

# RET-MAP: An International Multicenter Study on Clinicobiologic Features and Treatment Response in Patients With Lung Cancer Harboring a *RET* Fusion



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## ABSTRACT

**Introduction:** Nearly 1% to 2% of NSCLCs harbor *RET* fusions. Characterization of this rare population is still incomplete.

**Methods:** This retrospective multicenter study included patients with any-stage *RET* positive (*RET*+) NSCLC from 31 cancer centers. Molecular profiling included DNA/RNA sequencing or fluorescence in situ hybridization analyses. Clinicobiological features and treatment outcomes (per investigator) with surgery, chemotherapy (CT), immune checkpoint blockers (ICBs), CT-ICB, multityrosine kinase inhibitors, and *RET* inhibitors (*RET*is) were evaluated.

**Results:** For 218 patients included between February 2012 and April 2022, median age was 63 years, 56% were females, 93% had adenocarcinoma, and 41% were smokers. The most frequent fusion partner was *KIF5B* (72%). Median tumor mutational burden was 2.5 (range: 1–4) mutations per megabase, and median programmed death-ligand 1 expression was 10% (range: 0%–55%). The most common metastatic sites were the lung (50%), bone (43%), and pleura (40%). Central nervous system metastases were found at diagnosis of advanced NSCLC in 21% of the patients and at last follow-up or death in 31%. Overall response rate and median progression-free survival were 55% and 8.7 months with platinum doublet, 26% and 3.6 months with single-agent CT, 46% and 9.6 months with CT-ICB, 23% and 3.1 months with ICB, 37% and 3 months with multityrosine kinase inhibitor, and 76% and 16.2 months with *RET*i, respectively. Median overall survival was longer in patients treated with *RET*i versus no *RET*i (50.6 mo [37.7–72.1] versus 16.3 mo [12.7–28.8],  $p < 0.0001$ ).

**Conclusions:** Patients with *RET* NSCLC have mainly thoracic and bone disease and low tumor mutational burden and programmed death-ligand 1 expression. *RET*i markedly improved survival, whereas ICB may be active in selected patients.

**Keywords:** Non-small cell lung cancer; *RET* fusion; *RET* inhibitors; Immunotherapy; Chemotherapy

## Introduction

The receptor tyrosine kinase *RET* gene fusion is a potent oncogenic driver that leads to a constitutively active *RET* tyrosine kinase, which activates the MAPK and PI3K oncogenic pathways.<sup>1–3</sup> It is identified in 1% to 2% of patients with NSCLC<sup>1–3</sup> (*RET* positive [*RET*+] NSCLC). Because of the rarity of the *RET* fusion, clinical and molecular features of patients with *RET* NSCLC are still incompletely characterized and clinical outcomes with various targetable and nontargetable treatments need further investigation.

Early use of multikinase inhibitors (MTKis), such as cabozantinib, vandetanib, lenvatinib, and sorafenib, was found to have only modest activity in *RET* NSCLC.<sup>4–7</sup> With the advent of selective *RET* inhibitors (*RET*is), selpercatinib and pralsetinib, in early clinical studies, clinical outcomes in advanced *RET* NSCLC improved significantly. Tumor response rates range from 55% to 85% and median progression-free survival (PFS) ranges from 16 to 25 months, in prior platinum-treated patients and treatment-naïve patients, respectively, leading to approvals by the European Medicines Agency and Food and Drug Administration.<sup>8–13</sup> Nevertheless, data on overall survival (OS) from randomized clinical trials with these *RET*is have not been reported yet. Similar to other oncogene-addicted NSCLC, *RET* NSCLC is considered a “cold” tumor, with low programmed death-ligand 1 (PD-L1) expression and tumor mutational burden (TMB).<sup>14</sup> Conflicting results have been reported concerning immune checkpoint inhibitor (ICB) activity in small-sized cohorts or case series of *RET* NSCLC,<sup>14–19</sup> whereas data for chemoimmunotherapy are scarce.<sup>20,21</sup>

This study aims to provide an extensive characterization of patients with any-stage *RET* lung cancer, to evaluate their clinical and biological characteristics, including clinical outcomes under various treatments, providing insight into the natural history of this oncogene-addicted cancer.

## Materials and Methods

### Patient Population

The RET-MAP study is a multicenter, retrospective, international study, collecting real-world data from patients with lung cancer harboring a *RET* fusion, diagnosed between February 2012 and April 2022. Eligible patients may have had any-stage *RET*<sup>+</sup> NSCLC and any treatment. Patients receiving a RETi (pralsetinib, selpercatinib, other) within a clinical trial were also included. Patients with other oncogenic addiction (e.g., *EGFR*-mutated NSCLC) developing *RET* fusions as an acquired resistance mechanism to targeted therapy were excluded. A total of 31 cancer centers (30 European and one from Argentina) participated in this study. Clinical and biological data and treatment outcomes were collected using retrospective medical chart review, by each participating center. The last update of the database was performed in October 2022. The study was approved by the Institutional Review Board of the Gustave Roussy Cancer Center, and all living patients were informed about the collection of data.

### Molecular Diagnosis

*RET* gene fusions were detected by fluorescence in situ hybridization (FISH) or by next-generation sequencing (NGS) techniques, or through detection of imbalanced gene expression by means of nCounter gene fusion panels (NanoString Technologies). Molecular analyses were performed on tissue and/or plasma samples in certified laboratories. Genomic profiling was performed at each participating institution according to local practice with both in-house and commercially available platforms, including FoundationOne CDx, OncoPrint (Solid Tumour Fusion Transcript, Ion AmpliSeq Colon and Lung Cancer Research Panel, Focus Assay, Comprehensive Assay version 3), ArcherDx FusionPlex Lung, Guardant360, Nanostring, Illumina TruSight Tumor 170, and Myriad NGS Cancer panel RNA. When available, data for PD-L1 expression and TMB levels were collected from pathology and comprehensive NGS reports, respectively.

### Treatment

Treatment outcomes were analyzed separately for patients at time of localized and advanced disease, respectively. For patients with early stage NSCLC treated with surgery, disease-free survival was defined as the time from curative treatment start to disease relapse or death. For patients with advanced disease, treatment outcomes with chemotherapy (CT), ICB, CT-ICB, MTKis, and selective RETi were investigated by measuring the following: overall response rate (ORR) defined as proportion of patients who had a complete or partial

response to therapy; PFS defined as the time from treatment start to disease progression or death; OS defined as the time from treatment start to death from any cause; and duration of response, defined as the time from response to progression or death. Treatment response was evaluated in each participating center without centralized imaging review, according to investigator assessment or per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

### Safety

Treatment-related side effects were collected under ICB with or without CT and under RETi. Permanent treatment discontinuation owing to toxicity was registered.

### Statistical Analysis

Survival analyses curves were built using the Kaplan-Meier method, and survival outcomes were compared using a log-rank test. Survival outcomes for a specific treatment were calculated only when a minimum follow-up of 6 months was available, in the absence of progression or death. For patients with advanced disease, OS was calculated from the start of first-line treatment for advanced disease. To assess the impact of prognostic factors associated with OS, a multivariate Cox regression model adjusted for different variables (age, sex, Eastern Cooperative Oncology Group performance status, histologic types, smoking status, stage at diagnosis, and number of metastatic sites) was used. We compared the OS of patients with or without treatment with RETi as a global analysis irrespective of the number of systemic treatments received, and we did a subgroup analysis, stratifying according to the total number of systemic treatment lines received (<2 and ≥2). The latter was performed to reduce the impact of the immortal time bias and to compare groups more homogenous in terms of total number of treatment lines during disease evolution. In addition, landmark analysis was used to correct for immortal time bias before the start of RETi. All statistical analyses were performed with R version 4.1.3. Statistical significance was set at *p* value less than 0.05.

## Results

### Clinical Characteristics

Clinical characteristics of the 218 eligible patients are presented in Table 1. Median age was 63 years (interquartile range [IQR]: 54–71 y), and 56% of the patients were female. Nearly half of the population had a smoking history (41%), with median tobacco consumption estimated to be 18 pack-years (IQR: 8–30 pack-years). Five patients had a tobacco consumption of more than 50 pack-years. None of the patients had a known history of

**Table 1. Patient Clinical Characteristics**

Characteristics	Patients (N = 218)
Female, n (%)	122 (56)
Age, y, median [IQR]	63 [54-71]
Histologic type, n (%)	
Adenocarcinoma	203 (93)
Squamous carcinoma	1 (0.5)
Undifferentiated carcinoma	7 (3.2)
Neuroendocrine carcinoma	7 (3.2)
Stage at diagnosis, n (%)	
Stage I	17 (7.8)
Stage II	11 (5)
Stage III	27 (12)
Stage IV	163 (75)
N metastatic sites at time of advanced disease, median [IQR]	2 [1-3]
Smoking history, n (%)	
Nonsmoker	126 (59)
Former	76 (35)
Current	13 (6)
Unknown	3
Performance status ECOG, n (%)	
PS 0-1	175 (87)
PS 2	19 (9.4)
PS 3-4	8 (4)
Unknown	16
Grade I familial history of cancer, n (%)	48 (33.5)
Unknown	75
N treatment lines received, median [IQR]	2 [1-3]

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PS, performance status.

regular cannabis smoking. The most frequent histologic type was adenocarcinoma, in 93% of the cases. Other histologic types included seven patients with

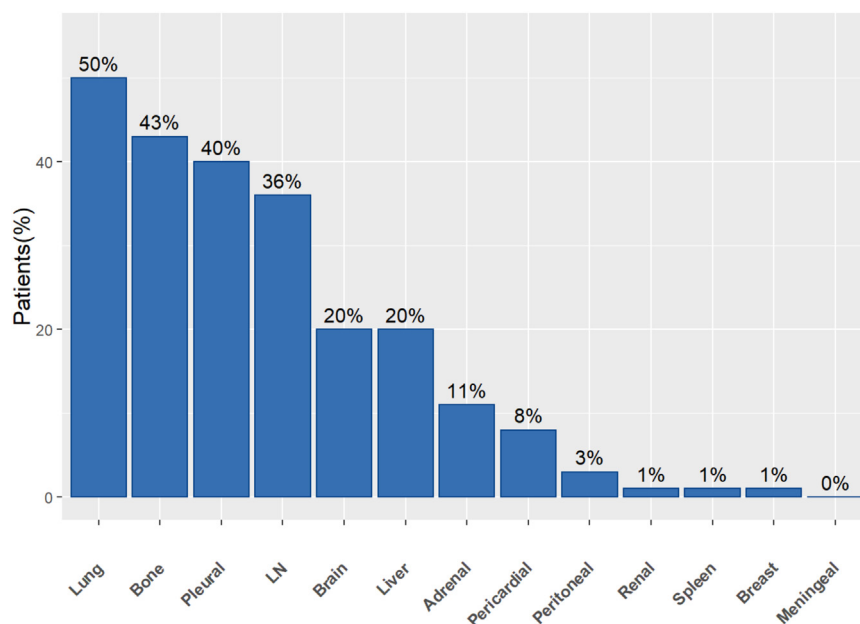
undifferentiated carcinoma (one with a squamous component), seven patients with neuroendocrine carcinoma (two atypical carcinoid, three large cell carcinoma, one small cell carcinoma, and one with mixed small cell and large cell carcinoma), and one with squamous cell carcinoma. Of 15 patients with nonadenocarcinoma histology, seven patients had a smoking history and were tested as part of molecular screening programs for treatment tailoring.

In patients with metastatic disease anytime during their disease evolution (205 of 218; 94%), the most frequently involved sites were the lung, bone, pleura, and lymph nodes, whereas the adrenal glands were only rarely involved (Fig. 1). Central nervous system metastases were present at diagnosis of advanced disease in nearly 21% of the cases (41 of 205) and at the last date of follow-up in 31% (63 of 205) of the cases.

### Molecular Characteristics

Patients had molecular testing before treatment start in 14 (25%) cases with localized disease (25%) and 123 (60%) cases with stage IV disease. *RET* testing was performed by NGS with or without FISH in 166 cases (76%), by FISH only in 29 cases (13%), by detection of gene imbalance (nCounter technology) in 18 cases (8%), and by reverse transcriptase-polymerase chain reaction in five cases (2%). NGS and nCounter analyses were performed on the DNA in 56 cases (30%), on the RNA in 64 cases (35%), and on both in 64 cases (35%).

For cases with a known fusion partner, the most frequent fusion partner was *KIF5B* (72% of the cases), followed by *CCDC6* (17%) (Supplementary Fig. 1). Three



**Figure 1.** Metastatic pattern of *RET*<sup>+</sup> stage IV lung cancer among the 205 patients. LN, extrathoracic lymph nodes.

patients had two synchronous *RET* fusions at baseline, and in each case, the pair included *KIF5B-RET*, with either *ARL9-RET*, *PLXDC2-RET*, or *BMS1-RET*. The most frequent co-mutation identified at baseline was *TP53* mutation in 19% of the cases (Supplementary Fig. 2).

Overall, in patients with known PD-L1 expression (N = 178), median PD-L1 expression was 10% (IQR: 0–55). A total of 62 (35%) patients had 0 PD-L1 expression, 62 (35%) had 1% to 49% PD-L1 expression, and 54 (30%) had high PD-L1 expression greater than or equal to 50%. TMB was assessable in 45 patients (21%), with a median of 2.5 mutations per megabase (IQR: 1–4).

**Treatment Outcomes**

**Locoregional Treatment in Patients With Localized RET+ NSCLC.** In our cohort, 55 patients had a localized disease at the time of diagnosis. A total of 44 patients diagnosed with having a resectable NSCLC received surgery and had a median disease-free survival of 25.5 months (95% confidence interval [CI]: 20.2–57), for a median follow-up of 56.3 months (95% CI: 45.8–not reached [NR]). Eight patients had locally advanced NSCLC and received chemoradiation, of whom two patients received durvalumab as a consolidation therapy.

**Systemic Treatment in Patients With Advanced RET+ NSCLC.** A total of 205 patients had metastatic disease (145 cases with stage IV from diagnosis). Outcomes with different systemic treatments are presented in Table 2. A total of seven patients rapidly died of disease progression in the absence of any treatment: four had poor performance status and were unfit for CT or trials evaluating RETi, whereas the rest experienced fatal disease-related complications while awaiting treatment. For those patients who received treatment, median follow-up from the start of first-line therapy for advanced disease was 38.2 months (95% CI: 34.1–45.8). The highest ORR was observed with RETi, followed by platinum-based doublet CT with or without

ICB. Across all types of treatment, there was no significant difference in terms of PFS between patients harboring *KIF5B-RET* fusions versus non-*KIF5B-RET* fusions (Supplementary Table 1).

**CT in Advanced RET+ NSCLC.** Patients treated with CT doublet received pemetrexed-based combinations in 71% of the cases. There was no significant difference in PFS between patients treated with platinum-pemetrexed versus non-pemetrexed combinations (median PFS: 9 mo [95% CI: 7.8–13.3] versus 7 mo [95% CI: 5.1–11.4], respectively, *p* = 0.15) (Supplementary Fig. 3).

**RET Inhibitors in Advanced RET+ NSCLC.** In assessable patients treated with RETi, the presence of *TP53* co-mutations at baseline (N = 24) did not significantly affect PFS under RETi (median PFS: 11.2 mo [95% CI: 5.8–NR] versus 16.2 mo [95% CI: 12.2–NR], respectively, *p* = 0.36).

Median OS was 28.3 months (95% CI: 21.8–NR) from the start of RETi. OS calculated from the start of first therapy for advanced disease was higher in patients treated with RETi versus no RETi (median OS, 50.6 mo [95% CI: 37.7–72.1] versus 16.3 mo [95% CI: 12.7–28.8], *p* < 0.0001), irrespective of the total number of prior therapy lines received. There were no significant differences across these two populations (Supplementary Table 2). A difference in OS between patients treated with RETi versus no RETi was maintained when considering the total number of lines received. RETi was found to have a benefit in all patients, irrespective of the total number of lines received; up to two lines (38.2 mo [95% CI: 24.5–NR] versus 17.7 mo [95% CI: 11–NR], *p* = 0.012; Fig. 2A) and more than two treatment lines (53.6 mo [95% CI: 40.8–NR] versus 21.8 mo [95% CI: 13.6–NR], *p* = 0.0005; Fig. 2B).

In patients with advanced *RET+* lung cancer, the multivariate analysis with landmark correction revealed that improved OS was independently associated with the use of RETi (hazard ratio [HR] = 0.55 [95% CI: 0.34–0.87],

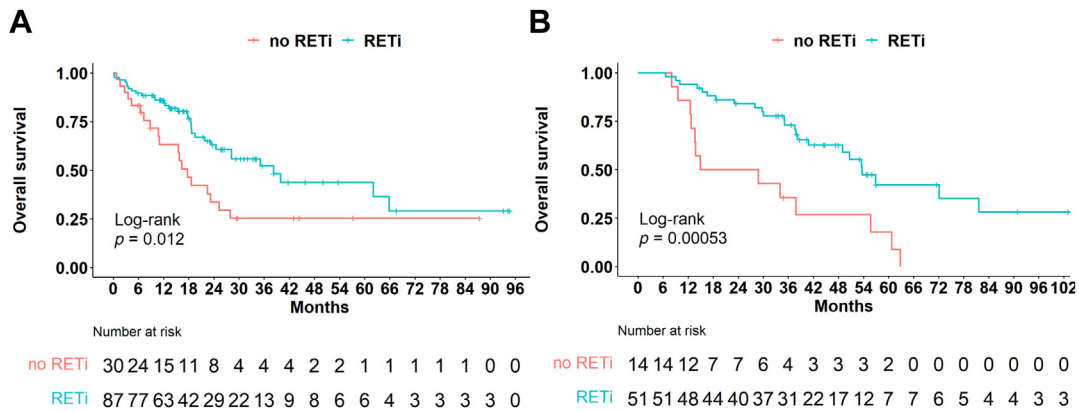
**Table 2. Outcomes After the First Use of Each Type of Therapy in Advanced RET+ NSCLC**

Systemic Therapy	Doublet CT (n = 108)	Single-Agent CT (n = 34)	CT-ICB (n = 41)	ICB (n = 52)	MTKi (n = 21)	RETi (n = 145)
N of treatment line, median (range)	1 (1-1)	2.5 (2-3)	1 (1-1)	2 (1-2)	3 (1-4)	2 (1-2)
ORR, n/N (%) <sup>a</sup>	56/102 (55)	8/31 (26)	17/37 (46)	12/52 (23)	7/19 (37)	99/131 (76)
Median PFS, mo [95% CI] <sup>b</sup>	8.7 [7.2-11.3]	3.6 [2.5-8.1]	9.6 [5.2-13.8]	3.1 [2.4-7]	3 [1.7-7.7]	16.2 [11.9-26.1]
Median DOR, mo [95% CI] <sup>b</sup>	7.5 [5.7-10.9]	6.5 [4.9-NR]	9 [8.2-NR]	9.4 [7.6-NR]	NA [small cohort]	21.1 [14.9-NR]

<sup>a</sup>ORR was calculated for patient with available assessable disease by RECIST v1.1 or investigator assessment.

<sup>b</sup>Survival outcomes were calculated only for patients with at least 6 months of follow-up, in the absence of progression or death.

CI, confidence interval; CT, chemotherapy; DOR, duration of response; ICB, immune checkpoint blocker; MTKi, multityrosine kinase inhibitor; NA, not applicable; NR, not reached; ORR, overall response rate; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; *RET+*, *RET* positive; RETi, RET inhibitor.



**Figure 2.** Overall survival in patients treated with selective RETis. (A) Patients treated with a maximum of two lines of therapy. (B) Patients treated with more than two lines of therapy. RETi, RET inhibitor.

$p = 0.011$ ), whereas worse OS was associated with baseline performance status greater than or equal to 2 (HR 2.8 [95% CI: 1.59–4.92],  $p < 0.001$ ). Sex, age, smoking status, and histologic type did not have a significant impact on OS ( $p < 0.05$ ).

**Immunotherapy in Advanced RET+ NSCLC.** In patients treated with ICB without CT, objective responses were observed in 23% of the cases. Two patients had a complete response and nine patients had a partial response with durable responses under ICB. There was a significant difference in terms of PFS favoring women treated with ICB compared with men (median PFS = 5.6 mo [95% CI: 3.1–10.5] versus 2.1 mo [95% CI: 1.3–4.3],  $p = 0.00018$ ) (Fig. 3). This was not observed in patients treated with CT-ICB (Fig. 3) or other therapies. Smoking history and PD-L1 expression did not significantly affect the ICB outcomes (Fig. 3), although patients with smoking history tended to have a numerically longer PFS under CT-ICB than those without a smoking history (11.4 mo [95% CI: 9.4–NR] versus 5.6 mo [95% CI: 3.8–NR],  $p = 0.13$ ). Median PD-L1 expression in assessable patients was 50% (range: 1–60) and 40% (range: 0–60) in the responders ( $n = 13$ ) and nonresponders ( $n = 25$ ) to ICB, respectively (Wilcoxon ranked sum test with continuity correction,  $p = 0.56$ ) (Supplementary Fig. 4).

**Treatment Discontinuation in Advanced RET+ NSCLC.** Treatment was permanently discontinued for toxicity in 10 patients (24%) treated with CT-ICB (three for immune-related side effects), five patients (10%) treated with ICB, and 18 patients (12%) treated with RETi. Reasons for treatment discontinuation are found in Supplementary Table 3. Two patients who stopped ICB (pembrolizumab and nivolumab plus ipilimumab) owing to immune-related side effects had a complete

response and stable disease, respectively, with responses lasting for nearly 7 months and more than 2 years, respectively.

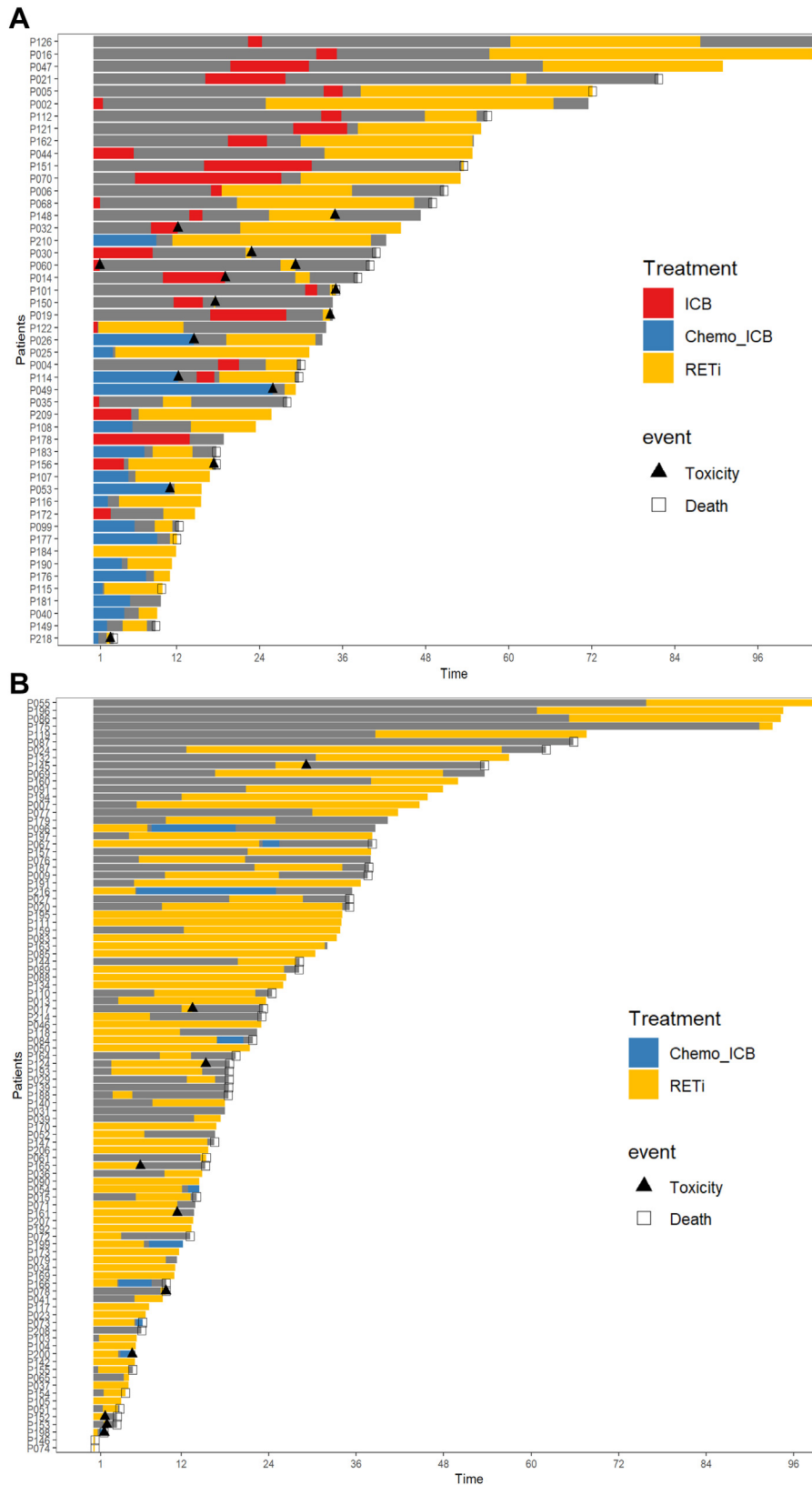
Permanent RETi discontinuation in patients pretreated or not by ICB with or without CT is found in Figure 4A and B. There were numerically more patients discontinuing RETi if a prior ICB was used, as compared with those without prior ICB (17% versus 9.6%,  $p = 0.27$ ). One patient who permanently discontinued ICB for immune-related grade 3 colitis under nivolumab-ipilimumab further permanently stopped RETi because of grade 3 colitis, at more than 2 years after the last dose of ICB.

## Discussion

To the best of our knowledge, the RET-MAP study is the largest cohort reported to date, evaluating the clinical and biological features, along with treatment outcomes, providing natural history data for 218 patients with RET+ lung cancer in a real-world setting. Analysis of the clinical characteristics of patients in our cohort highlights several particularities. A significant proportion of patients had a smoking history (nearly half of them), reiterating the importance of performing molecular testing in patients with NSCLC irrespective of their smoking habit. This is consistent with data reported by studies describing RET+ NSCLC, where the percentage of patients with a smoking history ranges from 29% to 50%.<sup>8,9,18,20,22</sup> Although most of our patients had adenocarcinoma, 7% had other histologic types. Among the metastatic sites identified at the time of diagnosis of advanced disease, the thorax and bones were frequent, whereas the adrenals were only rarely reported, unlike the typical adrenal tropism found in NSCLC. In our cohort, 21% of the patients had central nervous system metastases at diagnosis of advanced disease, coherent with published data.<sup>18,22</sup> The lifetime incidence of brain metastases in our cohort was 31%, which is less than the







**Figure 4.** (A) Permanent treatment discontinuation for toxicity in patients treated with ICB with or without chemo before RETi. (B) Permanent treatment discontinuation for toxicity in patients treated with RETi without prior ICB with or without chemo. Chemo, chemotherapy; ICB, immune checkpoint blocker; RETi, RET inhibitor.

The biological characteristics we identified in our cohort confirm that *RET*+ NSCLC are cold tumors, similar to other oncogene-addicted tumors, with low PD-L1 expression and low TMB. Coherent with this, survival outcomes were modest with ICB; however, 23% of the patients achieved objective responses with durable survival outcomes. This was not explained by either smoking history or PD-L1 expression, although median PD-L1 expression was numerically higher in patients responding to ICB. Surprisingly, ICB, but not CT-ICB, was significantly associated with longer PFS in women than in men, which has not been reported previously. In small published reports including between nine and 15 patients, ORRs with ICB ranged between 0% and 38% and median PFS ranged between 2.1 and 7.6 months.<sup>14–18</sup> In our study, the treatment outcomes with CT-ICB and CT doublets were similar. It is still not clear which patients benefit from the addition of ICB versus CT alone. In patients receiving CT-pembrolizumab according to the KEYNOTE-189 schedule in the first-line setting, there were no statistically significant differences between outcomes of patients with (N = 9) or without the *RET* fusion (N = 665) (median PFS of 6.6 mo and 5.7 mo, respectively; adjusted HR = 1.24; caution as small *RET*+ cohort).<sup>20</sup>

The limitations of the RET-MAP study include the lack of central confirmation of the *RET* fusion and the heterogeneity of molecular testing technologies, the absence of uniform imaging workup (including no mandatory check for brain metastases), and the reliance on assessments made by the investigators without central independent imaging evaluation. In addition, the RET-MAP study bears other inherent limitations of retrospective studies and should therefore be interpreted with caution.

In conclusion, RETi significantly improved OS in advanced NSCLC, irrespective of the number of lines of therapy. Patients with *RET*+ NSCLC frequently had a smoking history and only in rare cases they exhibited other histologic types than adenocarcinoma. *RET*+ tumors displayed elements of cold tumor microenvironment with generally low TMB and PD-L1 levels. Nevertheless, selected patients did respond to ICB revealing long benefit, and therefore patients with *RET*+ NSCLC should not be excluded from ICB treatment at some point during their disease evolution. Predictive biomarkers of response to therapy and the optimal therapeutic sequence between RETi and ICB with or without CT merit further investigation in this population.

## CRedit Authorship Contribution Statement

**Mihaela Aldea:** Concept, Methodology, Data curation, Investigation, Formal analysis, Writing—original draft, Writing—review and editing.

**Arianna Marinello:** Data curation, Investigation, Methodology, Writing—review and editing.

**Wael Zrafi:** Data curation, Methodology, Statistical analysis, Writing—review and editing.

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**Benjamin Besse:** Concept, Methodology, Writing—review and editing, Supervision.

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## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at [www.jto.org](http://www.jto.org) and at <https://doi.org/10.1016/j.jtho.2022.12.018>.

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