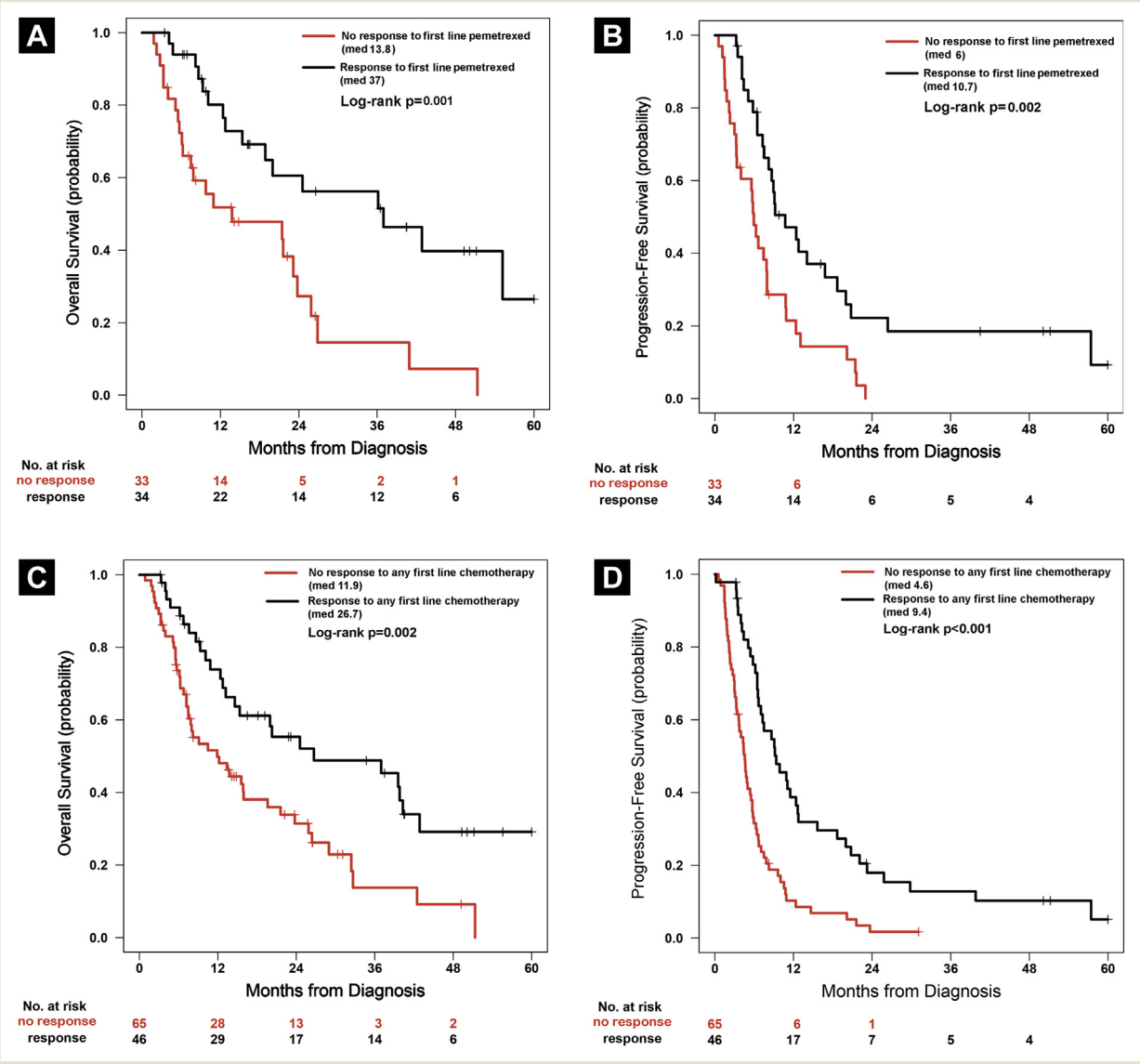
However, 37 of the 90 patients (41%) who had not received pemetrexed in the first-line setting had received pemetrexed in subsequent lines of therapy. Of these 37 patients who had received pemetrexed in the second line or later, 10 had a disease response to pemetrexed and 27 did not. Of the 27 patients with a disease response to first-line non−pemetrexed-containing platinum doublets, 3 of the 6 who had received next-line pemetrexed had a disease response (50%). Among the 63 patients without a disease response first-line non−pemetrexed-containing platinum doublets, 5 of the 23 who had received next-line pemetrexed had a disease response (22%).

Figure 2 (A) Comparison of Overall Survival (OS) and (B) Progression-Free Survival Between Patients With Metastatic *KRAS*-Mutant Non–Small-Cell Lung Cancer With and Without Soft Tissue Metastasis, Excluding Patients With Scalp Metastases



Abbreviation: Med = median.

Figure 3 (A) Comparison of Overall Survival (OS) and (B) Progression-Free Survival (PFS) Between Patients With Metastatic or Recurrent, Unresectable *KRAS*-Mutant Non–Small-Cell Lung Cancer (NSCLC) and a Response or No Response to Pemetrexed (Partial or Complete) in First-Line Therapy. Comparison of (C) OS and (D) PFS Between Patients With Metastatic *KRAS*-Mutant NSCLC and a Response or No Response to First-Line Chemotherapy



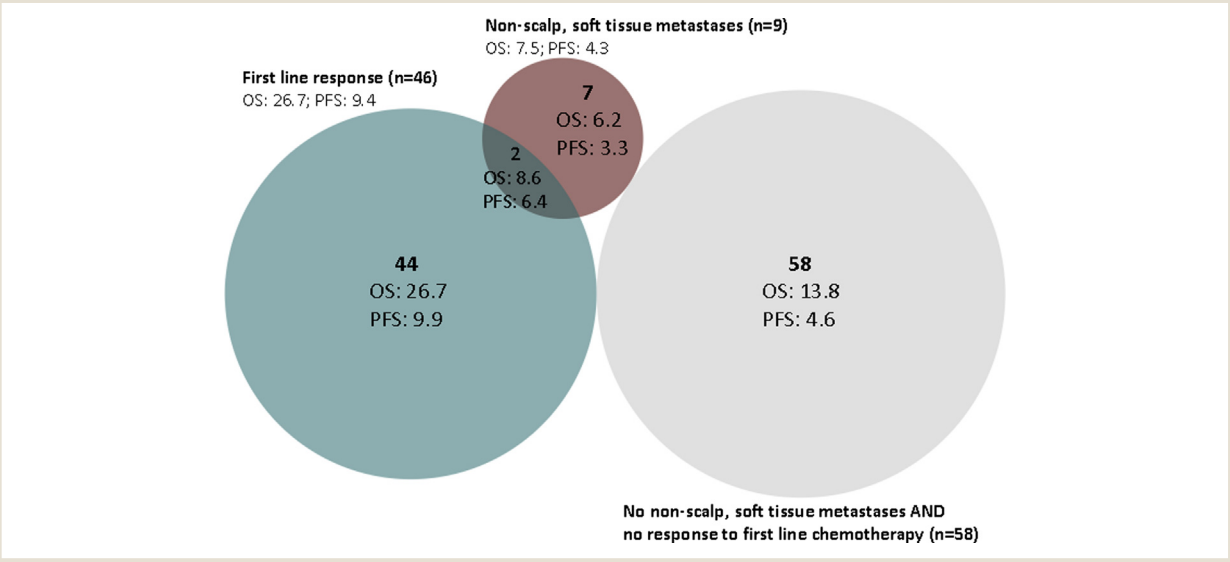
Abbreviation: Med = median.

We then compared the median PFS duration in the first-line setting between patients with a disease response to first-line pemetrexed (n = 34) and those with a disease response to first-line non–pemetrexed-containing chemotherapy (n = 26). This difference was not statistically significant (median PFS, 9.0 months vs. 9.8 months; $P = .62$).

We also compared the median OS and PFS between patients with metastatic *KRAS*-mutant NSCLC with a response to any first-line therapy (KRAS syndrome Y) and those without a response to first-line chemotherapy. We observed statistically significant differences (median OS, 26.7 months; 95% CI, 15.4 months to undefined; vs. 11.9 months, 95% CI, 7.5-21.6 months; $P = .002$; median PFS, 9.4 months; 95% CI, 7-12.8 months; vs. 4.6 months, 95% CI, 3.6-5.7 months; $P < .001$; Figure 3C, D).

Regarding the potential overlap between the poor prognosis, nonscalp, soft tissue disease group (KRAS syndrome X) and the good prognosis chemotherapy responsive group (KRAS syndrome Y), only 4 of 10 patients with nonscalp, soft tissue disease at the diagnosis of metastatic *KRAS*-mutant NSCLC had received first-line pemetrexed. Of those 4 patients, only 1 had had a disease response to that regimen. By focusing only on the 111 patients with metastatic disease at diagnosis for whom information was available for

Figure 4 Venn Diagram Detailing Overlap Between Proposed Clinical Syndromes (Nonscalp, Soft Tissue Metastasis and First-Line Chemotherapy Response) Within Patients With Metastatic *KRAS*-Mutant Non–Small-Cell Lung Cancer at Diagnosis and Their Median Overall Survival (OS) and Progression-Free Survival (PFS) to First-Line Chemotherapy. Log-Rank Test Showed that the Median OS and PFS Were Significantly Different Among the 3 Cohorts ($P < .001$ for Both Comparisons). This Finding Remained Statistically Significant Even When Patients in the Overlap Group Were Included in the Nonscalp, Soft Tissue Metastasis Group ($P < .001$ for Both OS and PFS Comparisons). The Associated Clinical Features for Each Group Are Listed in Tables 3 and 4



both the initial sites of metastatic disease and the response to first-line chemotherapy, a Venn diagram (Figure 4) was created to divide the patients into 3 groups (Tables 3 and 4). Of the 10 patients with nonscalp, soft tissue disease at the diagnosis of metastatic *KRAS*-mutant NSCLC, 9 received first-line therapy, but only 2 had a disease response. The median OS and PFS differed significantly among the different groups. We specifically compared the number of metastatic sites between patients with KRAS syndrome X and KRAS syndrome Y. The patients with KRAS syndrome X had significantly more sites of metastases (median, 4 vs. 2 for those with syndrome Y; $P < .001$). To assess the prognostic value of the 2 syndromes more rigorously, we also performed a multivariate Cox regression analysis for both OS and PFS for the patients with metastatic *KRAS*-mutant NSCLC. The multivariate analysis demonstrated a hazard ratio for death of 2.64 (95% CI, 1.13-6.14) for the nonscalp, soft tissue metastasis cohort and 0.45 (95% CI, 0.28-0.76) for the first-line chemotherapy response cohort. No other variable was a statistically significant predictor of OS or PFS, except for intrathoracic-limited disease. That was found to be a statistically significant predictor of prolonged PFS on multivariate analysis ($P = .045$).

Discussion

Advanced *KRAS*-mutant NSCLC has resisted all attempts to develop a KRAS-specific targeted therapy approach to date. Although this might partly reflect the "druggability" of the target, an additional factor might be that *KRAS*-mutant NSCLC might not represent a single disease entity. Preclinical and sequencing data have suggested that distinct molecular contexts of *KRAS*-mutant disease exist. For example, early data have suggested coincident LKB1 mutations occurring in ~30% of *KRAS*-mutant NSCLC cases might be associated with an immunotherapy-resistant phenotype.[20] However, the description of specific clinical syndromes present within patients with *KRAS*-mutant disease associated with distinct prognostic or predictive significance has been lacking. Such clinical heterogeneity is likely to underlie the contradictory clinical data regarding the prognostic role of *KRAS* mutations in patients with NSCLC.[21-23] By starting to define the relevant clinical syndromes present within patients with *KRAS*-mutant NSCLC, these subgroups could facilitate the exploration of different molecular contexts of *KRAS* mutations.

Using the OS and PFS to first-line chemotherapy as our metrics of clinical behavior, among our cohort of patients with advanced *KRAS*-mutant NSCLC, we found that patients with metastatic *KRAS*-mutant NSCLC at diagnosis had significantly worse OS and PFS to first-line chemotherapy compared with patients with recurrent, unresectable *KRAS*-mutant NSCLC (Figure 1). This finding is similar to reported observations from molecularly unselected groups of patients with NSCLC.[24] These differences could be a reflection of differences in the burden of disease between those with metastatic disease at diagnosis and those with recurrent disease. Also, it was notable that 28% of the patients with metastatic disease at diagnosis had M1a disease compared with 45% of the patients with recurrent, unresectable disease. First-line chemotherapy regimens were similar between the 2 groups, with the exception of a greater rate of platinum plus bevacizumab (20% vs. 4%) for patients with metastatic *KRAS*-mutant NSCLC at diagnosis. However, use of that regimen should result in a bias toward longer, not shorter,

Table 3 Clinical Characteristics Stratified by Metastasis Type and Response to Therapy

Characteristic	Nonscalp, Soft Tissue Metastasis[a]		Response to First-line Therapy; No Nonscalp, Soft Tissue Metastasis[b] (n = 44)
	No Response to First-line Therapy (n = 7)	Response to First-line Therapy (n = 2)	
Median age at diagnosis, y	56	60.5	64.5
Median tobacco use, pack-years	45	20.5	30
Male gender	3 (42.9)	0 (0)	25 (56.8)
Race			
White	6 (86)	1 (50)	41 (93)
African American	1 (14)	0 (0)	2 (5)
Asian	0 (0)	0 (0)	1 (2)
Hispanic	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	1 (50)	0 (0)
Intrathoracic disease only	0 (0)	0 (0)	11 (25)
Histologic type			
Adenocarcinoma	6 (86)	1 (50)	41 (93)
Adenosquamous	0 (0)	0 (0)	0 (0)
Squamous	0 (0)	0 (0)	2 (5)
Poorly differentiated	1 (14)	1 (50)	0 (0)
Large cell	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	1 (2)
First-line therapy			
Platinum based			
No pemetrexed/bevacizumab	3 (43)	1 (50)	10 (23)
Pemetrexed	3 (43)	1 (50)	18 (41)
Bevacizumab	1 (14)	0 (0)	10 (23)
Both pemetrexed/bevacizumab	0 (0)	0 (0)	4 (9)
None	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	2 (4)
Unknown	0 (0)	0 (0)	0 (0)
KRAS mutation type			
G12C	3 (43)	1 (50)	19 (44)
Q61H 183A>C	1 (14)	0 (0)	2 (4)
Q61H 183A>T	0 (0)	0 (0)	0 (0)
G12V	3 (43)	0 (0)	7 (17)
Q61L	0 (0)	1 (50)	0 (0)
G13D	0 (0)	0 (0)	2 (4)
G12A	0 (0)	0 (0)	2 (4)
G12D	0 (0)	0 (0)	5 (12)
G13C	0 (0)	0 (0)	0 (0)
G12S	0 (0)	0 (0)	3 (7)
Q61K	0 (0)	0 (0)	0 (0)
G12R	0 (0)	0 (0)	1 (2)
G13S	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	1 (2)
Unknown	0 (0)	0 (0)	2 (4)

Data presented as n (%).
No formal statistical comparison of the frequencies of metastatic sites among the groups was performed.
[a]KRAS syndrome X.
[b]KRAS syndrome Y.

Table 4 Sites of Metastases Stratified by Metastasis Type and Response to Therapy

Metastatic Site	Nonscalp, Soft Tissue Metastasis[a]		Response to First-line Therapy; No Nonscalp, Soft Tissue Metastasis[b] (n = 44)
	No Response to First-line Therapy (n = 7)	Response to First-line Therapy (n = 2)	
Lung parenchyma	1 (14)	0 (0)	20 (46)
Thoracic lymph node	2 (28)	0 (0)	10 (23)
Pleural	0 (0)	0 (0)	9 (21)
Adrenal	2 (28)	1 (50)	6 (14)
Renal	0 (0)	0 (0)	1 (2)
Liver	1 (14)	0 (0)	6 (14)
Abdominal lymph node	1 (14)	0 (0)	0 (0)
Bone	6 (86)	1 (50)	11 (25)
Brain	2 (28)	0 (0)	16 (36)
Soft tissue (including scalp)	5 (71)	2 (100)	1 (2)
Soft tissue (excluding scalp)	7 (100)	2 (100)	0 (0)
Other	5 (72)	2 (100)	2 (4)

Data presented as n (%).
No formal statistical comparison of the frequencies of metastatic sites among the groups was performed.
[a]KRAS syndrome X.
[b]KRAS syndrome Y.

PFS durations in the metastatic at diagnosis subgroup. No patient received first-line checkpoint inhibitors, because we reviewed the therapy for patients treated from 2005 to early 2015. In subsequent lines of therapy, 3 patients had received nivolumab in a clinical trial in the third line, and 2 patients had received nivolumab in a clinical trial in the fifth line of systemic therapy. No other checkpoint inhibitors were administered in our retrospective cohort. The patterns of metastatic spread were numerically different between the 2 groups, with greater rates of intrathoracic metastases in the recurrent, unresectable cohort and greater rates of hepatic and osseous involvement in the group with metastatic disease at diagnosis (Table 2). A formal statistical comparison between the frequencies of metastatic sites between the 2 groups was not undertaken.

Although we found numerical differences, we did not find any statistically significant differences in OS or PFS to first-line chemotherapy when stratified by intrathoracic-limited versus more widespread disease (except for on multivariate analysis, which showed intrathoracic-limited disease as a significant independent predictor of prolonged PFS to first-line therapy), the degree of previous tobacco exposure, or the presence versus absence of the most common *KRAS* mutation (G12C). These findings related to tobacco exposure and *KRAS* mutation subtype are congruent with those from previously reported retrospective studies.[25,26]

We have previously shown that the dominant oncogenic driver in NSCLC can influence the sites of metastatic disease at diagnosis. Therefore, we hypothesized that specific sites of metastatic disease among patients with *KRAS*-mutant NSCLC could be used to define clinical syndromes associated with different underlying *KRAS* molecular biology and clinical outcomes.[16] Using our *a priori* clinical observation, and consistent with this broad hypothesis, 1 particular pattern of spread—soft tissue spread, specifically excluding scalp metastasis—was associated with worse OS and PFS to first-line chemotherapy, defining a poor prognosis KRAS syndrome X (Figure 2). When scalp metastases were included in the soft tissue metastatic group, the statistical significance disappeared. In our validation analyses, no specific positive or negative effect for comparably sized metastatic subgroups of adrenal or brain metastases was identified. One other retrospective analysis has shown that uncommon sites of metastasis, in general, and soft tissue metastases, specifically, are poor prognostic factors for patients with metastatic NSCLC. However, these analyses did not address the underlying driver oncogenes present.[27] An additional retrospective analysis, again in nonmolecularly defined NSCLC, showed that skin metastases are associated with a poor prognosis in patients with NSCLC.[28] These consistent findings regarding the poor prognostic implications of skin and soft tissue metastasis for patients with NSCLC suggest a molecular overlap between skin and soft tissue tropism and chemorefractory, aggressive disease. This molecular underpinning might be absent in patients with scalp tropism.

Our previous data suggested that patients with *KRAS*-mutant NSCLC with prolonged PFS during pemetrexed therapy could represent a unique clinical subgroup. This was consistent with preclinical evidence that *KRAS*-mutant NSCLC cells might be particularly dependent on folate metabolism.[15,29] Within our enlarged data set, we were similarly able to demonstrate significantly prolonged PFS to first-line therapy and OS in association with the responsiveness to pemetrexed given as first line or any line of therapy. However, proving that this was a pemetrexed-specific effect was more challenging, given that patients with or without a response to a non−pemetrexed-containing regimen in the first line could have had a response or not have had a response to pemetrexed in subsequent lines. Because we could not show that the PFS to first-line therapy differed significantly between those responding to pemetrexed versus non−pemetrexed-containing first-line regimens, and the differences in OS and PFS remained statistically significant between a response to any first-line regimen versus no response to any first-line regimen, the good prognostic effect (KRAS syndrome Y) might most accurately reflect an inherently cytotoxic responsive effect, rather than a pemetrexed-specific effect (Figure 3). This finding is consistent with the previously documented improved

prognosis for patients with *KRAS*-mutant NSCLC with a response to cytotoxic chemotherapy.[30] Whether a more detailed exploration of the exact degree of shrinkage present in the SD group, in theory potentially containing both latent progression and latent responses, would have influenced these results remains unknown.

Crucially, the overlap among those with metastatic disease at diagnosis involving nonscalp, soft tissue spread and those with a first-line therapy response was only 2 of 111 patients analyzed with data available for both (Figure 4). Moreover, although the numbers were very small, the presence of nonscalp, soft tissue spread seemed to impart a dominant negative effect on the otherwise good OS and PFS associated with initial chemotherapy responsiveness. This suggests that these might truly represent distinct negative and positive prognostic clinical syndromes, respectively. KRAS syndrome X (non-scalp, soft tissue disease at stage IV diagnosis; associated with a median OS and PFS of 7.5 and 4.3 months, respectively) represented ~6% (95% CI, 2.5%-10.1%) of *KRAS*-mutant metastatic cancer, and KRAS syndrome Y (first-line chemotherapy responsivity; associated with a median OS and PFS of 26.7 and 9.4 months, respectively) represented 41% (95% CI, 32.3%-50.6%) of *KRAS*-mutant metastatic cancer. Our multivariate analysis confirmed these observations. The syndrome X hazard ratio for death was 2.64 (95% CI, 1.13-6.14) and that for syndrome Y was 0.45 (95% CI, 0.28-0.76). Although the moderate frequency and potentially nonspecific nature of chemotherapy responsiveness suggest that syndrome Y might include a range of different underlying biologic factors, syndrome X represents a more tightly encompassed group potentially highly likely to have distinct and identifiable underlying molecular biology. Syndrome X was associated with a greater number of organ sites involved compared with syndrome Y, although we were unable to establish whether this also correlated with tumor burden in terms of disease volume as a potential confounder.

The limitations of the present study included the retrospective nature of the analysis and the limited number of patients in our predefined clinical subcohorts. Also, determining inclusion into the KRAS syndrome Y cohort only occurred after first-line therapy, and its relevance in balancing clinical trials applies to those evaluating therapy in the second line or later. Staging imaging studies were not standardized, and the sites of metastatic disease had not all been confirmed by biopsy at diagnosis. In addition, the lack of performance status information made it difficult to ensure that this key prognostic factor was matched for all comparisons. Also, in the present retrospective analysis, we did not evaluate the predictive value of these syndromes as they relate to specific therapies beyond first-line chemotherapy and pemetrexed. Specifically, owing to the period during which the data were collected, we do not have information on immunotherapy sensitivity or other molecular markers. Equally, although our observations were made within KRAS-mutant stage IV NSCLC and could inform further study of the significance of underlying molecular heterogeneity and clinical outcomes from interventional trials conducted within this common subtype, we have not shown that any of these observations are specific to KRAS-mutant disease. Such work is warranted. However, we would also need to determine whether we can interpret previous observations of associations between some of these clinical features and prognosis in unselected NSCLC populations as reflecting non−KRAS-mutant disease in the absence of available molecular information.

A critical next step in the study of patients with advanced *KRAS*-mutant NSCLC will be to validate the current observations in additional data sets and explore *KRAS* molecular contextual signatures, seeking to align them with the specific clinical syndromes we have begun to describe.[13,14] Such an approach could then lead to additional research to understand why these contexts and behaviors are linked.

Conclusion

When the clinical and molecular heterogeneity of the cohort of patients with *KRAS*-mutant NSCLC is better understood, the likelihood of successful novel therapy development will increase, with improvement in patient outcomes. It is imperative to continue to work to understand this large group of patients with NSCLC who currently have no validated, personalized treatment options.

Clinical Practice Points

- Patients with *KRAS*-mutant recurrent, metastatic or de novo metastatic NSCLC with nonscalp, soft tissue metastases have had a uniquely poor prognosis, echoing findings for patients with NSCLC as a whole.
- Patients with *KRAS*-mutant recurrent, metastatic or de novo metastatic NSCLC with initially chemoresponsive disease had an improved clinical prognosis, echoing the findings for patients with NSCLC as a whole.

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Disclosure

The authors declare that they have no competing interests.

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