

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



Mihaela Aldea, MD, PhD,^{a,b} Arianna Marinello, MD,^{a,c} Michael Duruisseau, MD,^d Wael Zrafi, MD,^e Nicole Conci, MD,^f Giacomo Massa, MD,^g Giulio Metro, MD,^h Isabelle Monnet, MD,ⁱ Patricia Gomez Iranzo, MD,^j Fabrizio Tabbo, MD, PhD,^k Emilio Bria, MD,^l Florian Guisier, MD,^m Damien Vasseur, MD,ⁿ Colin R. Lindsay, MD, PhD,^o Santiago Ponce-Aix, MD,^p Sophie Cousin, MD,^q Fabrizio Citarella, MD,^r Vincent Fallet, MD,^s Jose Nicolas Minatta, MD,^t Anna Eisert, MD,^u Hortense de Saint Basile, MD,^v Clarisse Audigier-Valette, MD,^w Laura Mezquita, MD, PhD,^{x,y} Antonio Calles, MD,^z Giannis Mountzios, MD, PhD,^{aa} Marco Tagliamento, MD,^{bb} Jordi Remon Masip, MD, PhD,^{cc} Judith Raimbourg, MD, PhD,^{dd} Safae Terrisse, MD, PhD,^{ee} Alessandro Russo, MD, PhD,^{ff} Diego Cortinovis, MD,^{gg} Philippe Rochigneux, MD, PhD,^{hh} David James Pinato, MD, PhD,^{ii,jj} Alessio Cortellini, MD, PhD,^r Camille Leonce, PharmD, PhD,^{kk} Anas Gazzah, MD,^{ll} Maria-Rosa Ghigna, MD, PhD,^{mm} Roberto Ferrara, MD,^g Filippo Gustavo Dall'Olio, MD,^e Francesco Passiglia, MD,^k Vienna Ludovini, PhD,^h Fabrice Barlesi, MD, PhD,^{a,b} Enriqueta Felip, MD, PhD,^j David Planchard, MD, PhD,^a Benjamin Besse, MD, PhD,^{a,b,*}

*Corresponding author.

Disclosure: Aldea reports receiving expenses and research funding from Sandoz; serving on the advisory board for Viatrix. Duruisseau reports having as membership of an advisory council or committee for Bristol-Myers Squibb, GlaxoSmithKline, Sanofi, Merck Sharp & Dohme, AstraZeneca, AbbVie, Takeda, Boehringer Ingelheim, Merus, Amgen, Guardant, and Pfizer; receiving consulting fees from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, AstraZeneca, AbbVie, Takeda, Boehringer Ingelheim, Gamamabs Pharma, and Pfizer; and receiving research grants from Takeda, NanoString, Eli Lilly, and Blueprint. Bria is supported by institutional funds of Università Cattolica del Sacro Cuore (projects D1) and by the Fondazione Associazione Italiana per la Ricerca sul Cancro with investigator grant number IG20583. Bria received advisory and speakers' fees from Merck Sharp & Dohme, AstraZeneca, Celgene, Pfizer, Helsinn, Eli Lilly, Bristol-Myers Squibb, Novartis, and Roche. Barlesi reports having personal financial interests from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd., Novartis, Merck, Mirati, Merck Sharp & Dohme, Pierre Fabre, Pfizer, Seattle Genetics, and Takeda. Planchard reports having consulting, advisory role, or lectures from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, and Roche; receiving honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, and Roche; having clinical trial research from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmune, Sanofi Aventis, Taiho Pharma, Novocure, and Daiichi Sankyo; and having travel, accommodations, and expenses from AstraZeneca, Roche, Novartis, prIME Oncology, and Pfizer. Besse reports having sponsored research at Gustave Roussy Cancer Center from AbbVie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, Bristol-Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline, Ignyta, IPSEN, Merck KGaA, Merck Sharp & Dohme, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, and Tiziana Pharma, and investigator or co-investigator of trials for Nerviano,

GlaxoSmithKline, Pfizer, Roche-Genentech, Eli Lilly, OSE Pharma, Merck Sharp & Dohme, Celgene, Stemcentrx, Ignyta, AbbVie, Loxo Oncology, AstraZeneca, and Blueprint Medicines. Cortellini received consulting fees from Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, and Roche, and speakers' fee from AstraZeneca, Merck Sharp & Dohme, Novartis, and Astellas. Passiglia reports receiving consultant fee from AstraZeneca, Janssen, Amgen, Sanofi, Merck Sharp & Dohme, BeiGene, and Thermo Fisher Scientific. Eisert reports receiving honoraria from Amgen and Merck. Fallet reports receiving personal fees from Merck Sharp & Dohme, Novartis, Roche, Sanofi, and Boehringer; personal fees and nonfinancial support from AstraZeneca, Bristol-Myers Squibb, Takeda, Jansen, and Pfizer, all outside of the submitted work. Felip reports serving on the advisory board for Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, F. Hoffmann-La Roche, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Merck Serono, Novartis, Peptomyc, Pfizer, Sanofi, and Takeda; serving as invited speaker for Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Janssen, Medscape, Merck Sharp & Dohme, PeerVoice, Pfizer, Medical Trends, Merck Serono, Sanofi, Takeda, and Touchonology; and receiving research funding from Merck Healthcare KGaA and Fundación Merck Salud. Ferrara reports serving on the advisory board for Merck Sharp & Dohme and BeiGene. Gazzah reports receiving travel, accommodation, and congress registration expenses from Boehringer Ingelheim, Novartis, Pfizer, and Roche; serving as consultant/having expert role for Novartis; serving as principal/subinvestigator of clinical trials for Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca, Aveo, Bayer Healthcare AG, Bbb Technologies Bv, BeiGene, Bioalliance Pharma, BioNTech AG, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Ca, Celgene Corporation, Chugai Pharmaceutical Co., Clovis Oncology, Daiichi Sankyo, Debiopharm S.A., Eisai, Exelixis, Forma, Gamamabs, Genentech, Inc., Gilead Sciences, Inc., GlaxoSmithKline, Glenmark Pharmaceuticals, H3 Biomedicine, Inc., Hoffmann-La Roche AG, Incyte Corporation, Innate Pharma, Iris Servier, Janssen, Kura Oncology, Kyowa Kirin Pharm,

- ^aDepartment of Medical Oncology, International Center for Thoracic Cancers (CICT), Gustave Roussy, Villejuif, France
- ^bParis-Saclay University, Kremlin-Bicêtre, France
- ^cDepartment of Medical Oncology, Humanitas Research Hospital, Milan, Italy
- ^dRespiratory Department and Early Phase, Louis Pradel Hospital, Hospices Civils de Lyon; Cancer Research Center of Lyon (CRCL), INSERM 1052, CNRS 5286; Univ Lyon, Claude Bernard Lyon 1 University, Lyon, France
- ^eDepartment of Biostatistics and Bioinformatics, Gustave Roussy, Villejuif, France
- ^fDepartment of Medical Oncology, Scientific Institute for Research, Hospitalization and Healthcare (IRCCS) University Hospital of Bologna, Bologna, Italy
- ^gDepartment of Medical Oncology, National Cancer Institut, Milan, Italy
- ^hDepartment of Medical Oncology, Santa Maria della Misericordia Hospital, Perugia, Italy
- ⁱPneumology and Thoracic Oncology Department, Intercommunal Hospital of Creteil (CHI), Creteil, France
- ^jDepartment of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
- ^kDepartment of Oncology, University of Turin, San Luigi Hospital, Orbassano, Italy
- ^lDepartment of Medical Oncology, Comprehensive Cancer Center, IRCCS Agostino Gemelli, Catholic University of the Sacred Heart, Rome, Italy
- ^mDepartment of Medical Oncology, Rouen University Hospital, Rouen, France
- ⁿDepartment of Medical Biology and Pathology, Gustave Roussy, Villejuif, France
- ^oDepartment of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom
- ^pDepartment of Medical Oncology, University Hospital October 12, Madrid, Spain
- ^qDepartment of Medical Oncology, Bergonié Institut, Bordeaux, France
- ^rDepartment of Medical Oncology, Campus Biomedico, Rome, Italy
- ^sDepartment of Pneumology and Thoracic Oncology, Tenon Hospital, Assistance Publique Hôpitaux de Paris and GRC 4, Therascan, Sorbonne Université, Paris, France
- ^tDepartment of Medical Oncology, Hospital Italiano, Buenos Aires, Argentina
- ^uDepartment of Medical Oncology, University Hospital of Cologne, Cologne, Germany
- ^vDepartment of Medical Oncology, European Hospital Georges Pompidou, Paris, France
- ^wDepartment of Medical Oncology, Hospital Sainte Musse, Toulon, France
- ^xMedical Oncology Department, Hospital Clinic of Barcelona, Barcelona, Spain
- ^yLaboratory of Translational Genomics and Targeted Therapies in Solid Tumors, Institut D'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
- ^zDepartment of Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
- ^{aa}4th Oncology Department and Clinical Trials Unit, Henry Dunant Hospital Center, Athens, Greece
- ^{bb}Department of Internal Medicine and Medical Specialties, University of Genova, Genova, Italy
- ^{cc}Department of Medical Oncology, Centro Integral Oncológico Clara Campal (HM-CIOCC), Hospital HM Delfos, HM Hospitales, Barcelona, Spain

Lilly, Loxo Oncology, Lytix Biopharma As, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncomed, Oncopeptides, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, Pharma Mar, Pierre Fabre, Rigotec GmbH, Roche, Sanofi Aventis, Sierra Oncology, Taiho Pharma, Tesaro, Inc., Tioma Therapeutics, Inc., and Xencor; receiving research grants from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen-Cilag, Merck, Novartis, Pfizer, Roche, and Sanofi; receiving nonfinancial support (drug supplied) from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Johnson & Johnson, Eli Lilly, MedImmune, Merck, NH TherAGuiX, Pfizer, and Roche. Lindsay has received personal fees from Amgen for lectures/workshops; is a consultant/advisor for Amgen and CBPartners; and has received institutional research funding from Amgen, Apollomics, Boehringer Ingelheim, Mirati Therapeutics, Revolution Medicines, and Roche for his work as a chief/principal investigator on clinical trials. Ponce reports having consulting, advisory role, or lectures from AstraZeneca, Bristol-Myers Squibb, Roche, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, and Amgen. Masip reports receiving travel, accommodation, and congress registration expenses from Ose-immunotherapeutic; receiving advisory and consultation fees from Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen, and Takeda. Mezquita reports receiving research grant/funding (self) from Bristol-Myers Squibb, Boehringer Ingelheim, Amgen, Stilla, and Inivata; serving on the advisory/consultancy from Roche, Takeda; receiving honoraria (self) from Bristol-Myers Squibb, Roche, Takeda, and AstraZeneca; receiving travel/accommodation/expenses from Roche, Bristol-Myers Squibb, Takeda, and AstraZeneca; and having nonremunerated activity/ies from AstraZeneca. Calles reports receiving honoraria from AstraZeneca, Boehringer Ingelheim, Bayer, Pfizer, Roche, Novartis, Merck Sharp & Dohme, and Bristol-Myers Squibb; having consulting or advisory role from AstraZeneca, Boehringer Ingelheim, Pfizer, Roche/Genentech, Eli Lilly and Company, Novartis, Takeda, Merck Sharp & Dohme, and Bristol-Myers Squibb;

receiving research funding from Merck Sharp & Dohme; and receiving travel financial support from Roche, Boehringer Ingelheim, Merck Sharp & Dohme, and Bristol-Myers Squibb. Minatta reports receiving research grants from Pfizer; having consulting/advisory board/educational services from Merck Sharp & Dohme, Pfizer, Takeda, Roche, Merck, and Amgen. Mountzios reports receiving advisory and consultation fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, and Sanofi; receiving travel and accommodation fees from AstraZeneca, Amgen, Pfizer, Roche, Takeda, Novartis, GlaxoSmithKline, and Sanofi; and serving as principal investigator in sponsored clinical trials from Novartis, Roche, Merck Sharp & Dohme, AstraZeneca, Merck, Bristol-Myers Squibb, Amgen, Immunomedics, GlaxoSmithKline, and Sanofi. Pinato received lecture fees from ViiV Healthcare, Bayer Healthcare, Bristol-Myers Squibb, Roche, Eisai, and Falk Foundation; travel expenses from Bristol-Myers Squibb and Bayer Healthcare; consulting fees for Mina Therapeutics, Eisai, Roche, DaVolterra, and AstraZeneca; and research funding (to institution) from Merck Sharp & Dohme and Bristol-Myers Squibb. Rochigneux reports serving as speaker/board for Novartis, AstraZeneca, and Viatris, and receiving travel expenses from Pfizer. Tagliamento reports receiving travel grants from Roche, Bristol-Myers Squibb, AstraZeneca, Takeda, and Eli Lilly and honoraria as medical writer from Novartis, Amgen, and Merck Sharp & Dohme. The remaining authors declare no conflict of interest.

*Corresponding author. Address for correspondence: Benjamin Besse, MD, PhD, Department of Medical Oncology, International Center for Thoracic Cancers (CICT), Gustave Roussy, Villejuif, France. E-mail: benjamin.besse@gustaveroussy.fr

© 2023 International Association for the Study of Lung Cancer. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2022.12.018>

^{dd}Department of Medical Oncology, Institut de Cancérologie de l'Ouest, St Herblain, France

^{ee}Department of Medical Oncology, Saint Louis Hospital, Paris, France

^{ff}Department of Medical Oncology, Papardo Hospital, Messina, Italy

^{gg}Department of Medical Oncology, San Gerardo Hospital, Monza, Italy

^{hh}Department of Medical Oncology, Paoli-Calmettes Institute, Marseille, France

ⁱⁱDepartment of Surgery and Cancer, Imperial College London, Hammersmith Campus, London, United Kingdom

^{jj}Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

^{kk}Department of Molecular Pathology, Louis-Pradel Hospital, Lyon, France

^{ll}Department of Drug Development Department, International Center for Thoracic Cancers (CICT), Gustave Roussy, Villejuif, France

^{mm}Department of Pathology, International Center for Thoracic Cancers (CICT), Gustave Roussy, Villejuif, France

Received 24 May 2022; revised 5 November 2022; accepted 22 December 2022

Available online - 13 January 2023

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.^{1–3} It is identified in 1% to 2% of patients with NSCLC^{1–3} (*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.^{4–7} 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.^{8–13} 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).¹⁴ Conflicting results have been reported concerning immune checkpoint inhibitor (ICB) activity in small-sized cohorts or case series of *RET*+) NSCLC,^{14–19} whereas data for chemoimmunotherapy 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, 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*+ 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

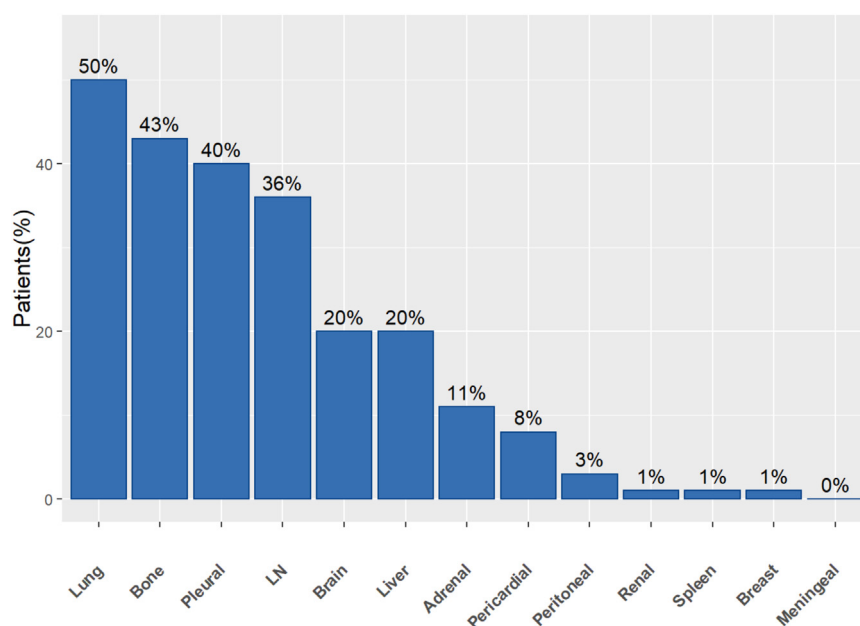


Figure 1. Metastatic pattern of *RET*+ stage IV lung cancer among the 205 patients. LN, extrathoracic lymph nodes.

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 pemtrexed-based combinations in 71% of the cases. There was no significant difference in PFS between patients treated with platinum-pemtrexed versus non-pemtrexed 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 (%) ^a	56/102 (55)	8/31 (26)	17/37 (46)	12/52 (23)	7/19 (37)	99/131 (76)
Median PFS, mo [95% CI] ^b	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] ^b	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]

^aORR was calculated for patient with available assessable disease by RECIST v1.1 or investigator assessment.

^bSurvival 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.

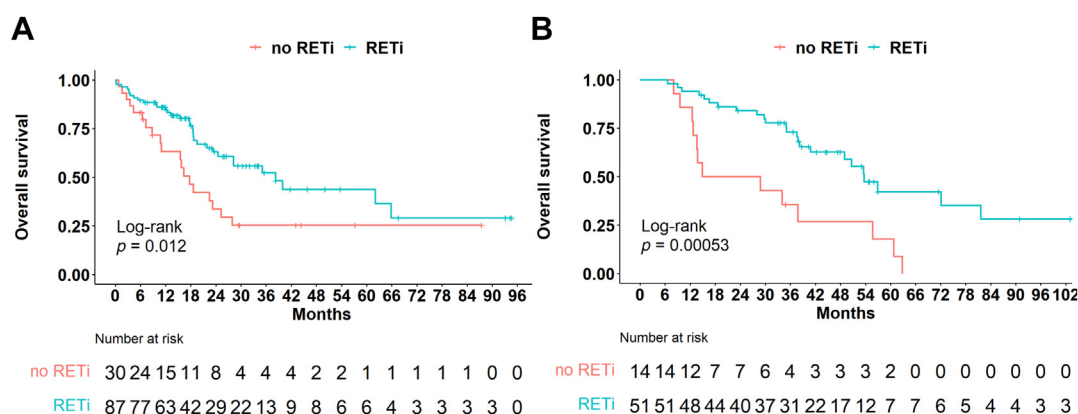


Figure 2. Overall survival in patients treated with selective RETis. (A) Patients treated with a maximum of two lines of therapy. (B) Patients treated with more than two lines of therapy. RETi, RET inhibitor.

$p = 0.011$), 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%.^{8,9,18,20,22} 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.^{18,22} The lifetime incidence of brain metastases in our cohort was 31%, which is less than the

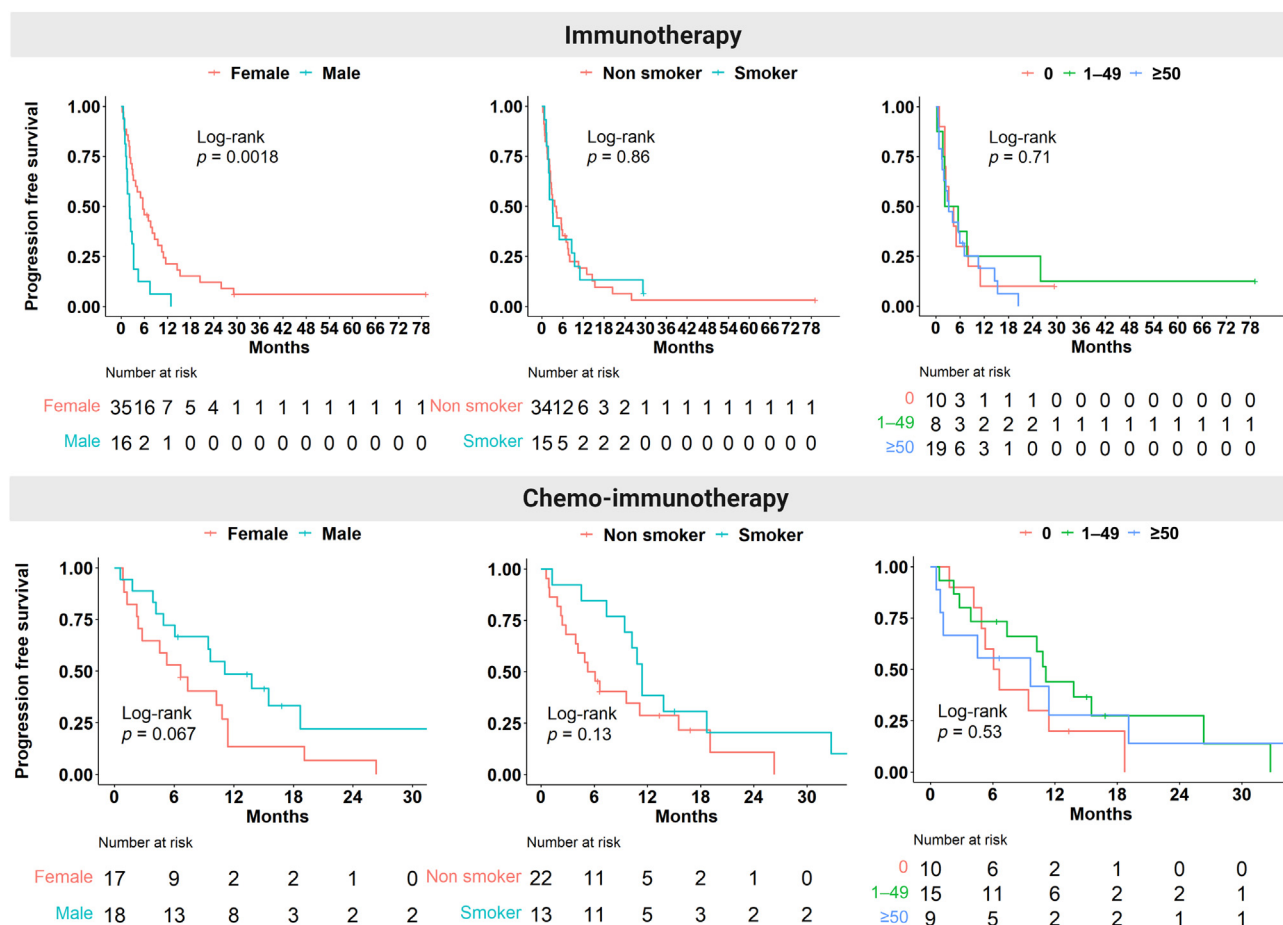


Figure 3. PFS subgroup analyses after stratification by sex, smoking history, and PD-L1 expression in patients treated with immunotherapy and chemoimmunotherapy. PD-L1, programmed death-ligand 1; PFS, progression-free survival.

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 activity,¹⁰ whereas the patients included in the cohort of Drilon et al. had only received MTKi. In addition, the type and frequency of brain imaging may differ between the two cohorts.

In our retrospective study, RETi significantly improved OS. Randomized, phase 3 studies, evaluating RETi in the first-line setting as compared with CT with or without immunotherapy, are ongoing, and results waited for 2024 to 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 affect PFS outcomes with RETi, as opposed to prior reports.²³ 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 micro-environment induced by RET inhibition would further affect the response to ICB.

Previous reports have revealed 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 with reports of this combination in *ROS1*- and *ALK*-rearranged NSCLC.²⁴ In a Korean population, outcomes with pemetrexed-based regimes were favorable, albeit less impressive, with a median PFS of 9 months.¹⁸ Our mainly European-based population did not have 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 nonsquamous NSCLC, smoking history may be associated with lower pemetrexed activity.²⁵

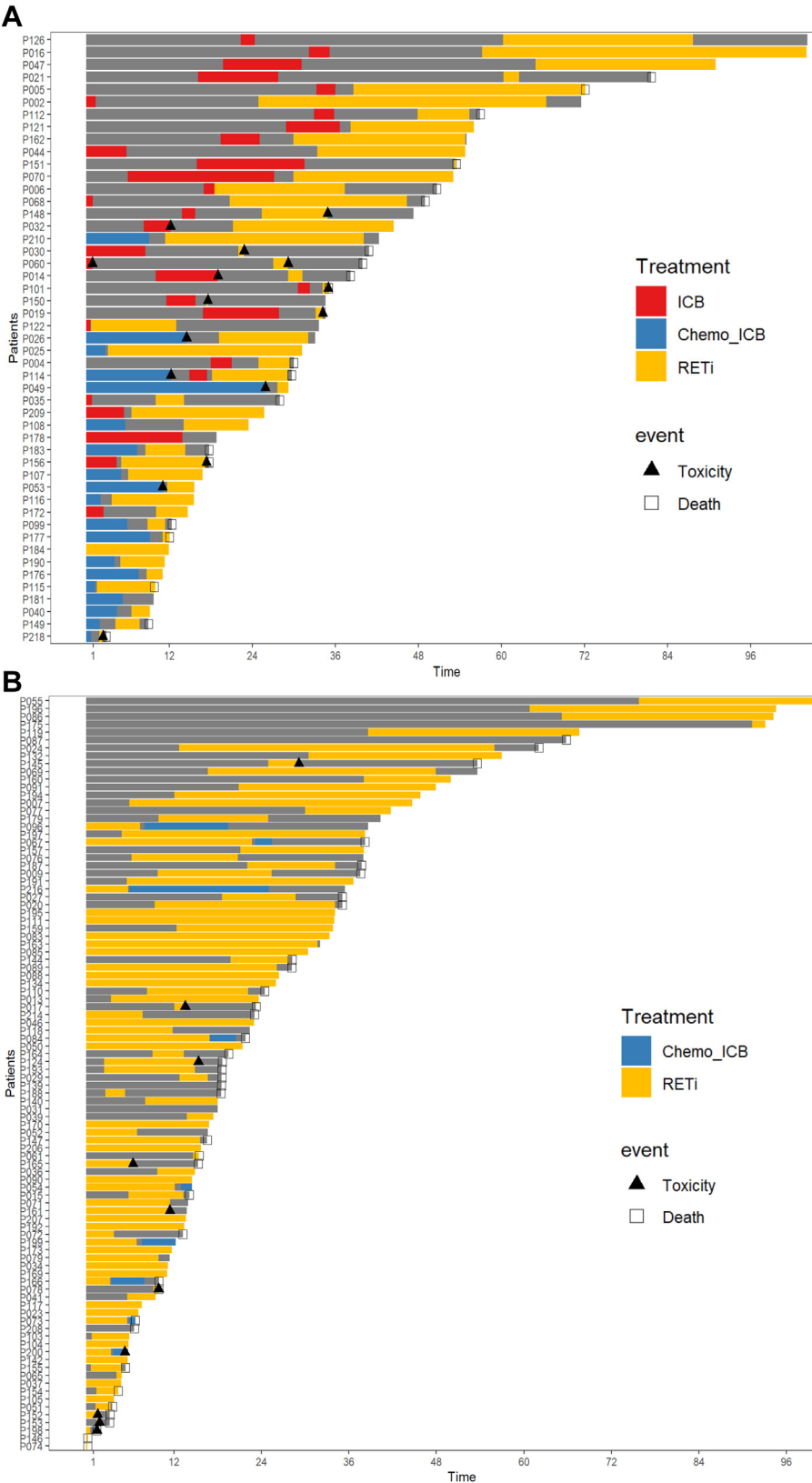


Figure 4. (A) Permanent treatment discontinuation for toxicity in patients treated with ICB with or without chemo before RETi. (B) Permanent treatment discontinuation for toxicity in patients treated with RETi without prior ICB with or without chemo. Chemo, chemotherapy; ICB, immune checkpoint blocker; 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.^{14–18} 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).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 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.

Michael Duruisseaux, Nicole Conci, Giacomo Massa, Giulio Metro, Isabelle Monnet, Patricia Iranzo Gomez, Fabrizio Tabbo, Emilio Bria, Florian Guisier, Damien Vasseur, Colin R. Lindsay, Santiago Ponce, Sophie Cousin, Fabrizio Citarella, Vincent Fallet, Jose Nicolas Minatta, Anna Eisert, Hortense de Saint Basile, Clarisse Audigier-Valette, Laura Mezquita, Antonio Calles, Giannis Mountzios, Marco Tagliamento, Jordi Remon Masip, Judith Raimbourg, Safae Terrisse, Alexandro Russo, Diego Cortinovis, Philippe Rochigneux, David James Pinato, Alessio Cortellini, Camille Leonce, Anas Gazzah, Maria-Rosa Ghigna, Roberto Ferrara, Filippo Gustavo Dall'Olio, Francesco Passiglia, Vienna Ludovini, Fabrice Barlesi, Enriqueta Felip, David Planchard: Investigation, Methodology, Writing—review and editing.

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

Acknowledgments

Writing assistance was provided by Mrs. Sarah Mackenzie. Dr. Marinello was the recipient for the grant for DUERTECC/EURONCO (Diplôme Universitaire Européen de Recherche Translationnelle Et Clinique en Cancérologie). Dr. Mezquita received support from the Contrato Juan Rodes 2020 (ISCIII, Ministry of Health); Ayuda de la Acción Estratégica en Salud-ISCIII FIS 2021 (PI21/01653); Ayuda SEOM-Juan Rodés 2020. Dr. Cortellini acknowledges the support from the National Institute for Health Research Imperial Biomedical Research Centre. Dr. Pinato acknowledges the support from the Wellcome Trust Strategic Fund (PS3416), Associazione Italiana per la Ricerca sul Cancro (Associazione Italiana per la Ricerca sul Cancro MFAG Grant ID 25697), National Institute for Health Research Imperial Biomedical Research Centre, Imperial Experimental Cancer Medicine Centre, and the Imperial College Tissue Bank.

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 and at <https://doi.org/10.1016/j.jtho.2022.12.018>.

References

1. Adashek JJ, Desai AP, Andreev-Drakhlin AY, Roszik J, Cote GJ, Subbiah V. Hallmarks of RET and co-occurring genomic alterations in RET-aberrant cancers. *Mol Cancer Ther.* 2021;20:1769–1776.

2. Ferrara R, Auger N, Auclin E, Besse B. Clinical and translational implications of RET rearrangements in non-small cell lung cancer. *J Thorac Oncol*. 2018;13:27-45.
3. Osta BE, Ramalingam SS. RET fusion: joining the ranks of targetable molecular drivers in NSCLC. *JTO Clin Res Rep*. 2020;1:100050.
4. Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol*. 2016;17:1653-1660.
5. Yoh K, Seto T, Satouchi M, et al. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. *Lancet Respir Med*. 2017;5:42-50.
6. Lee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. *Ann Oncol*. 2017;28:292-297.
7. Hida T, Velcheti V, Reckamp KL, et al. A phase 2 study of lenvatinib in patients with RET fusion-positive lung adenocarcinoma. *Lung Cancer*. 2019;138:124-130.
8. Gainor JF, Curigliano G, Kim DW, et al. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. *Lancet Oncol*. 2021;22:959-969.
9. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. *N Engl J Med*. 2020;383:813-824.
10. Subbiah V, Gainor JF, Oxnard GR, et al. Intracranial efficacy of selpercatinib in RET fusion-positive non-small cell lung cancers on the LIBRETTO-001 trial. *Clin Cancer Res*. 2021;27:4160-4167.
11. Drilon A, Subbiah V, Gautschi O, et al. 27P Durability of efficacy and safety with selpercatinib in patients (pts) with RET fusion+ non-small cell lung cancer (NSCLC). *Ann Oncol*. 2022;33(suppl 2):S43.
12. Drilon A, Subbiah V, Gautschi O, et al. Selpercatinib in patients with RET fusion-positive non-small-cell lung cancer: updated safety and efficacy from the registrational LIBRETTO-001 phase I/II trial. *J Clin Oncol*. 2023;41:385-394.
13. Griesinger F, Curigliano G, Thomas M, et al. Safety and efficacy of pralsetinib in RET fusion-positive non-small-cell lung cancer including as first-line therapy: update from the ARROW trial. *Ann Oncol*. 2022;33:1168-1178.
14. Offin M, Guo R, Wu SL, et al. Immunophenotype and response to immunotherapy of RET-rearranged lung cancers. *JCO Precis Oncol*. 2019;3:PO.18.00386.
15. Guisier F, Dubos-Arvis C, Vinas F, et al. Efficacy and safety of anti-PD-1 immunotherapy in patients with advanced NSCLC with BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018. *J Thorac Oncol*. 2020;15:628-636.
16. Hegde A, Andreev-Drakhlin AY, Roszik J, et al. Responsiveness to immune checkpoint inhibitors versus other systemic therapies in RET-aberrant malignancies. *ESMO Open*. 2020;5:e000799.
17. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the immunotarget registry. *Ann Oncol*. 2019;30:1321-1328.
18. Lee J, Ku BM, Shim JH, et al. Characteristics and outcomes of RET-rearranged Korean non-small cell lung cancer patients in real-world practice. *Jpn J Clin Oncol*. 2020;50:594-601.
19. Baglivo S, Ludovini V, Moretti R, et al. RET rearrangement as a predictor of unresponsiveness to immunotherapy in non-small cell lung cancer: report of two cases with review of the literature. *Oncol Ther*. 2020;8:333-339.
20. Hess LM, Han Y, Zhu YE, Bhandari NR, Sireci A. Characteristics and outcomes of patients with RET-fusion positive non-small lung cancer in real-world practice in the United States. *BMC Cancer*. 2021;21:28.
21. Drilon AE, Gautschi O, Besse B, et al. Response to selpercatinib versus prior systemic therapy in patients (pts) with RET fusion+ non-small-cell lung cancer (NSCLC). *J Clin Oncol*. 2021;39(suppl 15):9032-9032.
22. Drilon A, Lin JJ, Filleron T, et al. Frequency of brain metastases and multikinase inhibitor outcomes in patients with RET-rearranged lung cancers. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer*. 2018;13:1595-1601.
23. Rosen EY, Won HH, Zheng Y, et al. The evolution of RET inhibitor resistance in RET-driven lung and thyroid cancers. *Nat Commun*. 2022;13:1450.
24. Drilon A, Bergagnini I, Delasos L, et al. Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers. *Ann Oncol*. 2016;27:1286-1291.
25. Igawa S, Sasaki J, Otani S, et al. Smoking history as a predictor of pemetrexed monotherapy in patients with non-squamous non-small cell lung cancer. *Oncology*. 2016;91:41-47.