Characteristics and Survival Outcomes of Patients With Metastatic *RET* Fusion–Positive Solid Tumors Receiving Non-RET Inhibitor Standards of Care in a Real-World Setting

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ABSTRACT

PURPOSE *RET* fusions are oncogenic drivers across different solid tumors. However, the genomic landscape and natural history of patients with *RET* fusion–positive solid tumors are not well known. We describe the clinical characteristics of RET tyrosine kinase inhibitor (TKI)-naïve patients with *RET* fusion–positive solid tumors (excluding non–small-cell lung cancer [NSCLC]), treated in a real-world setting and assess the prognostic effect of *RET* fusions.

METHODS Data for RET TKI-naïve patients with metastatic solid tumors (excluding NSCLC) who had ≥one Foundation Medicine comprehensive genomic profiling test (January 1, 2011-March 31, 2022) were obtained from a deidentified nationwide (US-based) clinicogenomic database. The primary objective of this study was to compare the overall survival (OS) of patients with *RET* fusion–positive tumors versus matched patients with *RET* wild-type (*RET*-WT) tumors. Patients with *RET*-WT solid tumors were matched (4:1) to patients with *RET* fusion–positive tumors on the basis of preselected covariates.

RESULTS The study population included 26 patients in the *RET* fusion–positive cohort, 7,220 patients in the *RET*-WT cohort (before matching), and 104 patients in the matched *RET*-WT cohort. Co-occurring genomic alterations were rare in the *RET* fusion–positive cohort. Median OS was consistently lower in patients with *RET* fusion–positive tumors versus those with *RET*-WT tumors, using three different analyses (hazard ratios, 2.0, 1.7, and 2.2).

CONCLUSION These data suggest that *RET* fusions represent a negative prognostic factor in patients with metastatic solid tumors and highlight the need for wider genomic testing and use of RET-specific TKIs that could improve patient outcomes. Our study also highlights the value of real-world data when studying rare cancers or cancers with rare genomic alterations.

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INTRODUCTION

Fusions of the rearranged during transfection (*RET*) gene are oncogenic drivers across a number of solid tumors.[1-3] Treatment options for patients with *RET*-altered solid tumors were previously limited to multikinase inhibitors, but these can be associated with significant toxicities and high rates of dose reduction/discontinuation, and there may also be limited efficacy.[1,4,5] Therefore, there is a need for better precision therapies that selectively target *RET* alterations and anticipated resistance mechanisms.

Two RET-specific tyrosine kinase inhibitors (TKIs), selpercatinib and pralsetinib, have demonstrated durable antitumor activity and manageable toxicity profiles and are approved for the treatment of advanced/metastatic *RET* fusion–positive non–small-cell lung cancer (NSCLC; both drugs in the United States and Europe), advanced/metastatic *RET*-altered thyroid cancer (both drugs in the United States; selpercatinib in Europe), and advanced/metastatic *RET* fusion–positive solid tumors (selpercatinib in the United States; neither in Europe).[6-9]

RET fusions, although rare,[5,10,11] have been detected in a wide range of solid tumors.[5,12] However, the genomic landscape and natural history of patients with *RET* fusion–positive tumors are not well documented. It is important to understand whether *RET* fusion–positive tumors behave

CONTEXT

Key Objective

Rearranged during transfection (*RET*) gene fusions are known but rare oncogenic drivers across many solid tumors. This analysis examines the characteristics and overall survival of patients with *RET* fusion–positive and *RET* wild-type (*RET*-WT) tumors from the Flatiron Health-Foundation Medicine clinicogenomic database and evaluates the prognostic impact of *RET* alterations.

Knowledge Generated

Across three statistical models used, patients with *RET* fusion–positive solid tumors had consistently worse survival than their *RET*-WT counterparts.

Relevance

RET alterations are actionable in patients with non–small-cell lung cancer or thyroid cancer using RET-specific tyrosine kinase inhibitors (TKIs). Our data highlight an unmet need for wider genomic testing across different solid tumor types to identify *RET* alterations that may have a negative impact on survival. The use of RET-specific TKIs in these patients may improve outcomes beyond current standard of care options.

differently to *RET* wild-type (*RET*-WT) tumors of the same histology and whether *RET* fusions are prognostic.

Examining the association between rare alterations and patient outcomes is challenging in randomized treatment trials because of limited patient numbers. Therefore, large-scale real-world data provide a valuable alternative for evaluating these associations.

The study objectives were to (1) describe the clinical characteristics and overall survival (OS) of patients with *RET* fusion–positive (for which there are limited data) and *RET*-WT solid tumors and (2) provide an example of how real-world data collected from routine clinical practice can be used to determine the prognostic value of rare alterations. This can then be used to evaluate targeted therapies in tumor-agnostic clinical trials.

METHODS

Study Design and Data Sources

This retrospective, observational study of RET TKI-naïve patients with metastatic, *RET* fusion–positive or *RET*-WT solid tumors used real-world data collected during routine clinical practice from the nationwide (US-based) deidentified Flatiron Health-Foundation Medicine clinicogenomic database (CGDB).

Deidentified data were obtained from approximately 280 Flatiron Health cancer clinics in the United States (approximately 800 care sites); retrospective longitudinal clinical (patient-level structured and unstructured) data were derived from electronic health records and curated via technology-enabled abstraction. These data were linked to genomic data derived from the Foundation Medicine comprehensive genomic profiling (CGP) tests in the Flatiron Health-Foundation Medicine CGDB using deidentified, deterministic matching.[13] Ethics committee approval was not required because this study used anonymized patient data and did not directly enroll patients.

Study Population

Eligible patients had ≥one documented clinical visit in a Flatiron Health network center between January 1, 2011, and March 31, 2022, and underwent CGP testing by Foundation Medicine before April 1, 2022. Genomic alterations were identified via CGP of >300 cancer-related genes using FoundationOne, FoundationOneCDx, or FoundationOne-Heme assays.[14-16]

The study population included patients with a de novo metastatic diagnosis who had not previously been treated with a RET TKI in any therapy line. As Flatiron CGDB retains detailed documentation of all medications received by a patient, regardless of their on-label or off-label status, all patients who received a next-generation RET inhibitor (such as pralsetinib or selpercatinib) or a study drug as part of a clinical trial were excluded to eliminate any bias in the description of standard of care. Patients diagnosed with *RET* fusion–positive NSCLC were also excluded as this represents a well-defined population with published data,[17] and there are licensed drugs for this particular indication[6-9]; this exclusion is consistent with ongoing clinical trials.[18] Other patient exclusion criteria included multiple cancer diagnoses or no initial diagnosis date, >one type of CGP or a CGP report date before the initial diagnosis, an initial diagnosis within 3 months before the data cutoff; death before 2012 (when Foundation Medicine's CGP was established), and a visit gap of >90 days after the

initial diagnosis (patients may have been treated temporarily in a center outside of the Flatiron Health network postdiagnosis).

Determination of *RET* Status

RET positivity was defined as the presence of a fusion or rearrangement with a predicted known/likely functional status as defined by Foundation Medicine. This included a 3' *RET* fusion (breakpoint between exon 1 and intron 11) with a protein-coding 5' gene fusion partner, which was predicted to be in-frame with an intact kinase domain.[19] Fusions with non–protein-coding gene partners or intragenic fusions were excluded. *RET*-WT status was determined when CGP was unable to detect any qualifying *RET* fusions. To reduce the probability of misclassifying patients with false-negative results as *RET*-WT, we only analyzed solid tumor samples (using FoundationOne, FoundationOneCDx, or FoundationOneHeme assays).

Study Design

We used data from eligible patients with known *RET* status in the Flatiron Health-Foundation Medicine database. We also performed a nested case-control study within this database. Patients with *RET*-WT tumors were matched with patients with *RET* fusion–positive tumors (4:1 ratio) using Mahalanobis distance matching[20] on the basis of several covariates: age, sex, race, tumor type, practice type (academic *v* community), Eastern Cooperative Oncology Group performance status (ECOG PS) measured from 30 days before to 7 days after index date, year of CGP, time from initial diagnosis of metastatic disease to CGP report date, and number of oncologist-defined, rule-based treatment lines before CGP report date. An absolute mean difference of <0.1 was used as a quality metric to indicate negligible distance between groups.[21]

Statistical Analyses

The primary objective was to evaluate the association between OS and *RET* fusion status. OS was defined as time from the index date until death from any cause or the censoring date (ie, last follow-up date when last known to be alive). The index date could be the date of the CGP report or the date of metastatic diagnosis. We also examined patient characteristics, treatment patterns, and genomic alterations: tumor mutational burden (TMB), microsatellite instability (MSI), and co-occurring oncogenic functional alterations in *ALK*, *BRAF*, *ERBB2*, *EGFR*, *NTRK*, *ROS1*, *MET*, and *KRAS*.

Kaplan-Meier curves and Cox regression were used for the analysis of OS. R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and Python version 3.9.9 (Python Software Foundation, Wilmington, DE) were used for all analyses. A crude (unmatched) analysis used the CGP report date as the index for calculating time-to-event in the OS analysis as confirmation of biomarker status was a predefined inclusion criterion for study entry. Additionally, two different models analyzed OS on the basis of the nested case-control patients: model 1 used the CGP report date as the index (as for the crude analysis), whereas model 2 used the date of metastatic diagnosis as the index and also adjusted for immortal time bias with left truncation by considering the CGP report date.[22]

Time from metastatic diagnosis to CGP report may differ between patients, and the adjustment for immortal time bias accounts for patients having to survive long enough to receive a CGP report, during which time the outcome of interest (death) cannot occur (ie, they are immortal during that period).[23] This immortal time bias can result in overestimation of the outcome event rate in the control group, underestimation of the event rate in the exposed group, or both.[24] To address this issue, we used the date of metastatic diagnosis as the index and estimated survival using a left truncation model as proposed in the study by Mackenzie et al.[22]

Ethics

This study used deidentified patient data from the Flatiron Health-Foundation Medicine CGDB, a US-wide longitudinal database curated through technology-enabled abstraction, and did not directly enroll patients.

RESULTS

Patient Characteristics

Between January 1, 2011, and March 31, 2022, a total of 222 patients with *RET* fusion–positive tumors and ≥one documented clinical visit in a Flatiron Health network center were selected. In total, 196 patients were excluded on the basis of criteria described above, including 92 patients with NSCLC (Fig 1A); 26 patients constituted the *RET* fusion–positive cohort for this analysis. Baseline characteristics are presented in Table 1. The majority of patients with *RET* fusion–positive tumors were male (57.7%) and had ECOG PS 0/1 (53.8%); the mean age was 65.3 years. The median follow-up time from CGP report date for the *RET* fusion–positive cohort was 5.7 (IQR, 7.2) months while the median time from initial diagnosis of metastatic disease to CGP report date was 3.5 (IQR, 8.8) months.

The *RET* fusion–positive cohort consisted of nine distinct tumor/histology types, most commonly colorectal cancer (CRC; n = 9; 34.6%; Fig 2). Nine different *RET* fusion partners were detected, and the most common were *NCOA4* (n = 12; 46.2%), *CCDC6* (n = 6; 23.1%), and *ERC1* (n = 2; 7.7%). *CEP135*, *FAM13C*, *FGFR1OP*, *KIAA1217*, *KIF5B*, and *MACROD2* were detected in one patient each.

Fifteen patients had a CGDB record for prior antineoplastic therapy, of whom seven (46.7%) had received ≥two prior lines of therapy, six (40.0%) had received one prior line of therapy, and two (13.3%) were recorded as treatment naïve.

Of 62,456 patients with solid tumors in the CGDB, 7,220 patients with *RET*-WT solid tumors met the eligibility criteria

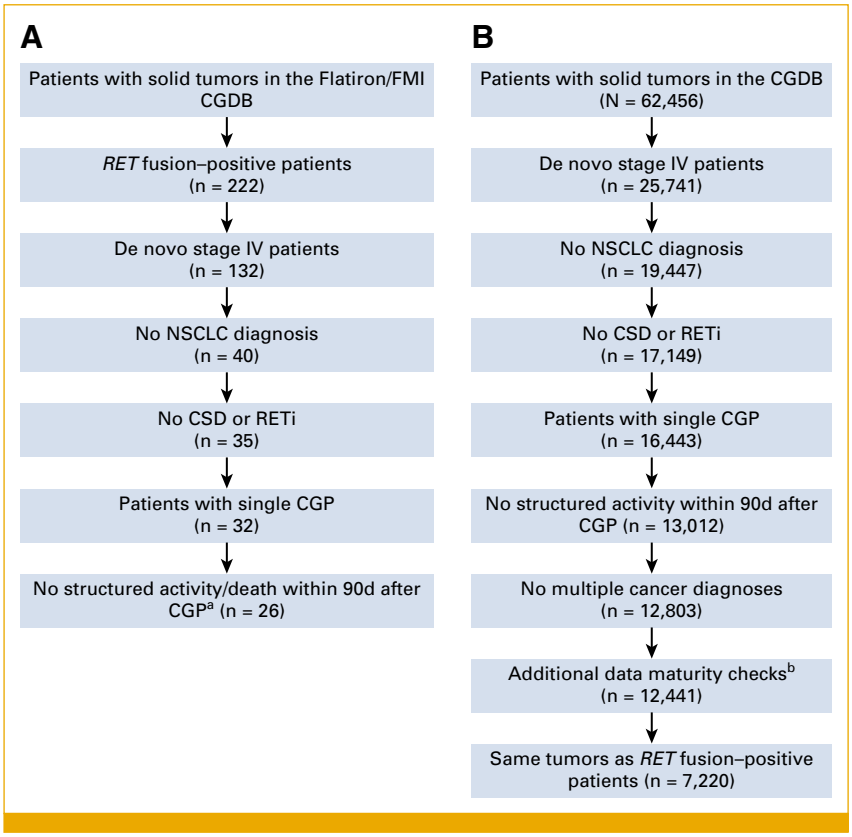

FIG 1. Cohort attrition for (A) the *RET* fusion–positive population and (B) the *RET*-WT population. Structured activity refers to a recording of vital information, a medication administration, a noncanceled drug order, or a reported laboratory test/result. [a]Also excluded patients with no initial metastatic disease diagnosis date or a diagnosis within 3 months before the data cutoff, patients who died before 2012, patients with multiple cancer diagnoses, and patients with a CGP report date before the initial diagnosis, with no impact on attrition. [b]Also excluded patients with no initial metastatic disease diagnosis date or a diagnosis within 3 months before the data cutoff, patients who died before 2012, and patients with a CGP report date before the initial diagnosis, with no impact on attrition. 90d, 90 days; CGDB, clinicogenomic database; CGP, comprehensive genomic profiling; CSD, clinical study drug; FMI, Foundation Medicine, Inc; NSCLC, non–small-cell lung cancer; *RET*, rearranged during transfection; RETi, RET inhibitor; WT, wild type.

(Fig 1B). These patients were matched for tumor type to the *RET* fusion–positive cohort to prevent inconsistencies from biasing the OS outcomes. After covariate matching for demographic and clinical characteristics, the matched *RET*-WT cohort included 104 patients. The *RET* fusion–positive and matched *RET*-WT cohorts had comparable baseline serum albumin levels and absolute neutrophil and platelet counts, although missing data ranged from 17.3% to 38.5% across the cohorts (Table 1). Most patients had missing PD-L1 status in the CGP report (76.9% in both the *RET* fusion–positive and matched *RET*-WT cohorts). Three patients (2.9%) in the matched *RET*-WT cohort had received prior PD-L1 therapy versus none in the *RET* fusion–positive cohort.

Presence of Co-Occurring Genomic Alterations

In the *RET* fusion–positive cohort, 17 patients (65.4%) had low TMB (<5.7 mut/Mb), and two patients (7.7%) were TMB-high (≥20 mut/Mb); 13 patients (50.0%) had low MSI, and one patient (3.8%) was MSI-high (Table 2). One patient in this cohort had an *ERBB2* amplification (3.8%); no other assessed oncogenic coalterations were identified.

Most patients in the matched *RET*-WT cohort had low TMB (84.6%) and low MSI (82.7%); none had high TMB or MSI (Table 2). The only genomic alterations observed in this cohort were *KRAS* alterations (36.5%), *BRAF* alterations (5.8%), and *ERBB2* amplifications (3.8%).

OS

In the crude analysis, the median OS was 6.0 months (95% CI, 1.6 to 9.9) for the *RET* fusion–positive cohort (N = 26) and 10.4 months (95% CI, 10.0 to 10.9) for the nonmatched *RET*-WT population (N = 7,220; Table 3; Fig 3A). The hazard ratio (HR) was 2.0 (95% CI, 1.3 to 3.1), indicating that

TABLE 1. Baseline Patient Characteristics

Characteristic	*RET* Fusion–Positive (N = 26)	*RET*-WT (N = 7,220)	
		Matched (n = 104)	Nonmatched (n = 7,116)
Sex,[a] No. (%)			
Female	11 (42.3)	43 (41.3)	4,035 (56.7)
Male	15 (57.7)	61 (58.7)	3,081 (43.3)
Age, years, mean (SD)	65.3 (10.3)	61.8 (12.0)	64.8 (9.9)
Race, No. (%)			
Asian	0	0	173 (2.4)
Black/African American	1 (3.8)	4 (3.8)	615 (8.6)
Hispanic/Latino	0	0	15 (0.2)
White	21 (80.8)	89 (85.6)	4,599 (64.6)
Other	3 (11.5)	9 (8.7)	1,120 (15.7)
Missing	1 (3.8)	2 (1.9)	594 (8.3)
Primary tumor type, No. (%)			
Colorectal	9 (34.6)	37 (35.6)	2,899 (40.7)
Pancreatic	4 (15.4)	15 (14.4)	1,089 (15.3)
Thyroid	4 (15.4)	16 (15.4)	83 (1.2)
Neuroendocrine[b]	3 (11.5)	12 (11.5)	338 (4.7)
Breast	2 (7.7)	8 (7.7)	1,167 (16.4)
Endometrial	1 (3.8)	4 (3.8)	335 (4.7)
Head and neck	1 (3.8)	4 (3.8)	418 (5.9)
SCLC	1 (3.8)	4 (3.8)	307 (4.3)
Occult/unknown primary	1 (3.8)	4 (3.8)	480 (6.7)
ECOG PS,[c] No. (%)			
0	7 (26.9)	30 (28.8)	1,652 (23.2)
1	7 (26.9)	31 (29.8)	2,342 (32.9)
≥2	1 (3.8)	4 (3.8)	869 (12.2)
Missing	11 (42.3)	39 (37.5)	2,253 (31.7)
Practice type, No. (%)			
Academic	4 (15.4)	12 (11.5)	1,002 (14.1)
Community	22 (84.6)	92 (88.5)	6,114 (85.9)
Serum albumin, g/dL[d]			
Mean (SD)	3.5 (0.5)	3.8 (0.6)	3.7 (0.6)
Missing, No. (%)	6 (23.1)	18 (17.3)	1,081 (15.2)
Absolute neutrophil count, 10^9/L)[d]			
Mean (SD)	5.1 (2.5)	5.4 (5.0)	6.4 (59.7)
Missing, No. (%)	10 (38.5)	28 (26.9)	1,957 (27.5)
Platelet count, 10^9/L[d]			
Mean (SD)	243.7 (114.9)	240.5 (120.1)	247.9 (122.5)
Missing, No. (%)	7 (26.9)	19 (18.3)	1,234 (17.3)
No. of prior lines of treatment, (%)			
0	2 (7.7)	8 (7.7)	807 (11.3)
1	6 (23.1)	24 (23.1)	2,580 (36.3)
≥2	7 (26.9)	27 (26.0)	1,933 (27.2)
Missing	11 (42.3)	45 (43.3)	1,796 (25.2)
PD-L1 status at CGP report, No. (%)			
High (>50)	0	3 (2.9)	70 (1.0)
Low (1-50)	1 (3.8)	10 (9.6)	502 (7.1)
Negative (<1)	5 (19.2)	11 (10.6)	1,315 (18.5)
Missing	20 (76.9)	80 (76.9)	5,229 (73.5)

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TABLE 1. Baseline Patient Characteristics (continued)

Characteristic	*RET* Fusion–Positive (N = 26)	*RET*-WT (N = 7,220)	
		Matched (n = 104)	Nonmatched (n = 7,116)
Documentation of any PD-L1 therapy, No. (%)			
Yes	0	3 (2.9)	301 (4.2)
No	26 (100)	101 (97.1)	6,815 (95.8)
PD-L1 therapy on or before CGP report date, No. (%)			
Yes	0	2 (1.9)	111 (1.6)
No	26 (100)	102 (98.1)	7,005 (98.4)
Year of CGP report, No. (%)			
2012	0	0	4 (0.1)
2013	0	0	64 (0.9)
2014	2 (7.7)	5 (4.8)	312 (4.4)
2015	3 (11.5)	12 (11.5)	492 (6.9)
2016	2 (7.7)	8 (7.7)	529 (7.4)
2017	4 (15.4)	16 (15.4)	799 (11.2)
2018	3 (11.5)	12 (11.5)	1,133 (15.9)
2019	7 (26.9)	29 (27.9)	1,401 (19.7)
2020	2 (7.7)	10 (9.6)	1,367 (19.2)
2021	3 (11.5)	12 (11.5)	1,015 (14.3)
Follow-up time from CGP report, median (IQR)	5.7 (7.2)	6.2 (9.8)	7.5 (13.6)
Time from initial diagnosis[e] to CGP report date, months, median (IQR)	3.5 (8.8)	4.0 (9.4)	4.5 (16.9)

Abbreviations: CGP, comprehensive genomic profiling; ECOG PS, Eastern Cooperative Oncology Group performance status; *RET*, rearranged during transfection; SCLC, small-cell lung cancer; SD, standard deviation; WT, wild type.
[a]Data missing for one patient in the nonmatched RET-WT cohort.
[b]Neuroendocrine tumors included one GI tumor and two unspecified anatomic locations.
[c]Closest value 30 days before to 7 days after index date.
[d]Closest value 90 days before to 7 days after index date.
[e]Of de novo metastatic (stage IV) disease.

patients in the *RET* fusion–positive cohort had a two-fold increase in risk of death compared with the nonmatched *RET*-WT cohort.

The results for models 1 and 2 (with matched controls) were consistent with the crude analysis. Using model 1 (CGP report date as the index date), the median OS was 6.0 months (95% CI, 1.6 to 9.9) in the *RET* fusion–positive cohort (N = 26) and 9.4 months (95% CI, 5.5 to 11.7) in the matched *RET*-WT cohort (N = 104; Table 3; Fig 3B), with an adjusted HR of 1.7 (95% CI, 1.0 to 2.9). Correspondingly, using model 2 (date of metastatic diagnosis as the index date, after adjusting for immortal time bias), the median OS was 6.9 months (95% CI, 1.6 to 9.6) in the *RET* fusion–positive cohort (N = 26) and 11.3 months (95% CI, 7.7 to 17.1) in the matched *RET*-WT cohort (N = 104; Table 3; Fig 3C). The adjusted HR was 2.2 (95% CI, 1.3 to 3.7), confirming that patients with *RET* fusion–positive tumors had approximately twice the risk of death compared with matched *RET*-WT controls.

DISCUSSION

This large-scale study investigated the prognostic association between *RET* fusion status and OS, and as far as we are aware, this is the first such study to include multiple tumor types. Other published studies have focused on NSCLC,[17] which we exclude, and there has been one study each in CRC[25] and medullary thyroid cancer.[26] NSCLC was excluded from this analysis for several reasons. First, *RET* fusion–positive NSCLC represents a well-defined population, for which data on the association between *RET* status and outcomes have already been published.[17] Second, if the 92 cases of NSCLC had been included alongside the 26 cases of other cancer types in the *RET* fusion–positive cohort, they would have biased the associations toward patterns in lung cancer while the focus of this analysis was on other and rare cancer types. Furthermore, there are already licensed drugs for *RET* fusion–positive lung cancer (namely selpercatinib and pralsetinib).[6-9] We included CRC and thyroid cancer because they are uncommon among *RET* fusion–positive patients, and there is limited evidence on the prognostic associations for *RET* in these cancers.

Co-occurrence of other assessed oncogenic alterations was not observed in the *RET* fusion–positive cohort, except for one patient with an *ERBB2* amplification. These data support the hypothesis that *RET* fusions are the primary oncogenic driver in these tumors.[1,5,11] Patients in the matched *RET*-WT

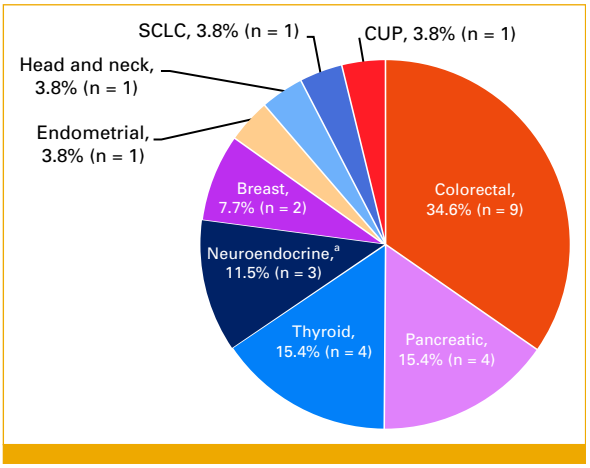

FIG 2. Tumor types in the *RET* fusion–positive cohort (N = 26). Patients with *RET* fusion–positive non–small-cell lung cancer were excluded. [a]Neuroendocrine tumors included one GI tumor and two unspecified anatomical locations. CUP, cancer of unknown primary; *RET*, rearranged during transfection; SCLC, small-cell lung cancer.

cohort had a high rate of *KRAS* alterations (36.5%) and some *BRAF* alterations (5.8%). There were no other notable baseline patient or molecular characteristics in the *RET* fusion–positive cohort.

In three different analyses (crude, model 1, model 2), patients with *RET* fusion–positive tumors consistently had a shorter median OS than those with *RET*-WT tumors. The approximate two-fold increase in risk of death suggests that *RET* fusions have a negative prognostic effect. A similar conclusion was reached in a study of patients with CRC (24 with *RET* fusion–positive and 291 with *RET*-WT tumors), in which the adjusted OS HR was 2.97 (95% CI, 1.25 to 7.07; P = .014).[25]

A study of patients with metastatic *RET* fusion–positive NSCLC suggested that *RET* positivity may be associated with improved survival.[17] However, some analyses were not statistically significant, and therefore, the data were inconclusive. A retrospective study of patients with medullary thyroid cancer found that at time points between 6 and 48 months, progression-free survival rates after first-line therapy were similar between all-comers and patients who had *RET* mutations; however, median progression-free survival was higher in patients with *RET* mutations.[26] It is possible that *RET* alterations have a different prognostic effect in different tumor types, which may justify examining them separately.

Our data indicate that patients with *RET* fusion–positive tumors may not be optimally treated by current standards of care, highlighting the unmet need for precision therapies

TABLE 2. Co-Occurring Biomarkers and Molecular Characteristics

Co-occurring Biomarkers/Molecular Characteristics	*RET* Fusion–Positive (N = 26), No. (%)	*RET*-WT (N = 7,220)	
		Matched (n = 104)	Nonmatched (n = 7,116)
TMB status, No. (%)			
High (≥20 mut/Mb)	2 (7.7)	0	215 (3.0)
Medium (<20, ≥5.7 mut/Mb)	5 (19.2)	16 (15.4)	1,323 (18.6)
Low (<5.7 mut/Mb)	17 (65.4)	88 (84.6)	5,578 (78.4)
Missing	2 (7.7)	0	0
MSI-high, No. (%)			
Yes	1 (3.8)	0	119 (1.7)
No	13 (50.0)	86 (82.7)	6,021 (84.6)
Unknown/missing	12 (46.2)	18 (17.3)	976 (13.7)
Oncogenic alterations, No. (%)			
ALK rearrangement	0	0	13 (0.2)
BRAF alteration	0	6 (5.8)	389 (5.5)
ERBB2 amplification	1 (3.8)	4 (3.8)	300 (4.2)
EGFR alteration	0	0	53 (0.7)
NTRK rearrangement	0	0	13 (0.2)
ROS1 alteration	0	0	11 (0.2)
MET alteration	0	0	9 (0.1)
KRAS alteration	0	38 (36.5)	2,623 (36.9)

NOTE. Only variants of known or likely functional status were included.
Abbreviations: *ALK*, anaplastic lymphoma kinase; *BRAF*, proto-oncogene *B-Raf*; *ERBB2*, Erb-B2 receptor tyrosine kinase 2; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *MET*, mesenchymal epithelial transition factor receptor; MSI, microsatellite instability; *NTRK*, neurotrophic tyrosine receptor kinase; *RET*, rearranged during transfection; *ROS1*, *ROS* proto-oncogene 1; TMB, tumor mutational burden; WT, wild type.

TABLE 3. Analysis of OS

Analysis	Cohort	No. of Deaths, (%)	Median OS, Months (95% CI)	HR (95% CI)
Crude	*RET* fusion–positive (N = 26)	20 (76.9)	6.0 (1.6 to 9.9)	2.0 (1.3 to 3.1)
	Nonmatched *RET*-WT (N = 7,220)	4,838 (67.0)	10.4 (10.0 to 10.9)	
Model 1[a]	*RET* fusion–positive (N = 26)	20 (76.9)	6.0 (1.6 to 9.9)	1.7 (1.0 to 2.9)
	Matched *RET*-WT (n = 104)	72 (69.2)	9.4 (5.5 to 11.7)	
Model 2[b]	*RET* fusion–positive (N = 26)	20 (76.9)	6.9 (1.6 to 9.6)	2.2 (1.3 to 3.7)
	Matched *RET*-WT (n = 104)	72 (69.2)	11.3 (7.7 to 17.1)	

Abbreviations: CGP, comprehensive genomic profiling; HR, hazard ratio; OS, overall survival; *RET*, rearranged during transfection; WT, wild type.
[a]Model 1: using the CGP report date as the index date.
[b]Model 2: using the date of metastatic disease diagnosis as the index date (corrected for immortal time bias).

that specifically target this biomarker.[3,27] Retrospective analyses from a multicenter study of 218 patients with *RET* fusion–positive NSCLC showed significantly improved survival using RET-specific TKIs (such as pralsetinib and selpercatinib).[28] Single-arm clinical trials have also shown good efficacy and safety with RET-specific TKIs in patients with *RET*-altered solid tumors.[29-34] In these trials, response rates in patients with previously treated *RET* fusion–positive NSCLC or thyroid cancer ranged from 63% to 84% with pralsetinib[29,30] and 61% to 77% with selpercatinib.[32,34] Consequently, both drugs achieved grade 3 in the ESMO Magnitude of Clinical Benefit Score version 1.1, the highest grade for single-arm evidence on the basis of response rates of >60%.[35] Taken together with our findings, these data suggest that RET-specific TKIs may represent better treatment options for patients with *RET* fusion–positive tumors than non-RET inhibitor standards of care.

RET fusions are rare in solid tumors,[5,10,11] making it difficult to conduct randomized head-to-head trials of new versus established therapies. Standards of care also differ across histologies and treatment lines; therefore, matching a control arm with the same disease entities and types/numbers of prior treatments is unfeasible. Using high-quality real-world data can robustly evaluate patient outcomes contingent on certain oncogenic drivers and can address key questions around the biological plausibility of using genetic biomarkers as novel therapeutic targets[36] or describe unmet needs for patients. A recent study in patients with *NTRK* fusion–positive solid tumors also used data from the Flatiron Health-Foundation Medicine CGDB and concluded that *NTRK* fusions may represent another negative prognostic factor in patients with locally advanced/metastatic tumors.[37] Again, this reflects the value of real-world data as an integral resource for clinical evidence generation beyond the confines of conventional clinical trials,[38-40] particularly when considering outcomes for patients with rare molecular alterations.

Strengths of our study include the use of real-world data from a large CGDB, with a broad network of sites, which has been used in published analyses of other biomarkers.[37,41] Consistent results across three different analyses, including one to account for immortal time bias, support the robustness of our findings.

Limitations of this study include its retrospective nature and the relatively small number of patients with *RET* fusion–positive tumors, reflecting the rarity of these fusions.[2] Our study cohort was heterogeneous, and it could not be determined if/how tumor types with relatively long survival or large censoring could influence the findings. We adjusted for several important factors in the regression analyses, but there may also be unmeasured confounding factors. In addition, some of these factors had a certain degree of missing data, and therefore, we could not totally assess their impact on the measured associations. It is unknown how well our data represent the wider spectrum of *RET* fusion–positive solid tumors as CGP is not yet a routine practice for all tumor types. Potential biases may exist if CGP was preferentially performed on patients who did not respond to treatment in the real-world setting.

In tumor-agnostic clinical trials, multiple tumor types with the same alteration are given an experimental targeted therapy. There may be a single control arm (including patients who are all given standard-of-care treatment) or no control arm. Ideally, each tumor type in the experimental arm would have corresponding control patients, and the trial would be powered for this comparison. In reality, the number of patients with a specific tumor type in the trial is too small for this to be feasible, especially when the overall prevalence of genetic alterations, such as *RET* or *NTRK* fusions,[42,43] is already low. If patients with an alteration-positive tumor have improved prognoses versus those who are alteration-negative, the apparent increased efficacy seen in tumor-agnostic trials could be partly or wholly due to the prognostic effect of the alteration (ie, confounding) and not the treatment. The prognostic association cannot be determined from these trials because, by design, they exclude patients without these alterations. However, we show that patients with *RET* fusion–positive tumors have worse OS; in tumor-agnostic trials, any improvements in efficacy associated with experimental therapies targeted for *RET* fusions are more likely to be due to the treatment. Such treatments essentially must not only

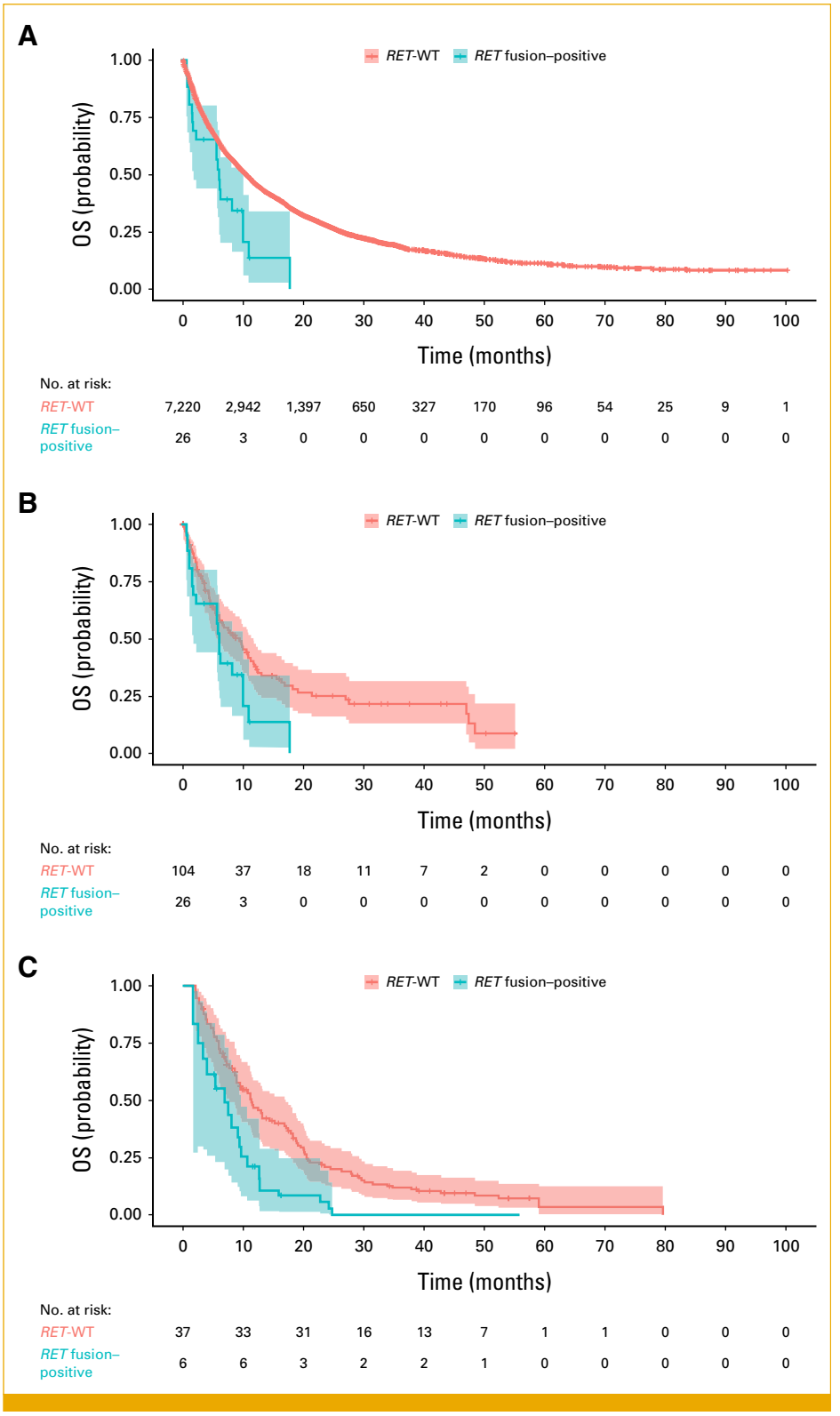

FIG 3. Kaplan-Meier estimates of OS (A) comparing the RET fusion–positive population (N = 26) with the crude RET-WT population (before matching; N = 7,220), using the CGP report date as the index date; (B) comparing the RET fusion–positive population with the matched RET-WT population (n = 104), using the CGP report date as the index date (model 1); (C) comparing the RET fusion–positive population with the matched RET-WT population (n = 104), using the initial diagnosis date as the index date (corrected for immortal time bias; model 2[a]). [a]The number of patients in model 1 (B) and model 2 (C) is the same (ie, N = 26 for the *RET* fusion–positive cohort and n = 104 for the *RET*-WT cohort); however, in model 2, where left truncation is used to (continued on following page)

FIG 3. (Continued). estimate survival, only six patients with *RET* fusion–positive tumors and 37 patients with *RET*-WT tumors had both a metastatic diagnosis and a CGP date at time zero. The remaining patients satisfied cohort entry criteria (ie, CGP report date) at later times, and this immortal time was taken into account when calculating OS. CGP, comprehensive genomic profiling; OS, overall survival; *RET*, rearranged during transfection; WT, wild type.

overcome the negative prognostic association but also provide extra benefit versus standard of care.

In conclusion, our study shows the value of real-world data by highlighting that large data sets are needed to yield a sufficient number of patients when studying rare cancers or genomic alterations. We focused on *RET* status, but there are plans to use the same CGDB to examine the prognostic performance of other uncommon alterations. Our study showed that patients with *RET* fusion–positive tumors, excluding NSCLC, have worse survival outcomes than patients with *RET*-WT tumors, highlighting the importance of these fusions as actionable drug targets and the need for widespread integration of CGP in routine clinical practice. This evidence may help interpret future clinical trials of tumor-agnostic therapies developed for *RET* fusions (other than in NSCLC); our findings indicate that the negative prognostic association would be unlikely to explain treatment benefits. This information could be used by researchers, regulators, and other decision makers. Combined efforts across industry, academia, health care authorities, and payers are needed to evaluate RET-specific TKIs for patients with *RET* fusion–positive tumors and potentially allow more patients to benefit from advances in precision oncology in the future.

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