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

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

Mihaela Aldea, Arianna Marinello, Michael Duruisseaux, Wael Zrafi, 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, Benjamin Besse

PII: S1556-0864(22)01994-3

DOI: https://doi.org/10.1016/j.jtho.2022.12.018

Reference: JTHO 2617

To appear in: *Journal of Thoracic Oncology*

Received Date: 24 May 2022

Revised Date: 5 November 2022

Accepted Date: 22 December 2022

Please cite this article as: Aldea M, Marinello A, Duruisseaux M, Zrafi W, Conci N, Massa G, Metro G, Monnet I, Gomez PI, Tabbo F, Bria E, Guisier F, Vasseur D, Lindsay CR, Ponce S, Cousin S, Citarella F, Fallet V, Minatta JN, Eisert A, de Saint Basile H, Audigier-Valette C, Mezquita L, Calles A, Mountzios G, Tagliamento M, Masip JR, Raimbourg J, Terrisse S, Russo A, Cortinovis D, Rochigneux P, Pinato DJ, Cortellini A, Leonce C, Gazzah A, Ghigna M-R, Ferrara R, Dall'Olio FG, Passiglia F, Ludovini V, Barlesi F, Felip E, Planchard D, Besse B, RET-MAP: An international multi-center study on clinicobiologic features and treatment response in patients with lung cancer harboring a *RET* fusion, *Journal of Thoracic Oncology* (2023), doi: https://doi.org/10.1016/j.jtho.2022.12.018.

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

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

a. Department of Medical Oncology, International Center for Thoracic Cancers (CICT), Gustave Roussy, Villejuif, France

b. Paris-Saclay University, Kremlin-Bicêtre, France

c. Department of Medical Oncology, Istituto Clinico Humanitas, Milan, Italy

d. Respiratory Department of Medical Oncology, Early Phase, Louis-Pradel Hospital, Hospices Civils de Lyon, Lyon France; Centre Léon Bérard, Centre de Recherche en Cancérologie de Lyon, Univ Lyon, Université Claude Bernard Lyon 1, INSERM 1052, CNRS 5286, Lyon, France

e. Department of Biostatistics and Bioinformatics, Gustave Roussy, Villejuif, France

f. Department of Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

g. Department of Medical Oncology, National Cancer Institut, Milan, Italy

h. Department of Medical Oncology, Azienda Ospedaliera di Perugia, Perugia, Italy

i. Pneumology and Thoracic Oncology Department, Intercommunal Hospital of Creteil (CHI), Creteil, France

j. Department of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain

k. Department of Oncology, University of Turin, AOU San Luigi, Orbassano, Italy

l. Department of Medical Oncology, Comprehensive Cancer Center, Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy

m. Department of Medical Oncology, Rouen University Hospital, Rouen, France

n. Department of Medical Biology and Pathology, Gustave Roussy, Villejuif, France

o. Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom

p. Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain

q. Department of Medical Oncology, Institute Bergonié, Bordeaux, France

r. Department of Medical Oncology, Campus Biomedico, Rome, Italy

s. Department of Pneumology and Thoracic Oncology, Tenon Hospital, Assistance Publique Hôpitaux de Paris and GRC 4, Theranoscan, Sorbonne Université, Paris, France

t. Department of Medical Oncology, Hospital Italiano, Buenos Aires, Argentina

u. Department of Medical Oncology, University Hospital of Cologne, Cologne, Germany

v. Department of Medical Oncology, European Hospital Georges Pompidou, Paris, France

w. Department of Medical Oncology, Centre hospitalier Toulon Sainte-Musse, Toulon, France

x. Medical Oncology Department, Hospital Clinic of Barcelona; Laboratory of Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain

y. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

z. 4th Oncology Department and Clinical Trials Unit, Henry Dunant Hospital Center, Athens, Greece

aa. Department of Internal Medicine and Medical Specialties, University of Genova, Genova, Italy

bb. Department of Medical Oncology, Centro Integral Oncológico Clara Campal (HM-CIOCC), Hospital HM Delfos, HM Hospitales, Barcelona, Spain

cc. Department of Medical Oncology, Institut de Cancérologie de l'Ouest, St Herblain, France

dd. Department of Medical Oncology, Saint Louis Hospital, Paris, France

ee. Department of Medical Oncology, Azienda Ospedaliera Papardo, Messina, Italy

ff. Department of Medical Oncology, Ospedale San Gerardo, Monza, Italy

gg. Department of Medical Oncology, Paoli-Calmettes Institute, Marseille, France

hh. Department of Surgery and Cancer, Imperial College London, Hammersmith Campus, London, UK; Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

ii. Department of Molecular Pathology, Louis-Pradel Hospital, Lyon, France

jj. Department of Drug Development Department, International Center for Thoracic Cancers (CICT), Gustave Roussy, Villejuif, France

kk. Department of Pathology, International Center for Thoracic Cancers (CICT), Gustave Roussy, Villejuif, France

Corresponding author:

Prof. Benjamin Besse, MD PhD

Department of Cancer Medicine, Gustave Roussy Cancer Centre, Villejuif, France

e-mail address: benjamin.besse@gustaveroussy.fr

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Keywords: non-small cell lung cancer, *RET* fusion, RET inhibitors, immunotherapy, chemotherapy

Disclosure Statement of Conflict of Interest

Mihaela Aldea (mihaela.aldea@gustaveroussy.fr) – Expenses: Sandoz; Advisory Board: Viatris; Research funding: Sandoz.

Arianna Marinello (arianna.marinello@gustaveroussy.fr) – no disclosures.

Michael Duruisseaux (michael.duruisseaux@chu-lyon.fr) - Membership of an advisory council or committee for BMS, GSK, Sanofi, MSD, AstraZeneca, Abbvie, Takeda, Boehringer Ingelheim, Merus, Amgen, Guardant and Pfizer; consulting fees from Roche, BMS, MSD, AstraZeneca, Abbvie, Takeda, Boehringer Ingelheim, Gamamabs Pharma and Pfizer; research grants from Takeda, NanoString, Lilly and Blueprint.

Wael Zrafi (Wael_Salem.ZRAFI@gustaveroussy.fr) – no disclosures.

Nicole Conci (nicole.conci@studio.unibo.it) - no disclosures.

Giacomo Massa (Giacomo.Massa@istitutotumori.mi.it) – no disclosures.

Giulio Metro (giulio.metro@yahoo.com) – no disclosures.

Isabelle Monnet (isabelle.monnet@chicreteil.fr) – no disclosures.

Patricia Iranzo Gomez (piranzo@vhio.net) – no disclosures.

Fabrizio Tabbo (fabrizio.tabbo@unito.it) – no disclosures.

Emilio Bria (emilio.bria@unicatt.it) - is supported by Institutional funds of Università Cattolica del Sacro Cuore (UCSC-projects D1) and by the Fondazione Associazione Italiana per la Ricerca sul Cancro (AIRC) with Investigator Grant (IG) No. IG20583. E.B. received advisory and speakers' fee from MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis, and Roche.

Florian Guisier (Florian.Guisier@chu-rouen.fr) – no disclosures.

Damien Vasseur (Damien.vasseur@gustaveroussy.fr) – no disclosures.

Colin R. Lindsay (colin.lindsay1@nhs.net) – has received personal fees from Amgen for lectures/workshops and is a consultant/advisor for Amgen and CBPartners. He 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.

Santiago Ponce (santiago.ponce@gustaveroussy.fr) - Consulting, advisory role or lectures from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Roche, Amgen.

Sophie Cousin (s.cousin@bordeax.unicancer.fr) – no disclosures.

Fabrizio Citarella (f.citarella@unicampus.it) - no disclosures.

Vincent Fallet (vincent.fallet@aphp.fr) - personal fees from MSD, Novartis, Roche, Sanofi and Boehringer; personal fees and non-financial support from Astra Zeneca, BMS, Takeda, Jansen and Pfizer, all outside the submitted work.no disclosures.

Jose Nicolas Minatta (jose.minatta@hospitalitaliano.org.ar) - Research Grants: Pfizer. Consulting/Advisory Board/ Educational: MSD, Pfizer, Takeda, Roche, Merck, Amgen.

Anna Eisert (anna.eisert@uk-koeln.de) – Honoraria: Amgen, Merck.

Hortense de Saint Basile (hortense.gaultierdesaintbasile@aphp.fr) – no disclosures.

Clarisse Audigier-Valette (Clarisse.Audigier-Valette@ch-toulon.fr) - no disclosures.

Laura Mezquita (LMEZQUITA@clinic.cat) - research grant/Funding (self) from Bristol Myers Squibb, Boehringer Ingelheim, Amgen, Stilla, Inivata; advisory/consultancy from Roche, Takeda; honoraria (self) from Bristol Myers Squibb, Roche, Takeda, AstraZeneca; travel/Accommodation/Expenses from Roche, Bristol Myers Squibb, Takeda, AstraZeneca; non-remunerated activity/ies from AstraZeneca.

Antonio Calles (antonio.calles@live.com) - Honoraria: AstraZeneca, Boehringer-Ingelheim, Bayer, Pfizer, Roche, Novartis, Merck Sharp & Dohme, and Bristol Myers Squibb; Consulting or advisory role: AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche/Genentech, Eli Lilly and Company, Novartis, Takeda, Merck Sharp & Dohme, and Bristol Myers Squibb; Research funding: Merck Sharp & Dome; Travel financial support: Roche, Boehringer-Ingelheim, Merck Sharp & Dohme, and Bristol Myers Squibb; Stock Ownership: None

Giannis Mountzios (gmountzios@gmail.com) – Advisory and consultation fees: AstraZeneca, BMS, MSD, Roche, Takeda, Novartis, AMGEN, Pfizer, Takeda, GSK, Sanofi; Travel and accommodation fees: AstraZeneca, BMS, MSD, Roche, Takeda, Novartis, GSK, Sanofi; PI in sponsored clinical trials: Novartis, Roche, MSD, AstraZeneca, Merck, BMS, AMGEN, Immunomedics, GSK, Sanofi

Marco Tagliamento (Marco.tagliamento@gustaveroussy.fr) - travel grants from Roche, Bristol-Myers Squibb, AstraZeneca, Takeda, Eli Lilly and Honoraria as medical writer from Novartis, Amgen, Merck Sharp & Dohme.

Jordi Remon Masip (jremon@hmhospitales.com) - Travel, accommodation, congress registration expenses from Ose-Immunotherapeutic ; advisory and consultation fees : BMS, MSD, Janssen, Takeda.

Judith Raimbourg (judith.raimbourg@ico.unicancer.fr) – no disclosures.

Safae Terrisse (safae.terrisse@aphp.fr) – no disclosures.

Alexandro Russo (ale.russo1986@gmail.com) - no disclosures.

Diego Cortinovis (d.cortinovis@asst-monza.it) - no disclosures.

Philippe Rochigneux (prochigneux@yahoo.fr) – Speaker/ board: Novartis, Astra Zeneca, Viatris. Travel expenses: Pfizer.

David James Pinato (david.pinato@imperial.ac.uk) - DJP received lecture fees from ViiV Healthcare, Bayer Healthcare, BMS, Roche, EISAI, Falk Foundation, travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, DaVolterra and Astra Zeneca; research funding (to institution) from MSD and BMS.

Alessio Cortellini (alessiocortellini@gmail.com) – AC received consulting fees from MSD, BMS, AstraZeneca, Roche; speakers' fee from AstraZeneca, MSD, Novartis and Astellas.

Camille Leonce (camille.leonce@chu-lyon.fr) - no disclosures.

Anas Gazzah (Anas.GAZZAH@gustaveroussy.fr) - Travel, accommodation, congress registration expenses from Boehringer Ingelheim, Novartis, Pfizer, Roche; Consultant/Expert role for Novartis; Principal/sub-Investigator of Clinical Trials for Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, Astra Zeneca, 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, 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 , Rigontec Gmbh, Roche, Sanofi Aventis, Sierra Oncology, Taiho Pharma, Tesaro, Inc, Tioma Therapeutics, Inc., Xencor; Research Grants from Astrazeneca, BMS, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi; Non-financial support (drug supplied) from Astrazeneca, Bayer, BMS, Boringher Ingelheim, Johnson & Johnson, Lilly, Medimmune, Merck, NH TherAGuiX, Pfizer, Roche

Maria-Rosa Ghigna (maria-rosa.ghigna@gustaveroussy.fr) - no disclosures.

Roberto Ferreira (Roberto.Ferrara@istitutotumori.mi.it) - advisory board MSD, Beigene.

Filippo Gustavo Dall'Olio (filippodallolio@gmail.com) - no disclosures.

Francesco Passiglia (francesco.passiglia@unito.it) - consultant fee from Astra Zeneca, Janssen, Amgen, Sanofi, Merck Sharp and Dohme, Beigene, Thermo Fisher Scientifics.

Enriqueta Felip (efelip@vhio.net) - Advisory Board: Amgen, Astra Zeneca, Bayer, Bristol-Myers Squibb, Daichii Sankyo, Eli Lilly, F. Hoffmann-La Roche, Glaxo Smith Kline, Janssen, Merck Sharp &Dohme, Merck Serono, Novartis, Peptomyc, Pfizer, Sanofi, Takeda; Invited Speaker: Amgen, Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Janssen, Medscape, Merck Sharp & Dohme, Peervoice, Pfizer, Medical Trends, Merck Serono, Sanofi, Takeda, Touchoncology; Research Funding: Merck Healthcare Kgaa, Fundación Merck Salud.

Vienna Ludovini (vienna.ludovini@ospedale.perugia.it) – no disclosures.

Fabrice Barlesi (fabrice.barlesi@gustaveroussy.fr) - Personal financial interests - Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, Mirati, MSD, Pierre Fabre, Pfizer, Seattle Genetics and Takeda.

David Planchard (david.planchard@gustaveroussy.fr) - Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche. Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche. Clinical trials research: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo. Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer.

Benjamin Besse (benjamin.besse@gustaveroussy.fr) - Sponsored Research at Gustave Roussy Cancer Center: Abbvie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, Tiziana Pharma. Investigator or co-investigator of trials: Nerviano, GSK, Pfizer, Roche-Genentech, Lilly, OSE Pharma, MSD, Celgene, Stemcentrx, Ignyta, Abbvie, Loxo Oncology, AstraZeneca, Blueprint Medicines.

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 (RETi) 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 RETi, respectively. Median overall survival was longer in patients treated with RETi versus no RETi (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. RETi 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 pathways[1-3]. It is identified in 1% to2% 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*+ NSCLC[4-7]. With the advent of selective RET inhibitors (RETi), 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) range from 16 to 25 months, in prior platinum-treated patients and treatment naïve patients, respectively, leading to approvals by EMA and FDA[8-13]. 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*+ NSCLC[14-19], 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-word 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, 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, Oncomine (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 Squamous carcinoma Undifferentiated carcinoma Neuroendocrine carcinoma	 203 (93%) 1 (0.5%) 7 (3.2%) 7 (3.2%)
Stage at diagnosis, N (%) Stage I Stage II Stage III Stage IV	 17 (7.8%) 11 (5%) 27 (12%) 163 (75%)
N metastatic sites at time of advanced disease, median [IQR]	2 [1-3]
Smoking history, N (%) Non-smoker Former Current Unknown	 126 (59%) 76 (35%) 13 (6%) 3
Performance status ECOG, N (%) PS 0-1 PS 2 PS 3-4 Unknown	 175 (87%) 19 (9.4%) 8 (4%) 16
Grade I familial history of cancer, N (%) Unknown	48 (33.5%) 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.

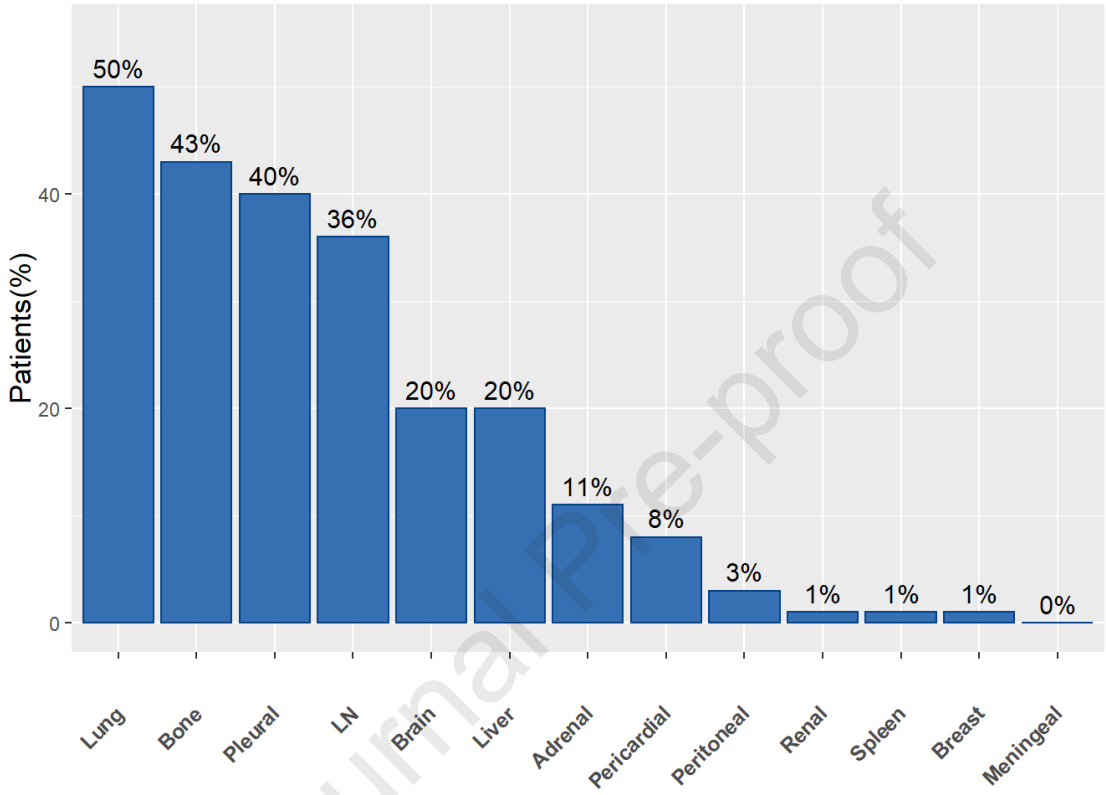


Figure 1. Metastatic pattern of *RET*+ stage IV lung cancer among the 205 patients. LN: extra-thoracic lymph nodes.

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 ≥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; [£]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.

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).

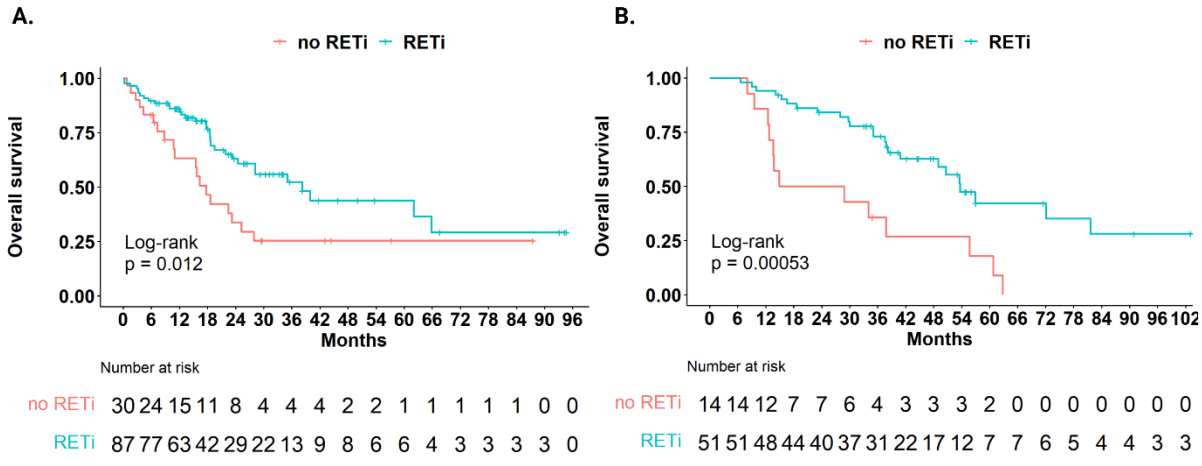


Figure 2. Overall survival in patients treated with selective RET inhibitors (RETi). A) Patients treated with a maximum of two lines of therapy; B) Patients treated with more than two lines of therapy.

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).

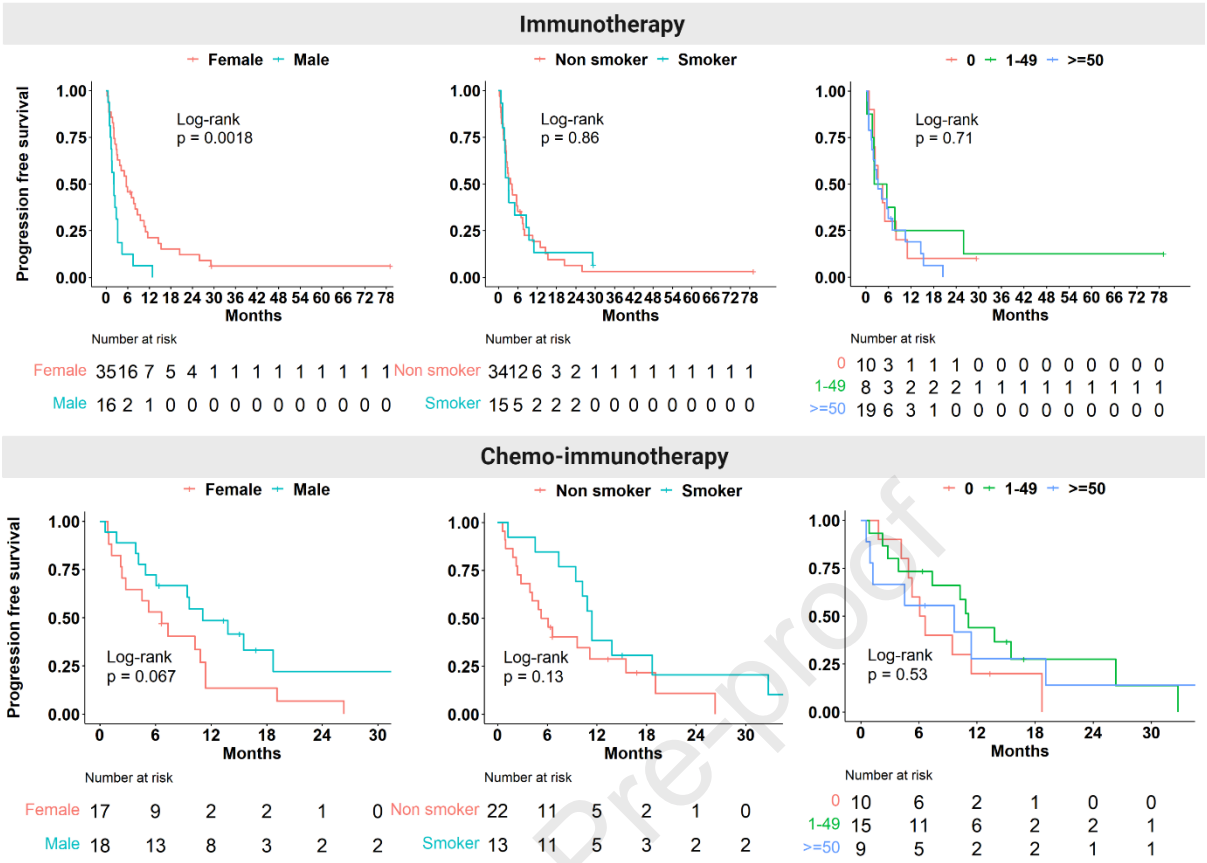


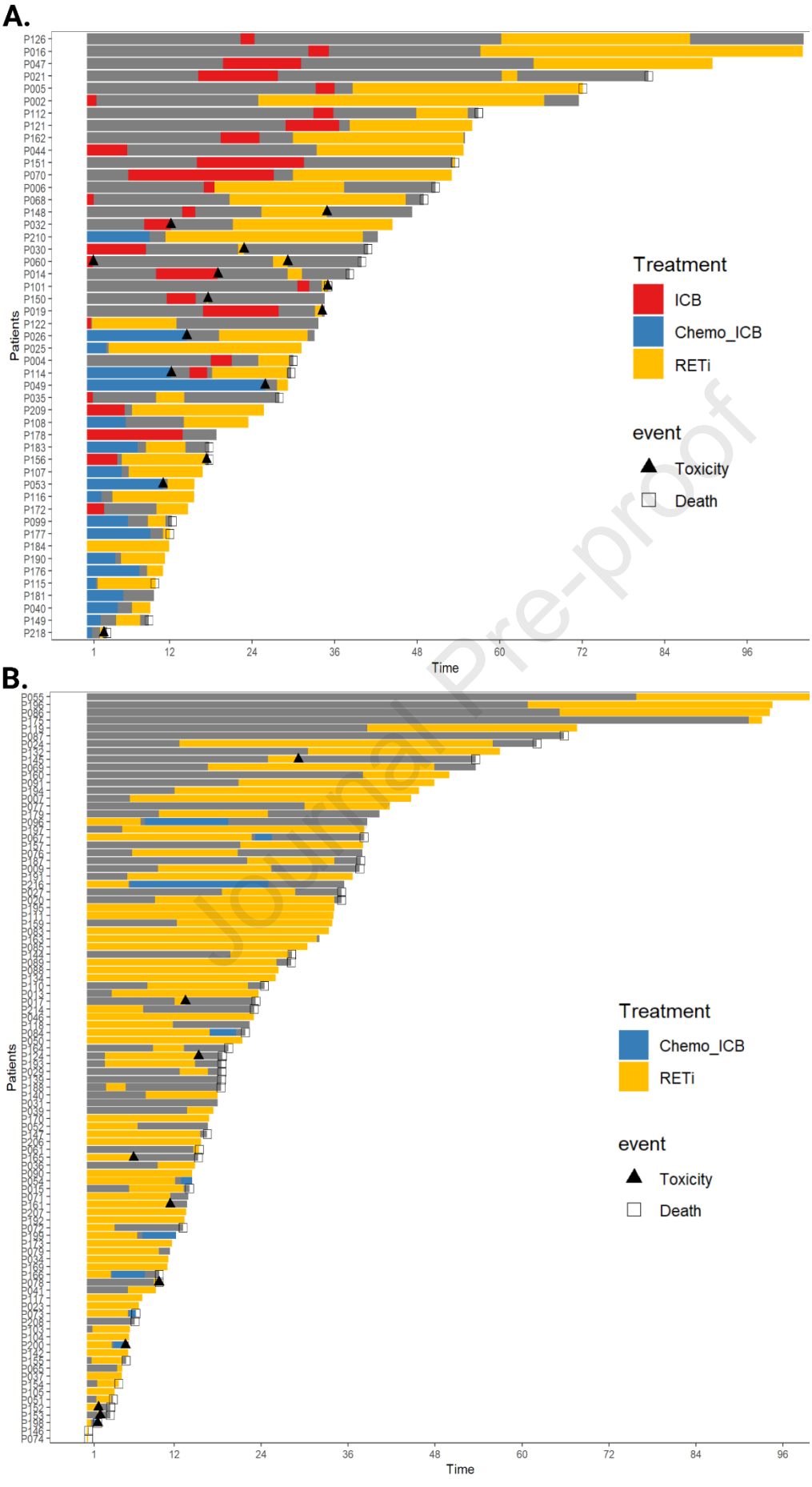
Figure 3. PFS subgroup analyses after stratification by sex, smoking history and PD-L1 expression in patients treated with immunotherapy and chemo-immunotherapy.

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.



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 activity[10], 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 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 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 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 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 activity[25].

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 months[14-18]. 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.

Acknowledgements:

Writing assistance was provided by Sarah Mackenzie.

Arianna Marinello was the recipient for the grant for DUERTECC/EURONCO (Diplôme Universitaire Européen de Recherche Translationnelle Et Clinique en Cancérologie).

Laura 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.

Alessio Cortellini would like to acknowledge the support from the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC).

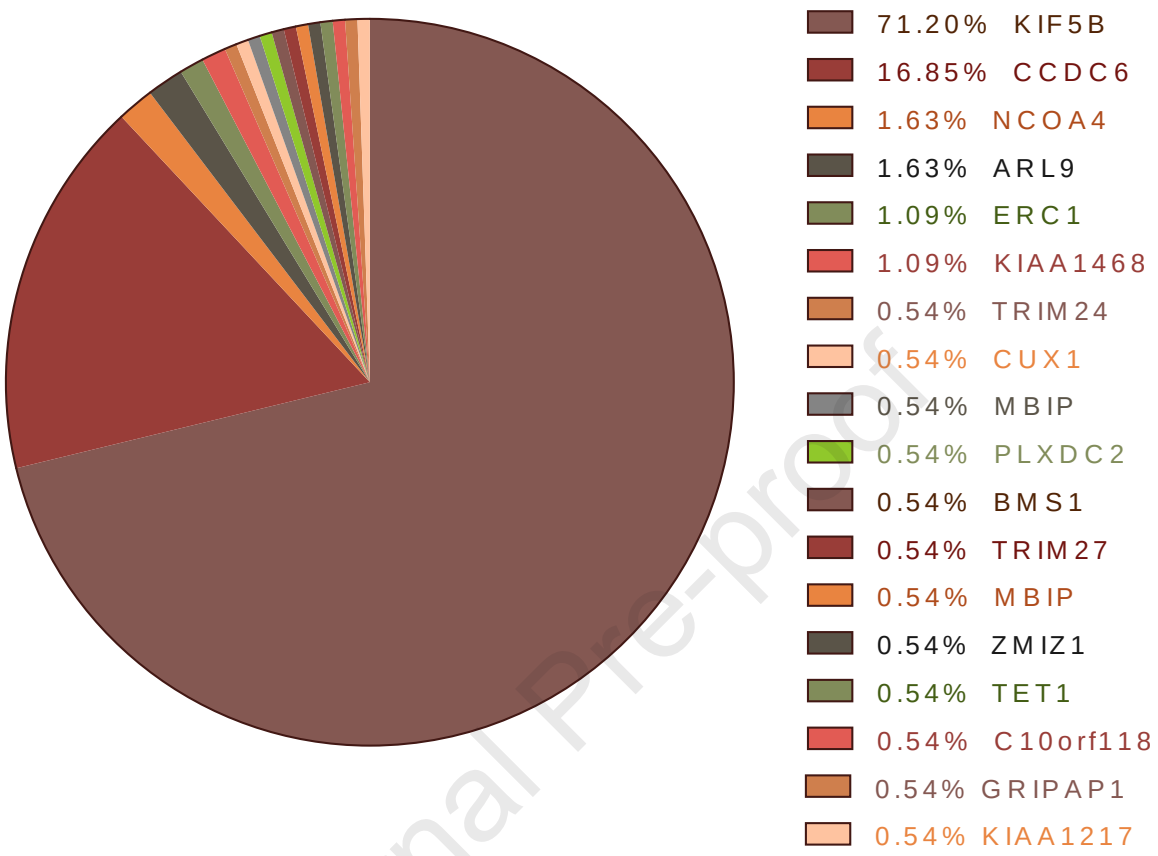
David J Pinato would like to acknowledge the support from the Wellcome Trust Strategic Fund (PS3416), from the Associazione Italiana per la Ricerca sul Cancro (AIRC MFAG Grant ID 25697), from the NIHR Imperial Biomedical Research Centre (BRC), from the Imperial Experimental Cancer Medicine Centre (ECMC) and from the Imperial College Tissue Bank.

References

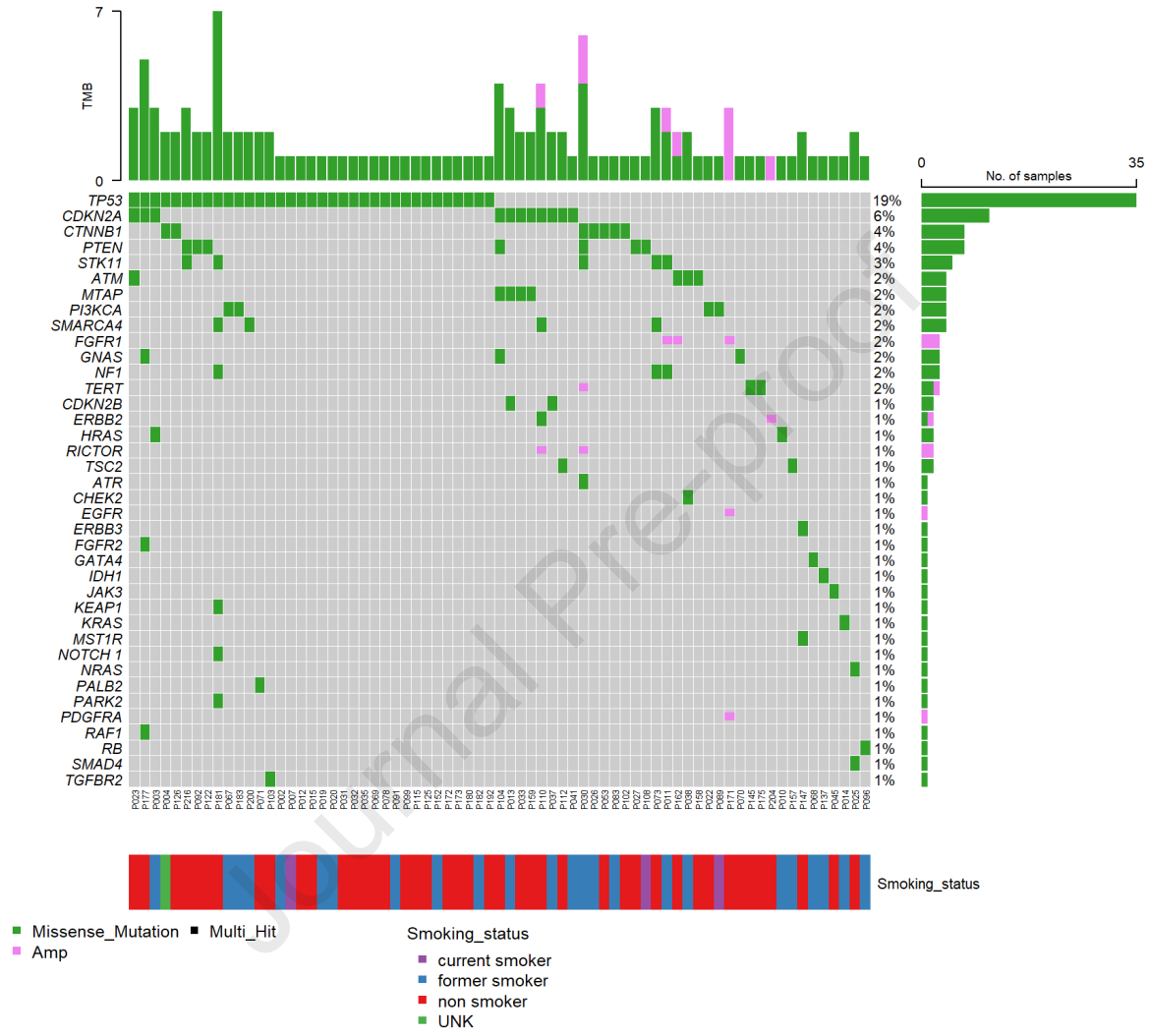
1. Adashek JJ, Desai AP, Andreev-Drakhlin AY, et al. Hallmarks of RET and Co-occuring Genomic Alterations in RET-aberrant Cancers. *Molecular cancer therapeutics* 2021;20:1769-1776.
2. Ferrara R, Auger N, Auclin E, et al. Clinical and Translational Implications of RET Rearrangements in Non-Small Cell Lung Cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 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. *The Lancet Oncology* 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. *The Lancet Respiratory medicine* 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. *Annals of oncology : official journal of the European Society for Medical Oncology* 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. *The Lancet Oncology* 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. *The New England journal of medicine* 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. *Clinical cancer research : an official journal of the American Association for Cancer Research* 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). *Annals of Oncology* 2022;33: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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2022:JCO2200393.
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. *Annals of oncology : official journal of the European Society for Medical Oncology* 2022;33:1168-1178.
14. Offin M, Guo R, Wu SL, et al. Immunophenotype and Response to Immunotherapy of RET-Rearranged Lung Cancers. *JCO precision oncology* 2019;3.
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. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 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. *Annals of oncology : official journal of the European Society for Medical Oncology* 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. *Japanese journal of clinical oncology* 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. *Oncology and therapy* 2020;8:333-339.
20. Hess LM, Han Y, Zhu YE, et al. 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). *Journal of Clinical Oncology* 2021;39:9032-9032.
22. Drilon A, Lin JJ, Filleron T, et al. Frequency of Brain Metastases and Multikinase Inhibitor Outcomes in Patients With RET-Rearranged Lung Cancers. *Journal of thoracic oncology : official publication of the International Association for the Study of 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. *Nature communications* 2022;13:1450.
24. Drilon A, Bergagnini I, Delasos L, et al. Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers. *Annals of oncology : official journal of the European Society for Medical Oncology* 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.

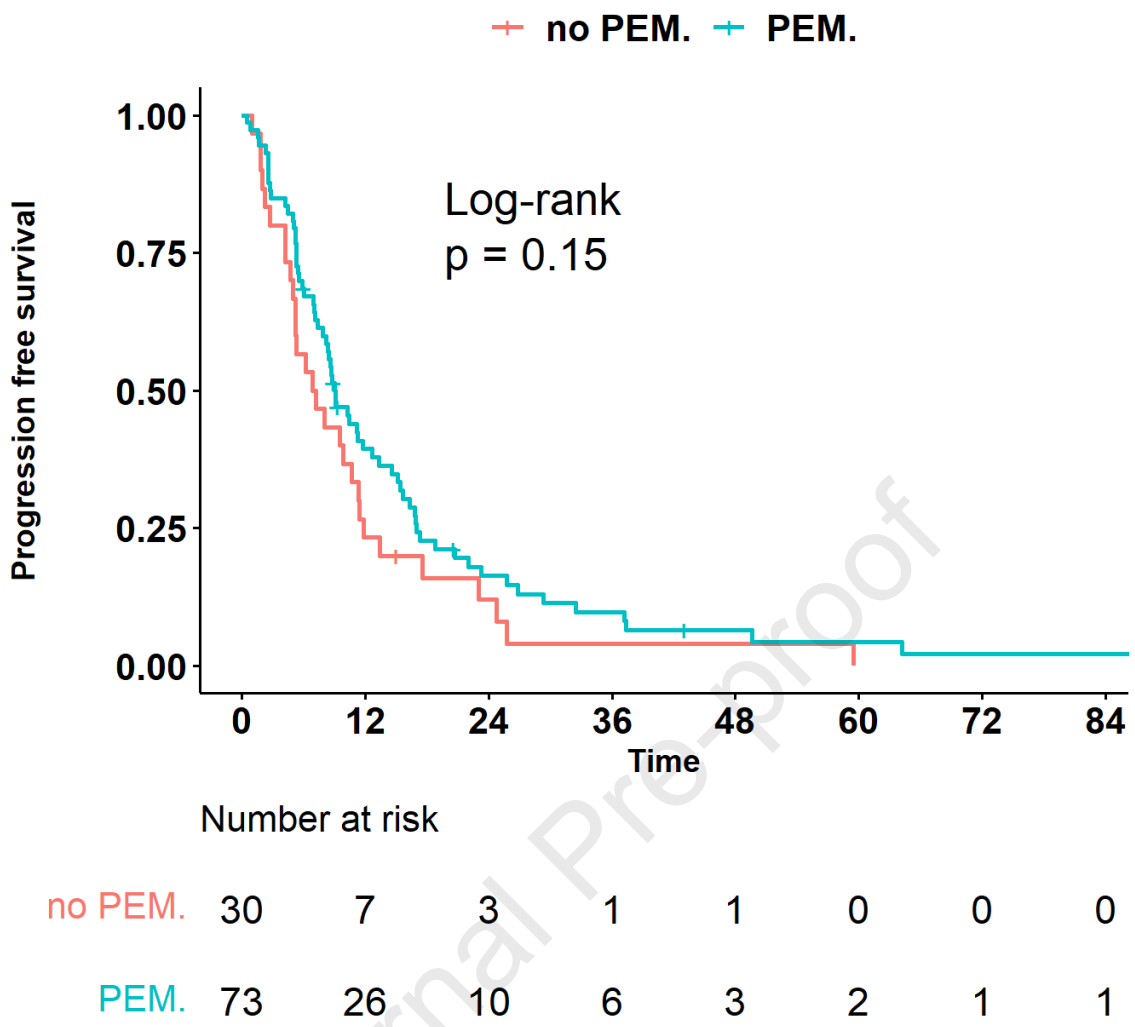
Supplementary Figures



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)**
KIF5B-RET	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-*KIF5B-RET*	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]
P value	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**	***P* value**
Sex, N (%)			0.5
Female	85 (59%)	32 (53%)	
Age at time of advanced disease , median [IQR]	63 [55-71]	62 [52-68]	0.2
ECOG performance status, N (%)			0.5
PS ≤1	124 (87%)	50 (86%)	
PS >1	19 (13%)	8 (14%)	
Unknown	2	2	
Smoking status, N (%)			0.1
Former or current smoker	61 (43%)	22 (37%)	
Non-smoker	82 (57%)	37 (63%)	
Unknown	2	1	
Histology, N (%)			0.1
Adenocarcinoma	137 (94%)	53 (92%)	
Non-adenocarcinoma	8 (6%)	7 (8%)	
Stage at diagnosis according AJCC 8th edition			0.4
I	6 (4.1%)	2 (3.3%)	
II	9 (6.2%)	2 (3.3%)	

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

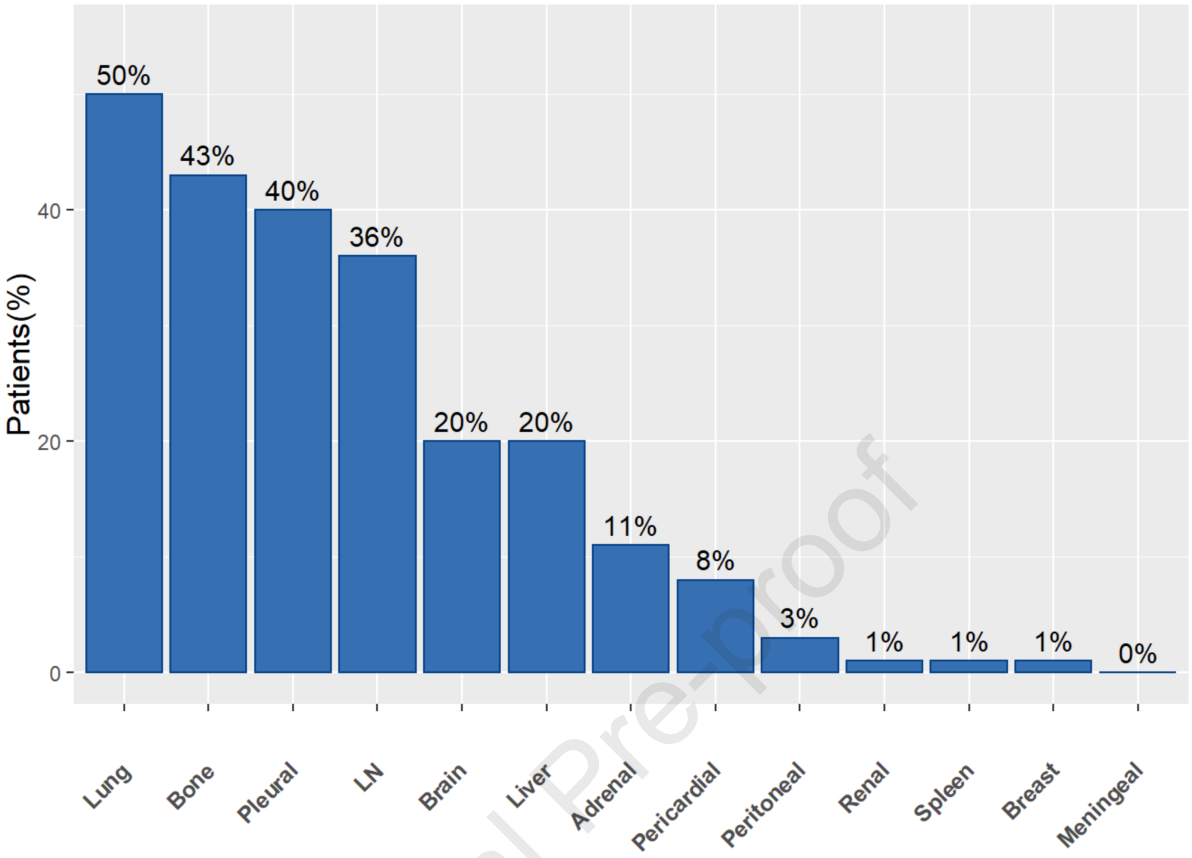
	Patients (N=218)
Female, N (%)	122 (56%)
Age in years, median [IQR]	63 [54-71]
Histology, N (%) Adenocarcinoma Squamous carcinoma Undifferentiated carcinoma Neuroendocrine carcinoma	 203 (93%) 1 (0.5%) 7 (3.2%) 7 (3.2%)
Stage at diagnosis, N (%) Stage I Stage II Stage III Stage IV	 17 (7.8%) 11 (5%)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

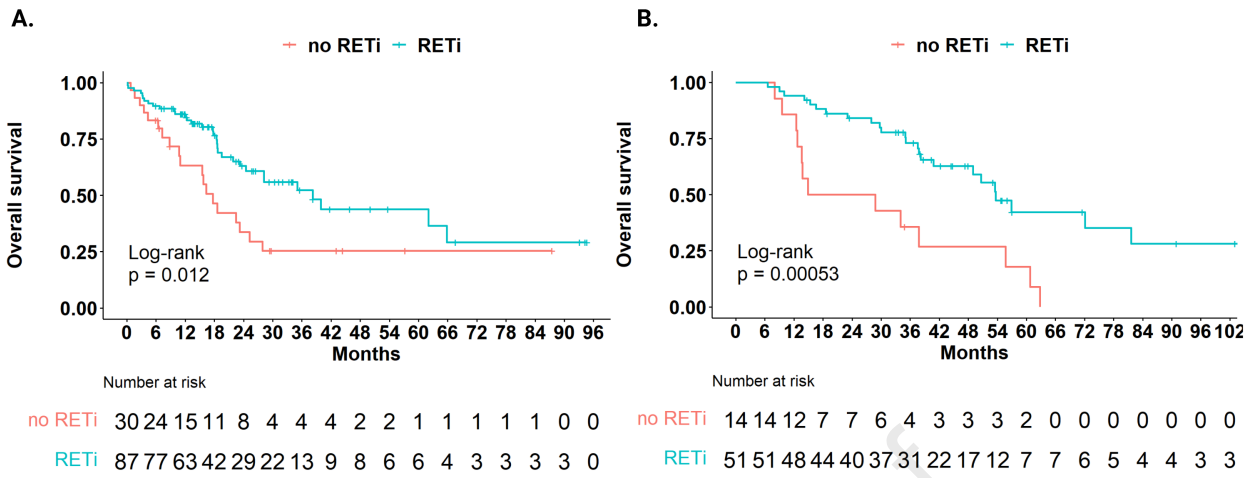
N, number; PS, performance status

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

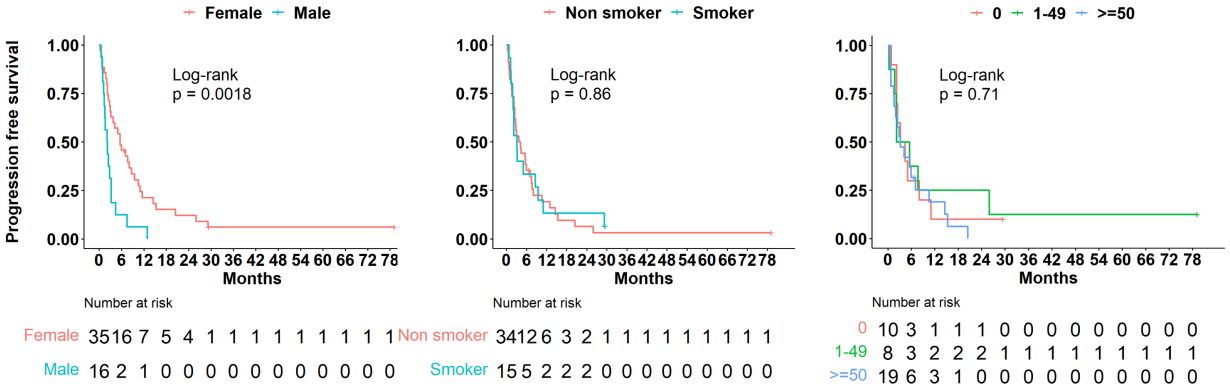
	Doublet CT (N=108)	**Single agent CT (N=34)**	**CT-ICB (N=41)**	**ICB (N=52)**	**MTKi (N=21)**	**RETi (N=145)**
N of treatment line, median (range)	1 (1-1)	2.5 (2-3)	1 (1-1)	2 (1-2)	3 (1-4)	2 (1-2)
ORR, N (%)[£]	56/102 (55%)	8/31 (26%)	17/37 (46%)	12/52 (23%)	7/19 (37%)	99/131 (76%)
Median PFS, months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

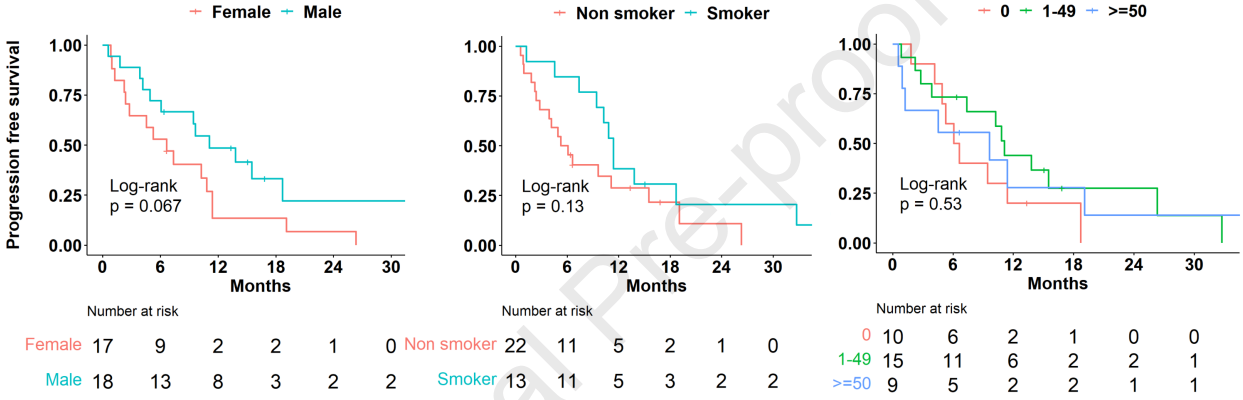


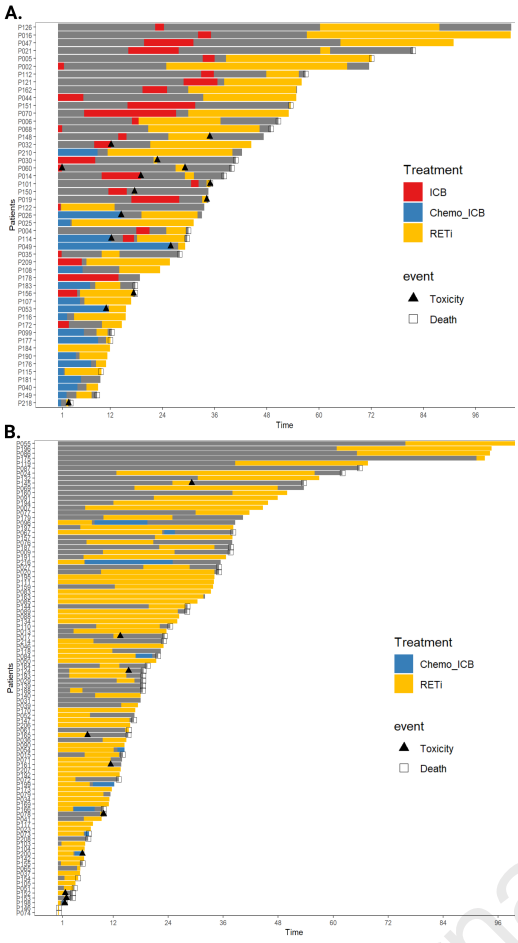


Immunotherapy



Chemo-immunotherapy





CRediT Authorship Contribution Statement

Mihaela Aldea: Concept, Methodology, Data curation, Investigation, Formal analysis, Writing - original draft, Writing - review & editing.

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

Wael Zrafi: Data curation, Methodology, Statistical analysis, Writing - review & 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 & editing.

Benjamin Besse: Concept, Methodology, Writing - review & editing, Supervision.