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RET-MAP: An international multi-center study on clinicobiologic features and treatment response in patients with lung cancer harboring a *RET* fusion

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RET-MAP: An international multi-center study on clinicobiologic features and treatment response in patients with lung cancer harboring a *RET* fusion

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ABSTRACT

Introduction

Nearly 1-2% of non-small cell lung cancers (NSCLC) harbor *RET* fusions. Characterization of this rare population is still incomplete.

Methods

This retrospective multi-center study included patients with any-stage *RET*+ NSCLC from 31 cancer centers. Molecular profiling included DNA/RNA sequencing and/or FISH analyses. Clinico-biological features and treatment outcomes (per investigator) with surgery, chemotherapy, immune-checkpoint blockers (ICB), chemotherapy-ICB, multi-tyrosine kinase inhibitors (MTKi) and *RET* inhibitors (*RET*i) 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 (TMB) was 2.5 [range, 1-4] mut/Mb and median PD-L1 expression was 10% [range, 0-55]. The most common metastatic sites were lung (50%), bone (43%) and pleura (40%). Central nervous system metastases were found at diagnosis of advanced NSCLC in 21% of 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 chemotherapy, 46% and 9.6 months with chemotherapy-ICB, 23% and 3.1 months with ICB, 37% and 3 months with MTKi, 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 months [37.7-72.1] versus 16.3 months [12.7-28.8], $P < 0.0001$).

Conclusions

Patients with *RET*+ NSCLC have mainly thoracic and bone disease, and low TMB and PD-L1 expression. *RET*i significantly improve survival, while ICB may be active in selected patients.

INTRODUCTION

The receptor-tyrosine kinase rearranged during transfection (*RET*) gene fusion is a potent oncogenic driver that leads to a constitutively active RET tyrosine kinase, which activates MAPK and PI3K oncogenic pathways¹⁻³. It is identified in 1% to 2% of patients with non-small cell lung cancer (NSCLC)¹⁻³ (*RET*+ NSCLC). Because of the rarity of *RET* fusion, clinical and molecular features of patients with *RET*+ NSCLC are still incompletely characterized and clinical outcomes with various targetable and non-targetable treatments need further investigation.

Early use of multikinase inhibitors (MTKi) such as cabozantinib, vandetanib, lenvatinib, and sorafenib, showed only modest activity in *RET*+ NSCLC⁴⁻⁷. With the advent of selective RET inhibitors (RETi), seliperatinib 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) range from 16 to 25 months, in prior platinum-treated patients and treatment naïve patients, respectively, leading to approvals by EMA and FDA⁸⁻¹³. However, data on overall survival (OS) from randomized clinical trials with these RETi 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)¹⁴. Conflicting results have been reported concerning immune-checkpoint inhibitors (ICB) activity in small-size cohorts or case series of *RET*+ NSCLC¹⁴⁻¹⁹, while data for chemo-immunotherapy are scarce^{20, 21}.

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

PATIENTS AND METHODS

Patient population

The RET-MAP study is a multi-center, 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*+ NSCLC and any treatment. Patients receiving a RETi (pralsetinib, seliperatinib, BOS172738) within a clinical trial were also included. Patients with other oncogenic addiction (e.g., *EGFR* mutated NSCLC) developing *RET* fusions as an acquired resistance mechanisms 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 via 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 Foundation One CDx, OncoPrint (Solid Tumour Fusion Transcript, Ion AmpliSeq

Colon and Lung Cancer Research Panel, Focus Assay, Comprehensive Assay v3), ArcherDx FusionPlex Lung, Guardant 360, Nanostring, Illumina TruSight Tumor 170, Myriapod 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 (DFS) was defined as the time from curative treatment start to disease relapse or death. For patients with advanced disease, treatment outcomes with chemotherapy, ICB, chemotherapy-ICB, multi-tyrosine kinase inhibitors, 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 (DOR), 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 RECIST v.1.1.

Safety

Treatment-related side effects were collected under ICB +/- chemotherapy and under RETi. Permanent treatment discontinuation due to toxicity was registered.

Statistical analysis

Survival analyses curves were performed 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, ECOG performance status, histology, 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). This 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. Also, 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 $p < 0.05$.

RESULTS

Clinical characteristics

Clinical characteristics of the 218 eligible patients are presented in Table 1. Median age was 63 years [IQR, 54-71] and 56% of 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]. Five patients had a tobacco consumption of more than 50 pack-years. None of the patients had a known history of

regular cannabis smoking. The most frequent histology was adenocarcinoma, in 93% of cases. Other histology types included 7 patients with undifferentiated carcinoma (one with a squamous component), 7 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. Out of 15 patients with non-adenocarcinoma histology, 7 patients had a smoking history and were tested as part of molecular screening programs for treatment tailoring.

Table 1. Patient clinical characteristics

	Patients (N=218)
Female, N (%)	122 (56%)
Age in years, median [IQR]	63 [54-71]
Histology, 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 (%)	
Non-smoker	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]

N, number; PS, performance status

In patients with metastatic disease anytime during their disease evolution (205/218; 94%), the most frequently involved sites were lung, bone, pleura, and lymph nodes, while adrenal glands were only rarely involved (Figure 1). Central nervous system (CNS) metastases were present at diagnosis of

advanced disease in nearly 21% of cases (41/205), and at the last date of follow-up in 31% (63/205) of cases.

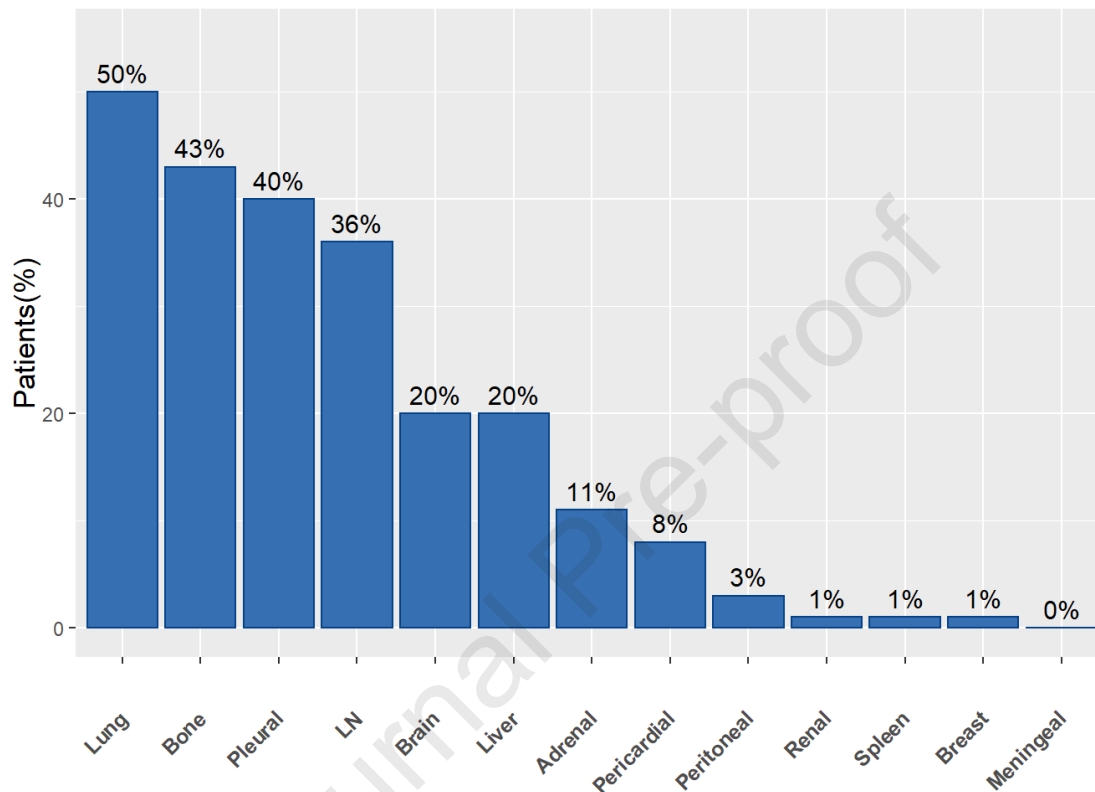


Figure 1. Metastatic pattern of *RET*+ stage IV lung cancer among the 205 patients. LN: extra-thoracic lymph nodes.

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 RT-PCR in 5 cases (2%). NGS and nCounter analyses were performed on DNA in 56 cases (30%), on 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 cases), followed by *CCDC6* (17%) (Supplementary Figure 1). Three patients had two synchronous *RET* fusions at baseline, 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 were *TP53* mutations in 19% cases (Supplementary Figure 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 1-49% PD-L1 expression and

and 54 (30%) had high PDL1 expression $\geq 50\%$. TMB was evaluable in 45 patients (21%), with a median of 2.5 mut/Mb [IQR, 1-4].

Treatment outcomes

Locoregional treatment in patients with localized RET+ NSCLC

In our cohort, 55 patients had a localized disease at time of diagnosis. A total of 44 patients diagnosed with a resectable NSCLC received surgery and had a median DFS of 25.5 months [95%CI 20.2-57], for a median follow-up of 56.3 months [95%CI 45.8-NR]. Eight patients had locally advanced NSCLC and received chemoradiation, out of whom 2 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 7 patients rapidly died of disease progression in the absence of any treatment: four had poor performance status and were unfit for chemotherapy or trials evaluating RETi, while 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 34.1.4-45.8]. The highest ORR was observed with RETi, followed by platinum-based doublet chemotherapy 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).

Table 2. Outcomes following the first use of each type of therapy in advanced *RET+* NSCLC.

	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 (%)[‡]	56/102 (55%)	8/31 (26%)	17/37 (46%)	12/52 (23%)	7/19 (37%)	99/131 (76%)
Median PFS, months [95%CI]*	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, months [95%CI]*	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]

CT: chemotherapy; ICB, immune checkpoint blocker; DOR, duration of response; MTKi, multi-tyrosine kinase inhibitor; NR, not reached; ORR, overall response rate; PFS, progression-free survival; RETi, RET inhibitor; ^fORR was calculated for patient with available evaluable disease by RECIST v1.1. or investigator assessment; *survival outcomes were calculated only for patients with at least 6 months of follow-up, in the absence of progression or death.

Chemotherapy in advanced RET+ NSCLC

Patients treated with chemotherapy doublet received pemetrexed-based combinations in 71% of cases. There was no significant difference in PFS between patients treated with platinum-pemetrexed versus non-pemetrexed combinations (median PFS: 9 months [95%CI 7.8-13.3] versus 7 months [95%CI 5.1-11.4], respectively, P=0.15) (Supplementary Figure 3).

RET inhibitors in advanced RET+ NSCLC

In evaluable patients treated with RETi, the presence of *TP53* co-mutations at baseline (N=24) did not significantly impact PFS under RETi (median PFS: 11.2 months [95%CI 5.8-not reached] versus 16.2 months [95%CI 12.2-not reached], 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 months [95%CI 37.7-72.1] versus 16.3 months [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 showed a benefit in all patients, irrespective of the total number of lines received; up to 2 lines (38.2 months [95%CI 24.5-not reached] vs 17.7 months [95%CI 11-not reached], P=0.012; Figure 2A) and more than 2 treatment lines (53.6 months [95%CI 40.8-not reached] vs 21.8 months [95%CI 13.6-not reached], P=0.0005; Figure 2B).

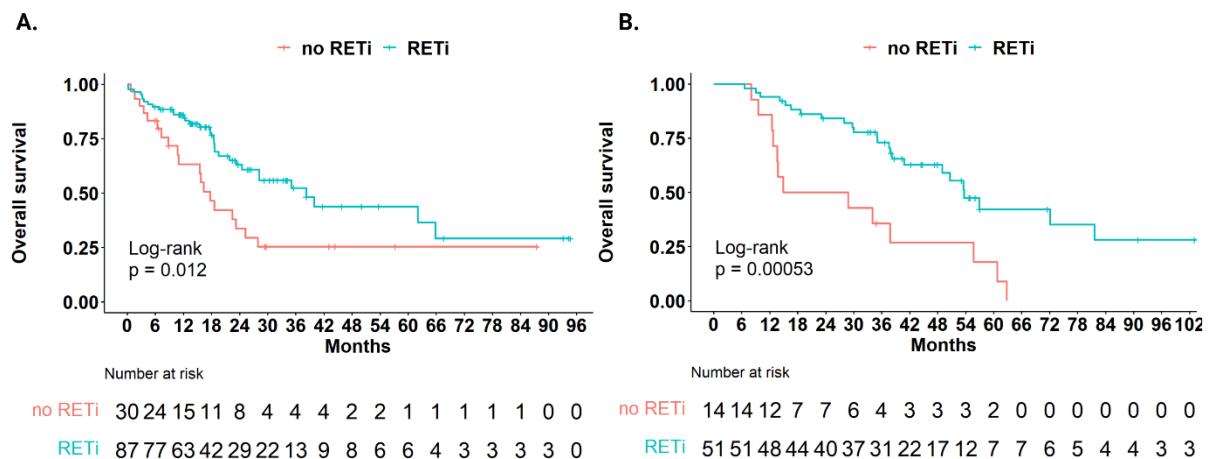


Figure 2. Overall survival in patients treated with selective RET inhibitors (RETi). A) Patients treated with a maximum of two lines of therapy; B) Patients treated with more than two lines of therapy.

In patients with advanced *RET*+ lung cancer, the multivariate analysis with landmark correction showed that improved OS was independently associated with the use of RETi (HR 0.55 [95%CI 0.34-0.87], $P=0.011$), while worse OS was associated with baseline performance status ≥ 2 (HR 2.8 [95%CI 1.59-4.92], $P<0.001$). Sex, age, smoking status and histology did not show a significant impact on OS ($P<0.05$).

Immunotherapy in advanced RET+ NSCLC

In patients treated with ICB without chemotherapy, objective responses were observed in 23% of cases. Two patients had a complete response and 9 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 to men (median PFS 5.6 months [95%CI 3.1-10.5] versus 2.1 months [95%CI 1.3-4.3], $P=0.00018$) (Figure 3). This was not observed in patients treated with chemo-immunotherapy (Figure 3) or other therapies. Smoking history and PD-L1 expression did not significantly impact ICB outcomes (Figure 3), although patients with smoking history tended to have a numerically longer PFS under CT-ICB than those without a smoking history (11.4 months [95%CI 9.4 – NR] vs 5.6 months [95%CI 3.8 – NR], $P=0.13$). Median PD-L1 expression in evaluable patients was 50% [range, 1-60] and 40% [range, 0-60] in responders ($N=13$) and non-responders ($N=25$) to ICB, respectively (Wilcoxon rank sum test with continuity correction, $P=0.56$) (Supplementary Figure 4).

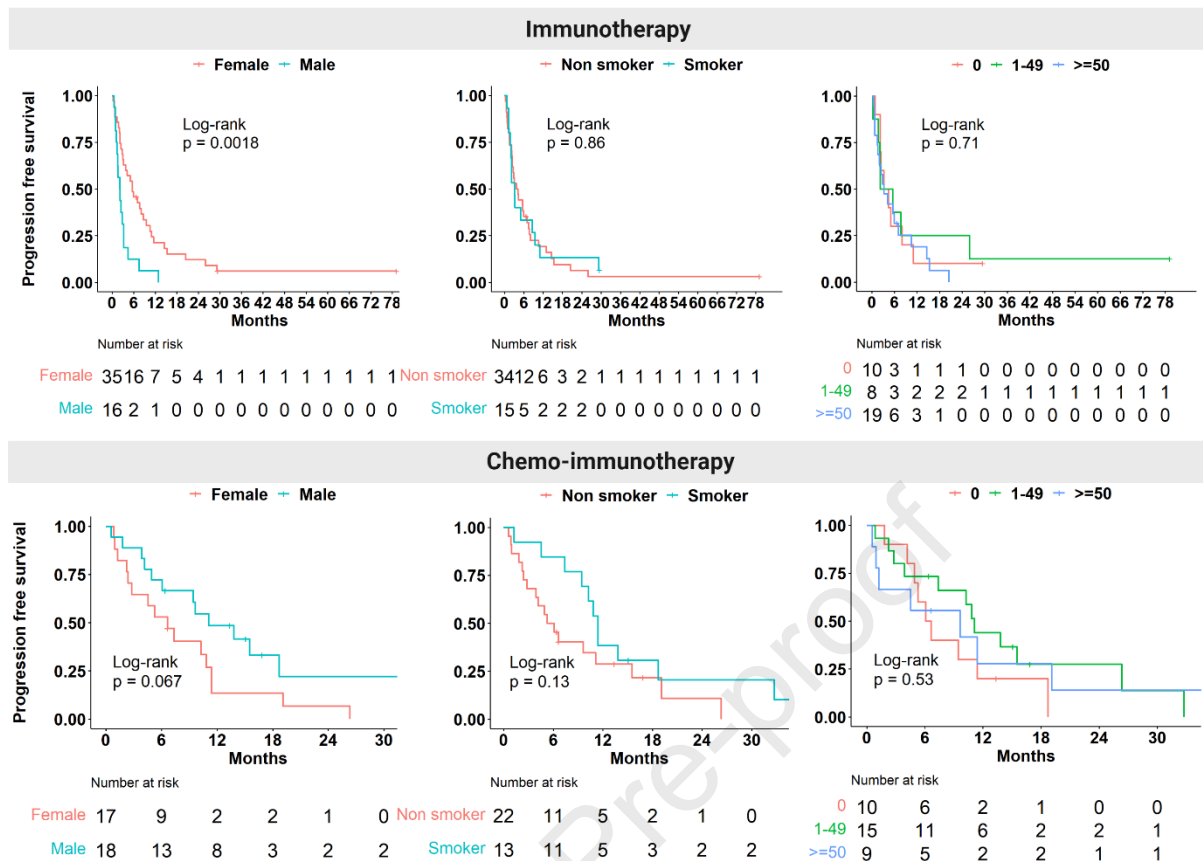


Figure 3. PFS subgroup analyses after stratification by sex, smoking history and PD-L1 expression in patients treated with immunotherapy and chemo-immunotherapy.

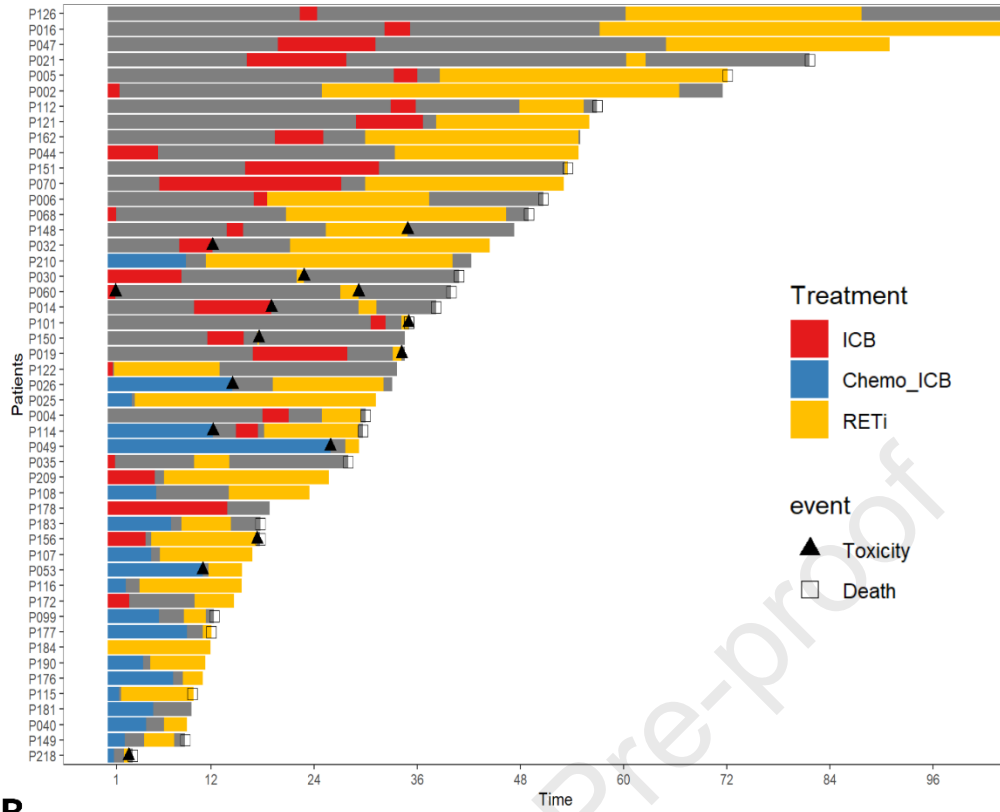
Treatment discontinuation in advanced RET+ NSCLC

Treatment was permanently discontinued for toxicity in 10 (24%) patients treated with chemotherapy-ICB (3 for immune-related side effects), 5 (10%) patients treated with ICB, and 18 (12%) patients treated with RETi. Reasons for treatment discontinuation are shown in Supplementary Table 3. Two patients who stopped ICB (pembrolizumab and nivolumab plus ipilimumab) due 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.

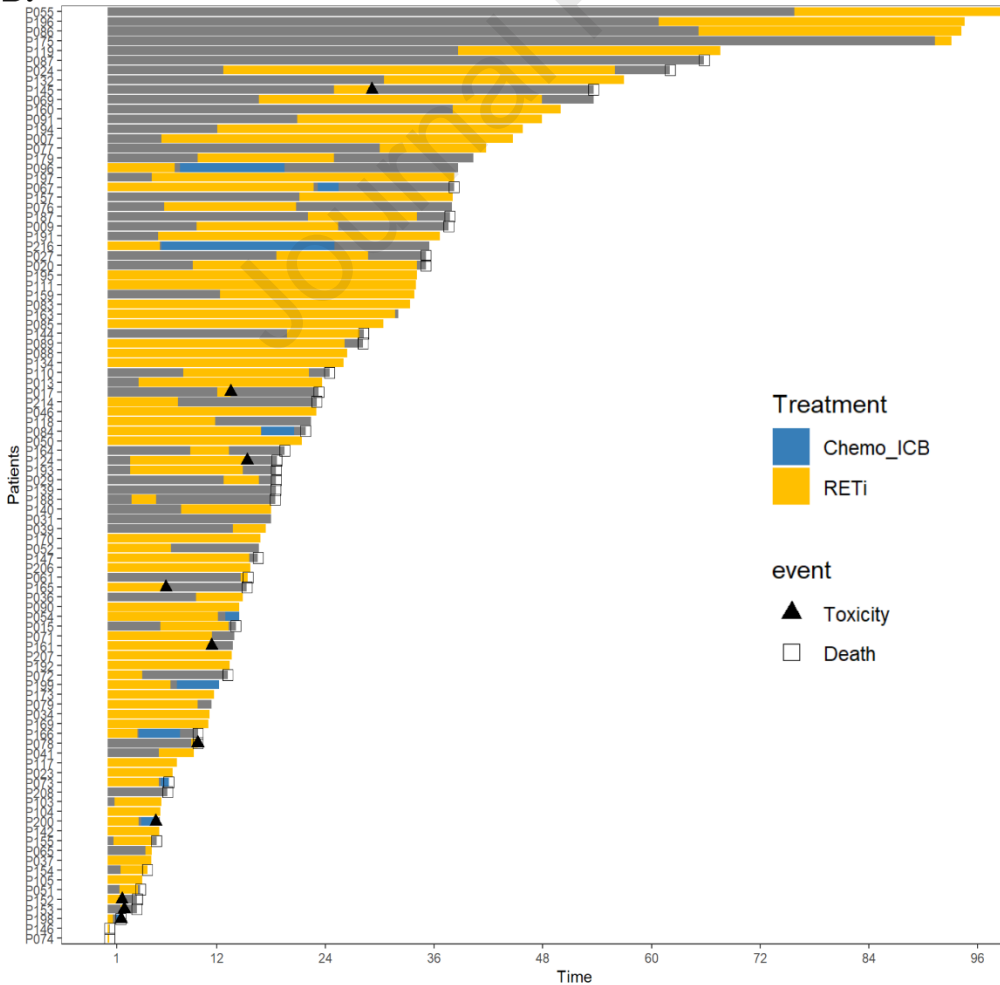
Permanent RETi discontinuation in patients pretreated or not by ICB+/- chemotherapy is shown in Figure 4. There were numerically more patients discontinuing RETi if a prior ICB was used, as compared to those without prior ICB (17% versus 9.6%, $p=0.27$). One patient who permanently discontinued ICB for 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.

Figure 4. A) Permanent treatment discontinuation for toxicity in patients treated with ICB+/- chemotherapy prior to RETi; B) Permanent treatment discontinuation for toxicity in patients treated with RETi without prior ICB+/-chemotherapy.

A.



B.



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 highlight several particularities. A significant proportion of patients had a smoking history (nearly half of them), reiterating the importance of performing molecular testing in NSCLC patients 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 range from 29% to 50%^{8,9,18,20,22}. Although the majority of our patients had adenocarcinoma, 7% had other histology types. Among the metastatic sites identified at the time of diagnosis of advanced disease, the thorax and bones were frequent, while adrenals were only rarely reported, unlike the typical adrenal tropism seen in NSCLC. In our cohort, 21% of patients had CNS metastases at diagnosis of advanced disease, coherent with published data^{18,22}. The lifetime incidence of brain metastases in our cohort was 31%, which is less than the 46% reported by Drilon *et al*²². This may be explained by the fact that 70% of patients in our cohort of advanced disease had received a RETi, which has significant intracranial activity¹⁰, whereas the patients included in the cohort of Drilon *et al* had only received MTKi. Additionally, the type and frequency of brain imaging may differ between the two cohorts.

In our retrospective study, RETi significantly improved OS. Randomized, phase III studies, evaluating RETi in the first line setting as compared with chemotherapy +/- immunotherapy, are ongoing and results waited for 2024-2025 (AcceleRET-Lung: NCT04222972, LIBRETTO-431: NCT04194944). It should be noted that as randomized trials may offer patients treated in the control arm to crossover to a RETi, this would decrease the chance of detecting an OS benefit. In our cohort, the presence of *TP53* mutations at baseline did not significantly impact survival outcomes with RETi, as opposed to prior reports²³. Treatment with ICB before RETi may be associated with poorer tolerability, as adverse events may result in a higher rate of permanent treatment discontinuation of RETi. In patients receiving ICB after RETi, it is currently unknown whether potential changes in the tumor microenvironment induced by RET inhibition would further impact the response to ICB.

Previous reports have shown that platinum-doublets are highly active in *RET*+ NSCLC, especially associations including pemetrexed^{18,24}. In a published series of 18 patients with *RET*+ NSCLC treated with pemetrexed-based regimens, the ORR was 45% and median PFS was 19 months, which are comparable to reports of this combination in *ROS1*- and *ALK*-rearranged NSCLC²⁴. In a Korean population, outcomes with pemetrexed-based regimes were favorable, albeit less impressive, with a median PFS of 9 months¹⁸. Our mainly European-based population did not show a significant difference between pemetrexed-based combinations and other platinum doublets, with a median PFS of 9 months with pemetrexed-platinum treatment. This could be related to the high percentage of patients with a smoking history in our population. As suggested by a study on non-squamous NSCLC, smoking history may be associated with lower pemetrexed activity²⁵.

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 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 chemotherapy-ICB, was significantly associated with longer PFS in women than in men, which has not been reported previously. In small published reports including between 9 and 15 patients, ORRs with ICB ranged between 0% and 38% and median PFS ranged

between 2.1 and 7.6 months¹⁴⁻¹⁸. In our study, treatment outcomes with chemotherapy-ICB and chemotherapy doublets were similar. It is still not clear which patients benefit from the addition of ICB versus chemotherapy alone. In patients receiving chemotherapy-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 months and 5.7 months, respectively; adjusted HR=1.24; caution as small *RET*+ cohort)²⁰.

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 histology types than adenocarcinoma. *RET*+ NSCLC displayed elements of cold tumors with generally low TMB and PD-L1 levels. However, selected patients did respond to ICB showing 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 chemotherapy merits further investigation in this population.

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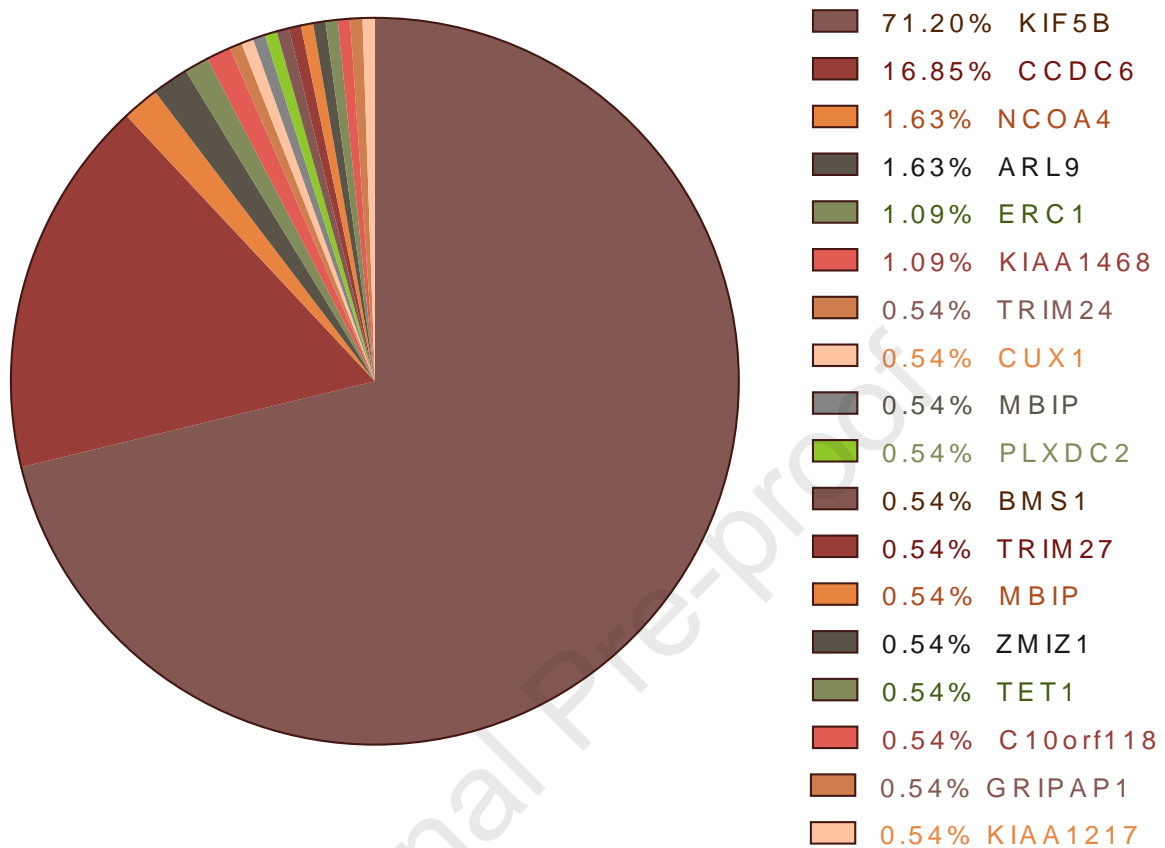
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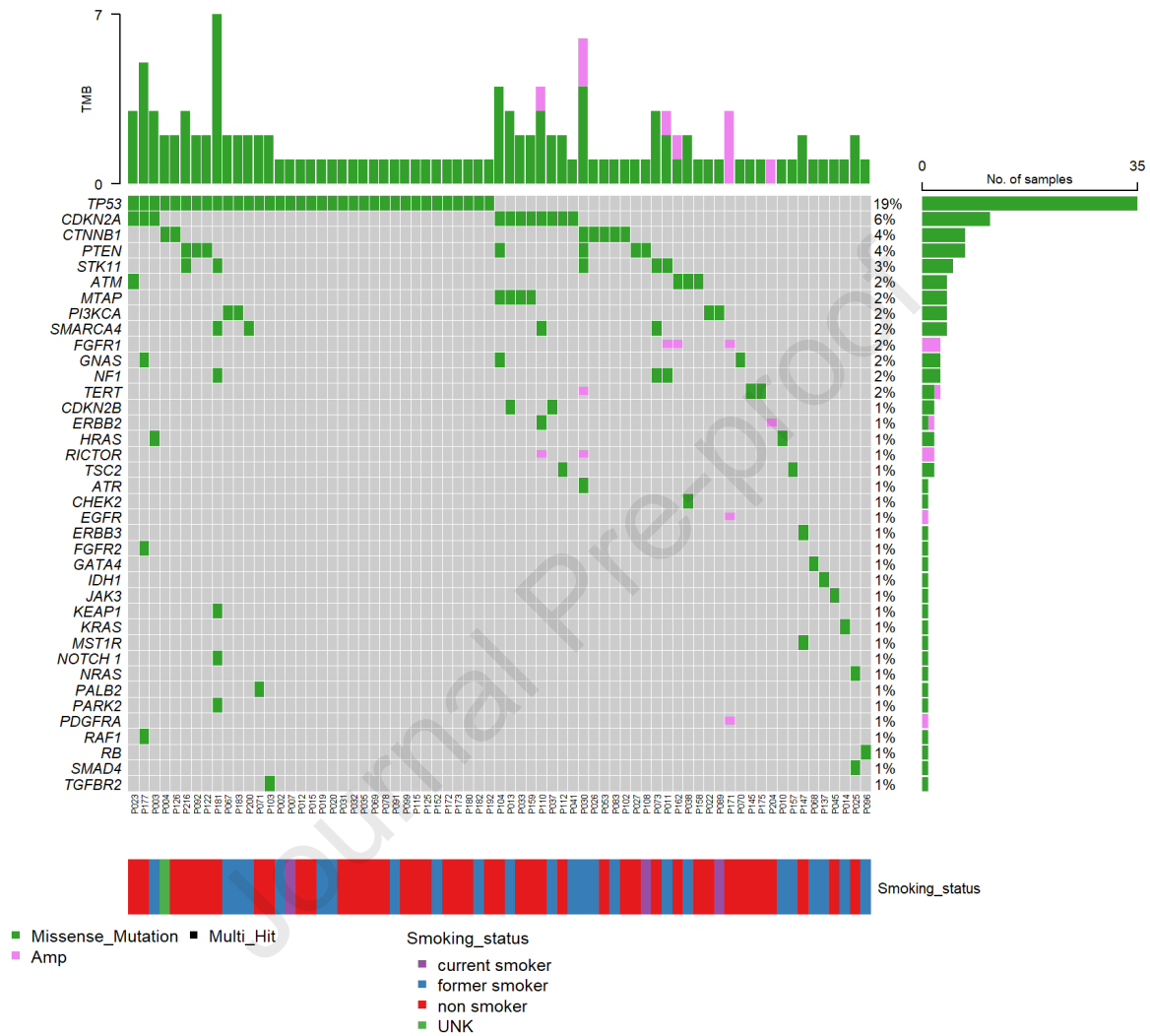
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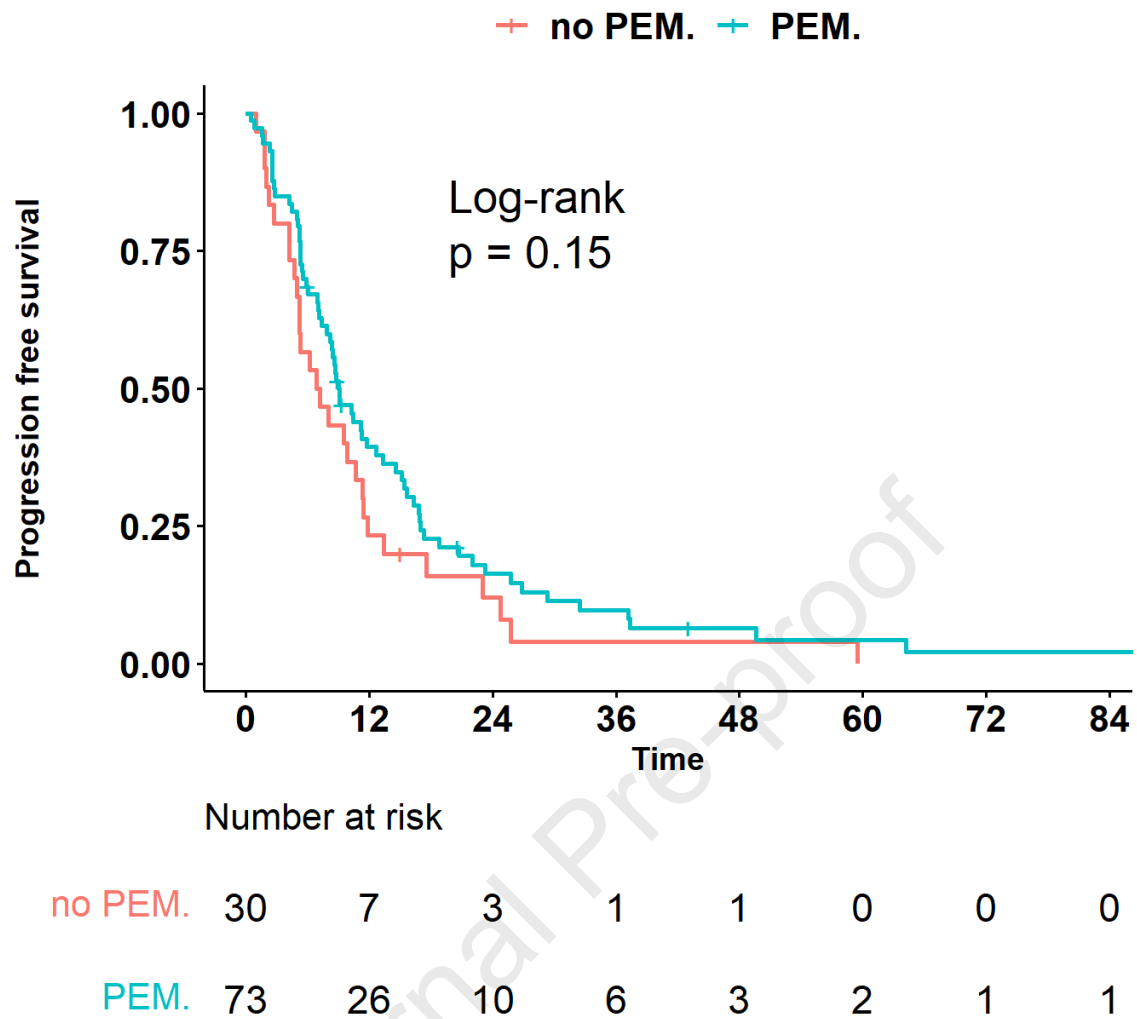
Supplementary Figures



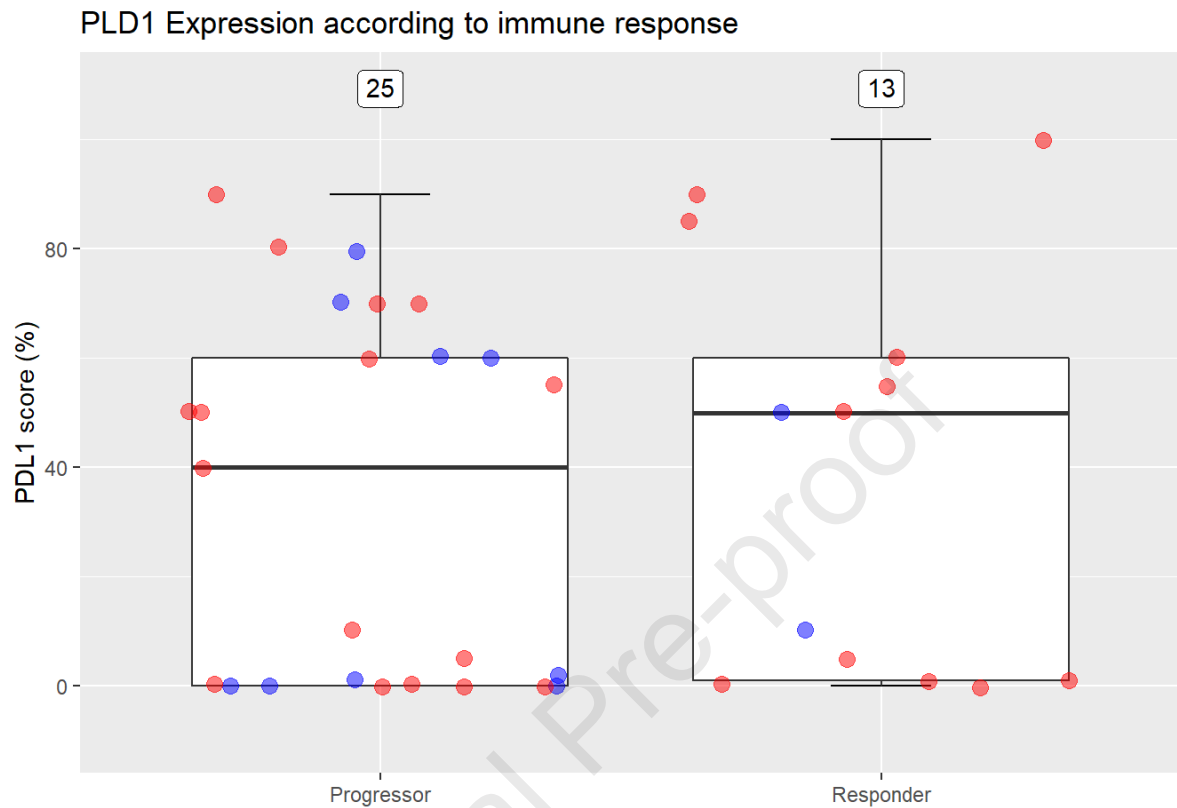
Supplementary Figure 1. Frequency of *RET* fusions according to the fusion partner.



Supplementary Figure 2. Genomic alterations concurrent with *RET* fusions in baseline tumor samples were identified in a total of 38% samples. Amp: amplification.



Supplementary Figure 3. Progression-free survival (PFS) in patients treated with platinum-pemetrexed treatment versus other platinum-based doublets. PEM: pemetrexed.



Supplementary Figure 4. Box-plot showing distribution of PD-L1 expression in patients progressing versus responding under immune checkpoint blockers. Responders were defined as patients obtaining complete response, partial response or stable disease for at least 6 months under ICB. Red points: PD-L1 values of females; Blue points: PD-L1 values of males.

Supplementary Table 1. Progression-free survival to various systemic treatments according to the type of the *RET* fusion partner in patients with a known *RET* fusion partner

	Doublet CT (N=77)	Single agent CT (N=19)	CT-ICB (N=32)	ICB (N=41)	MTKi (N=13)	RETi (N=110)
<i>KIF5B-RET</i>	9 [8-16.3]	3.9 [2-8.9]	7.3 [4.5-13.8]	3.1 [2-8.6]	5.3 [2.8-NR]	15 [11.1-23.2]
Non-<i>KIF5B-RET</i>	10.7 [8.3-20.7]	8.9 [2.4-NR]	10.8 [2.7-NR]	2.9 [2.4-NR]	5.4 [3.8-NR]	43.2 [11.5-NR]
<i>P value</i>	0.91	0.08	0.29	0.33	0.77	0.07

PFS expressed in months [95%CI]. NR, not reached.

Supplementary Table 2. Baseline characteristics at time of advanced disease in patients treated with RETi versus those without RETi

Characteristics	RETi N=145	No RETi N=60	<i>P value</i>
Sex, N (%) Female	85 (59%)	32 (53%)	0.5
Age at time of advanced disease , median [IQR]	63 [55-71]	62 [52-68]	0.2
ECOG performance status, N (%) PS ≤1 PS >1 Unknown	124 (87%) 19 (13%) 2	50 (86%) 8 (14%) 2	0.5
Smoking status, N (%) Former or current smoker Non-smoker Unknown	61 (43%) 82 (57%) 2	22 (37%) 37 (63%) 1	0.1
Histology, N (%) Adenocarcinoma Non-adenocarcinoma	137 (94%) 8 (6%)	53 (92%) 7 (8%)	0.1
Stage at diagnosis according AJCC 8 th edition I II	6 (4.1%) 9 (6.2%)	2 (3.3%) 2 (3.3%)	0.4

III	19 (13%)	4 (6.7%)	
IV	111 (77%)	52 (87%)	
Total N of metastatic sites			0.6
1 site	46 (32%)	24 (40%)	
≥ 2 sites	99 (68%)	36 (60%)	

N, number.

Supplementary Table 3. Adverse events leading to permanent treatment discontinuation

Adverse events	Chemotherapy- ICB N=41	ICB N=51	RETi N=145
Pneumonitis	1	1 [€]	2 [£] + 1
Acute hypertension			2
Hematologic toxicity	2 [€]		3
Pericardial effusion	1		
Renal failure	4		1+1 [£]
Colitis	1 [€] + 1	2 [€]	1 [£]
Increased liver enzymes		1 [€]	1+1 [£]
Increased CPK			1+1 [£]
Pancreatitis			1
Gastrointestinal bleeding			1
Arthritis		1 [€]	
Asthenia			1
Neuropathy			1
Proteinuria			1 [£]
Toxidermia			1 [£]

ICB, immune checkpoint blockade; [€]immune-related; RETi, RET inhibitor

[€]immune-related; [£] prior ICB anytime before RETi.

Table 1. Patient clinical characteristics

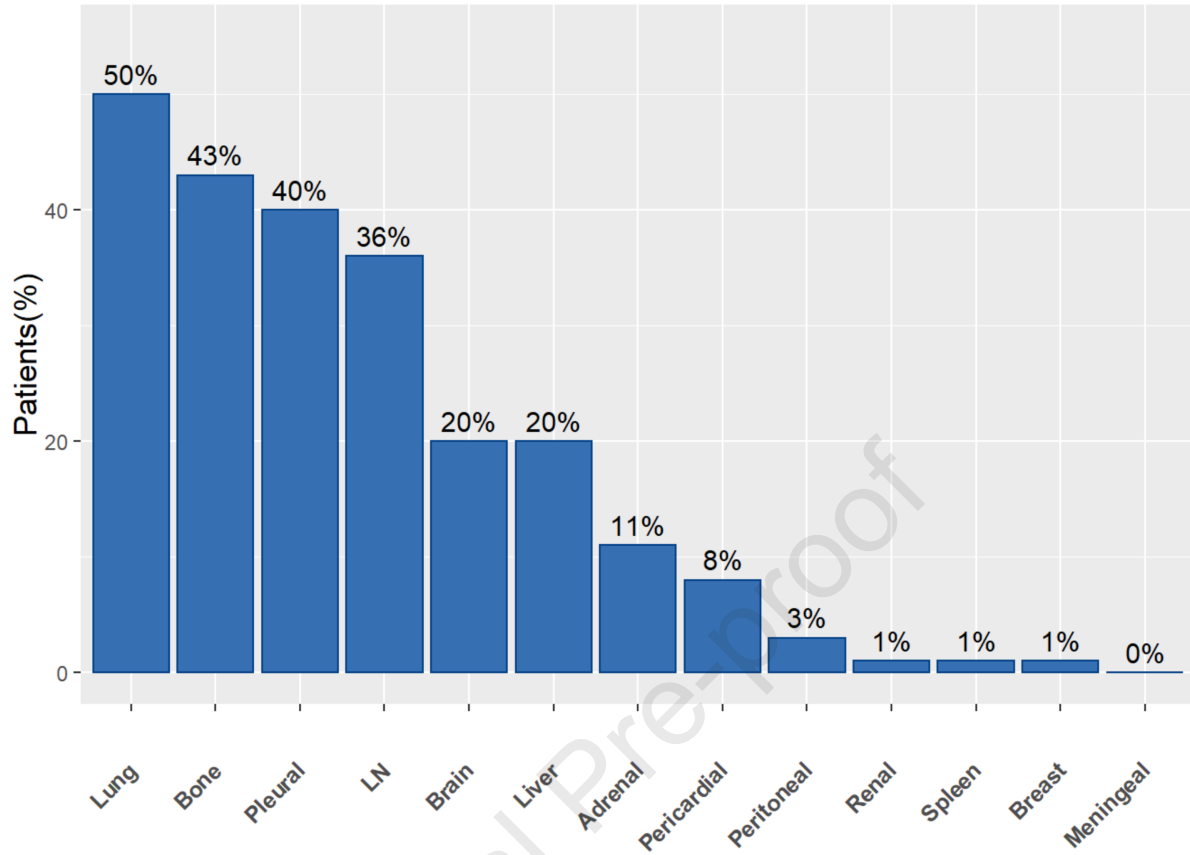
	Patients (N=218)
Female, N (%)	122 (56%)
Age in years, median [IQR]	63 [54-71]
Histology, N (%)	
Adenocarcinoma	203 (93%)
Squamous carcinoma	1 (0.5%)
Undifferentiated carcinoma	7 (3.2%)
Neuroendocrine carcinoma	7 (3.2%)
Stage at diagnosis, N (%)	
Stage I	17 (7.8%)
Stage II	11 (5%)
Stage III	27 (12%)
Stage IV	163 (75%)
N metastatic sites at time of advanced disease, median [IQR]	2 [1-3]
Smoking history, N (%)	
Non-smoker	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]

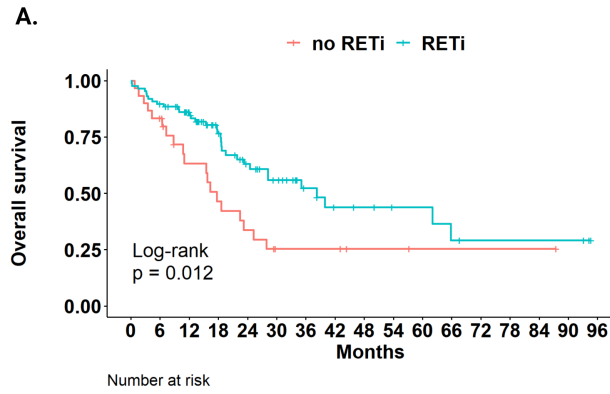
N, number; PS, performance status

Table 2. Outcomes following the first use of each type of therapy in advanced *RET*+ NSCLC.

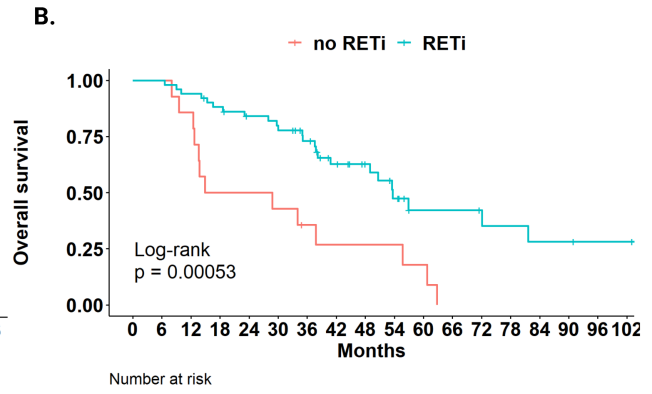
	Doublet CT (N=108)	Single agent CT (N=34)	CT-ICB (N=41)	ICB (N=52)	MTKi (N=21)	RETi (N=145)
N of treatment line, median (range)	1 (1-1)	2.5 (2-3)	1 (1-1)	2 (1-2)	3 (1-4)	2 (1-2)
ORR, N (%)[‡]	56/102 (55%)	8/31 (26%)	17/37 (46%)	12/52 (23%)	7/19 (37%)	99/131 (76%)
Median PFS, months [95%CI][*]	8.7 [7.2-11.3]	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, months [95%CI][*]	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]

CT: chemotherapy; ICB, immune checkpoint blocker; DOR, duration of response; MTKi, multi-tyrosine kinase inhibitor; NR, not reached; ORR, overall response rate; PFS, progression-free survival; RETi, RET inhibitor; [‡]ORR was calculated for patient with available evaluable disease by RECIST v1.1. or investigator assessment; ^{*}survival outcomes were calculated only for patients with at least 6 months of follow-up, in the absence of progression or death.





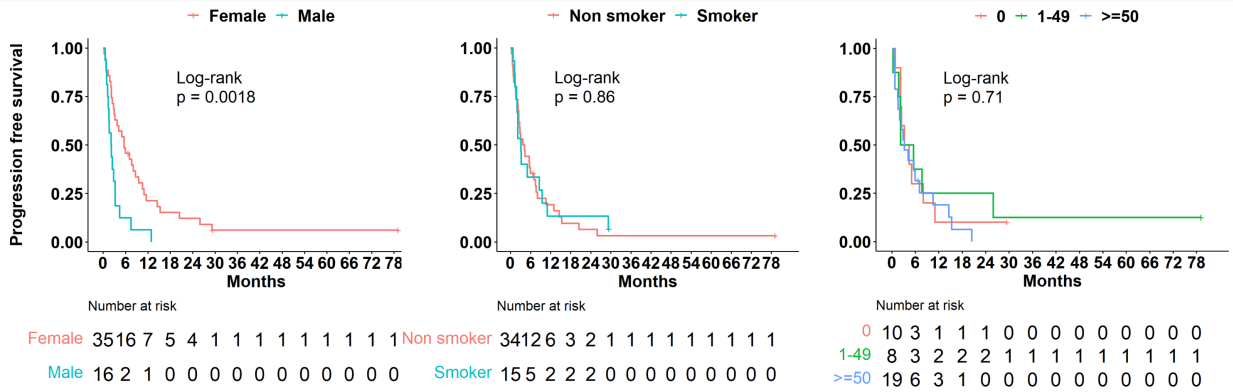
no RETi	30	24	15	11	8	4	4	4	2	2	1	1	1	1	1	0	0
RETi	87	77	63	42	29	22	13	9	8	6	6	4	3	3	3	3	0



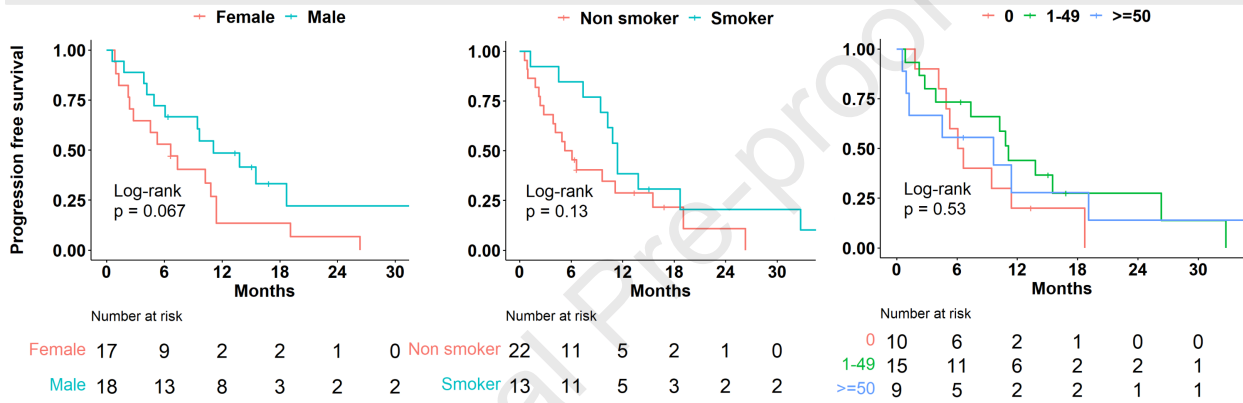
no RETi	14	14	12	7	7	6	4	3	3	3	2	0	0	0	0	0	0
RETi	51	51	48	44	40	37	31	22	17	12	7	7	6	5	4	4	3

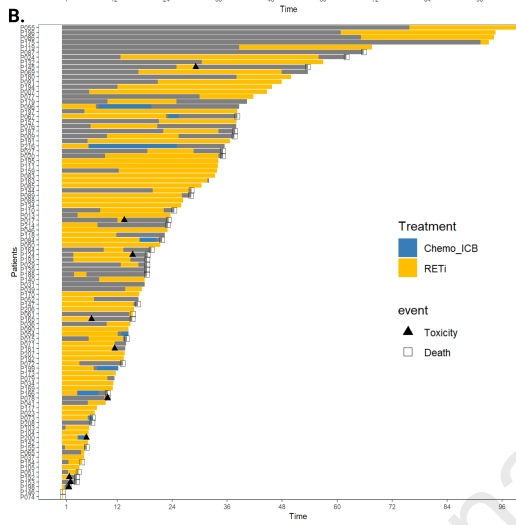
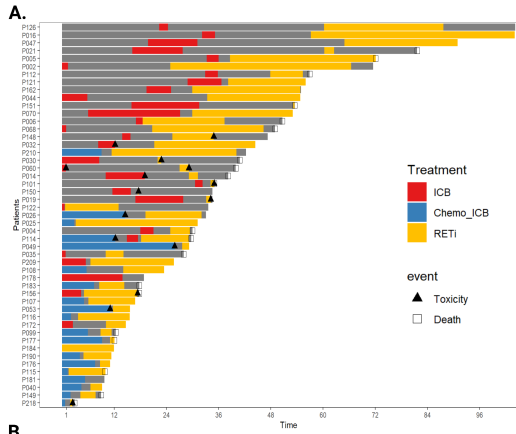
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Immunotherapy



Chemo-immunotherapy





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Arianna Marinello: Data curation, Investigation, Methodology, Writing - review & editing.

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