

Clinico-biological characteristics and treatment outcomes in patients with RET+ lung cancer with non-LUAD histology

Arianna Marinello¹, Meghanne Lomibao², Julia C F Quintanilha³, Adeyelu Tolulope⁴, Maria Rosa Ghigna⁵, Daniela Miliziano¹, Rita Leporati⁶, Barliz Waissengrin⁷, Gheorghe Emilian Olteanu⁸, Isabelle Monnet⁹, Michael Duruisseaux¹⁰, Emilio Bria¹¹, Mariana Brandão¹², Florian Guisier¹³, Annarita Avanzo¹⁴, Francesco Cortiula¹⁵, Judith Raimbourg¹⁶, Marco Tagliamento¹⁷, Helena Bote-de Cabo¹⁸, Jamie Feng¹⁹, Andrea De Giglio²⁰, Massimiliano Cani^{21,1}, Francesca Colamartini^{22,1}, Fabrizio Citarella²³, Teresa Gorria²⁴, Anna Eisert²⁵, Patricia Iranzo²⁶, Colin R. Lindsay²⁷, Vladmir Lima²⁸, Amin H. Nassar²⁹, Nicolas Minatta³⁰, Alessio Cortellini³¹, Skyler Taylor³², Elizabeth Fabre³³, Ayesha Aijaz³⁴, Sophie Cousin³⁵, Katarzyna Szymczak³⁶, Alessandro Russo³⁷, Vincent Fallet³⁸, Hélène Doubre³⁹, Nicolas Girard⁴⁰, Philippe Rochigneux⁴¹, Jose Carlos Benitez⁴², Matteo Fila⁴³, Andrew Elliott⁴, Ole Gjoerup³, Julia K. Rotow⁴⁴, Alexander Drilon², Benjamin Besse^{1,45}, Mihaela Aldea^{1,45}

1. Department of Medical Oncology, Gustave Roussy, Villejuif, France; 2. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3. Foundation Medicine, Boston, Massachusetts; 4. Caris Life Sciences, Phoenix, Arizona, USA; 5. Biopathology Department, Gustave Roussy Cancer Campus, Villejuif, France; 6. Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 7. Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; 8. Department of Pathology, British Columbia Cancer Agency, Vancouver, BC, Canada; 9. Pneumology and Thoracic Oncology Department, Intercommunal Hospital of Créteil (CHI), Créteil, France; 10. Respiratory Department and Early Phase (EPSILYON), Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute, Lyon, France; 11. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; 12. Clinic of Thoracic Oncology & Phase 1 Clinical Trials Unit, Institut Jules Bordet-Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Brussels, Belgium; 13. Normandie Univ, UNIROUEN, AIMS Lab QuantIF team, CHU Rouen, Department of Pneumology and Inserm CIC-CRB 1404, Rouen, France; 14. Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy; 15. Department of Oncology, University Hospital of Udine, Udine, Italy; 16. Institut de Cancérologie de l'Ouest, St Herblain, France; ; 17. Department of Internal Medicine and Medical Specialties, University of Genova, Genova, Italy; 18. Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; 19. Division of Medical Oncology, Princess Margaret Cancer Centre, University Health Network (UHN), Toronto, ON, Canada; 20. Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; 21. Department of Oncology, University of Turin, S. Luigi Gonzaga Hospital, Orbassano, Turin, Italy; 22. Medical Oncology, Santa Maria Della Misericordia Hospital, University of Perugia, Perugia, Italy; 23. Thoracic Oncology Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; 24. Medical Oncology Department, Hospital Clinic of Barcelona, Barcelona, Spain; 25. Department of Medical Oncology, University Hospital of Cologne, Cologne, Germany; 26. Medical Oncology Department, Vall d'Hebron Hospital Universitari/Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; 27. Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; 28. Department of Medical Oncology, A. C. Camargo Cancer Center, São Paulo, Brazil; 29. Division of Oncology, Yale University School of Medicine, New Haven, CT, USA; 30. Department of Medical Oncology, Hospital Italiano, Buenos Aires, Argentina; 31. Department of Medical Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy; 32. Department of Hematology-Oncology, Mayo Clinic Arizona, Phoenix, USA; 33. Department of Thoracic Oncology, European Hospital Georges Pompidou, Paris, France; 34. Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; 35. Department of Medical Oncology, Institut Bergonié, Bordeaux, France; 36. Department of Oncology and Radiotherapy and Early Phase Clinical Trials Center, University of Gdańsk, Gdańsk, Poland; 37. Department of Medical Oncology, Azienda Ospedaliera Papardo, Messina, Italy; 38. Department of Pneumology and Thoracic Oncology, Tenon Hospital, Assistance Publique Hôpitaux de Paris and GRC 4, TheraNOScan, Sorbonne Université, Paris, France; 39. Department of Pulmonary Medicine, Hôpital Foch, Suresnes, France; 40. Department of Medical Oncology, Institut Curie, Paris, France; 41. Department of Medical Oncology, Paoli-Calmettes Institute, Marseille, France; 42. Department of Medical Oncology, Virgen de la Victoria University Hospital, Biomedical Research Institute of Malaga (IBIMA plataforma BIONAND), Malaga, Spain; 43. Oncology, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Italy; 44. Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 45. Paris-Saclay University, Kremlin-Bicêtre, France

BACKGROUND

RET fusions occur in 1-2% of non-small cell lung cancer, predominantly in adenocarcinoma (LUAD), while ~7% present with non-adenocarcinoma (non-LUAD) histologies. This study aimed to characterize the clinical and biological features of RET-rearranged (RET+) non-LUAD and evaluate outcomes with selective RET inhibitors (SRI) and chemotherapy.

METHODS

Multicenter international retrospective study of RET+ patients from the RET-MAP registry (52 institutions), irrespective of stage or treatment.

- **Central pathological review** of non-LUAD cases.
- **Clinical outcomes** with SRI and first-line chemotherapy assessed by overall response rate (ORR), progression-free survival (PFS), and overall survival (OS), calculated from treatment initiation. **Multivariable Cox proportional hazards models** were adjusted for sex, TP53 alterations, fusion partner, brain metastases, and line of treatment.
- **Genomic profiles** of non-LUAD and LUAD cases explored in independent Foundation Medicine (FMI) and CARIS cohorts.
- **Whole-transcriptome sequencing and pathway analyses** performed in the Caris cohort.

Contact: arianna.marinello@gustaveroussy.fr

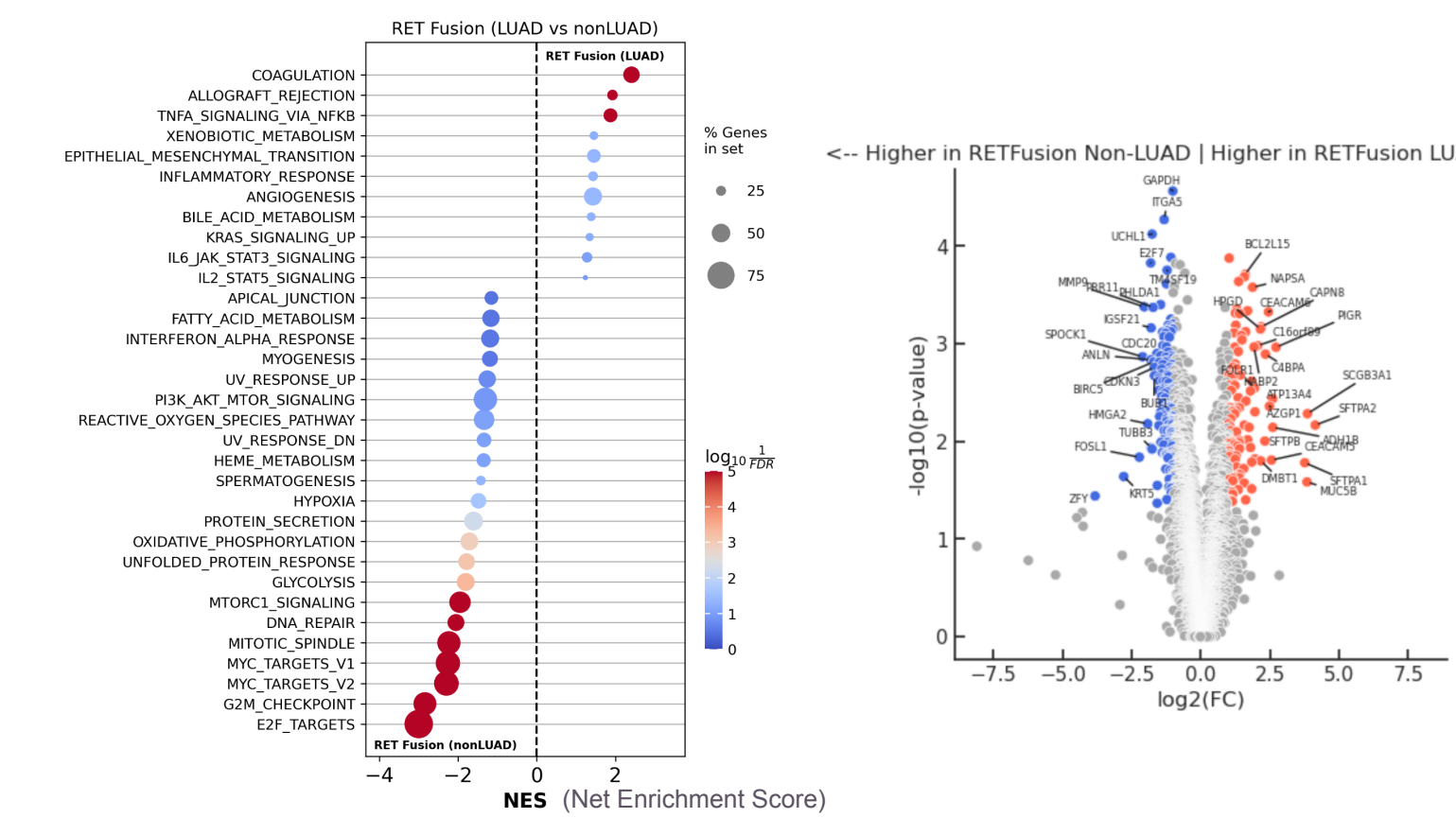
No conflicts of interest to declare.

RESULTS

Clinical and biological characteristics

Characteristic	LUAD (n=600)	non-LUAD (n=47)	p value
Female sex, n(%)	350/600 (58)	26/47 (55)	0.7
Age, median (IQR)	62 (54-70)	64 (50-72)	0.7
Never smoker, n(%)	375/598 (76)	26/46 (57)	0.4
TP53-mutant, n(%)	116 /430 (27)	9/39 (26)	0.6
Uncommon fusion partner, n(%)	45/538 (8)	8/39 (21)	0.031
Brain metastases at diagnosis, n(%)	130/600 (22)	18/47 (38)	0.009
PS <2 at treatment start, n(%)	412/468 (88)	38/43 (88)	>0.9

WTS and pathway activation (Caris cohort)

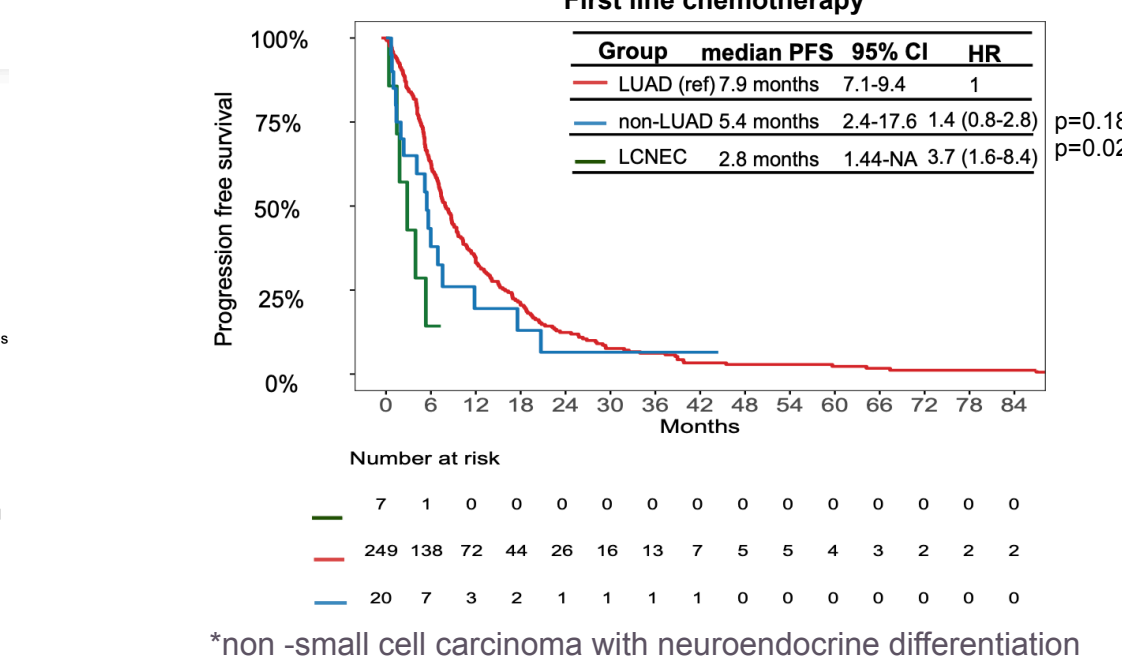
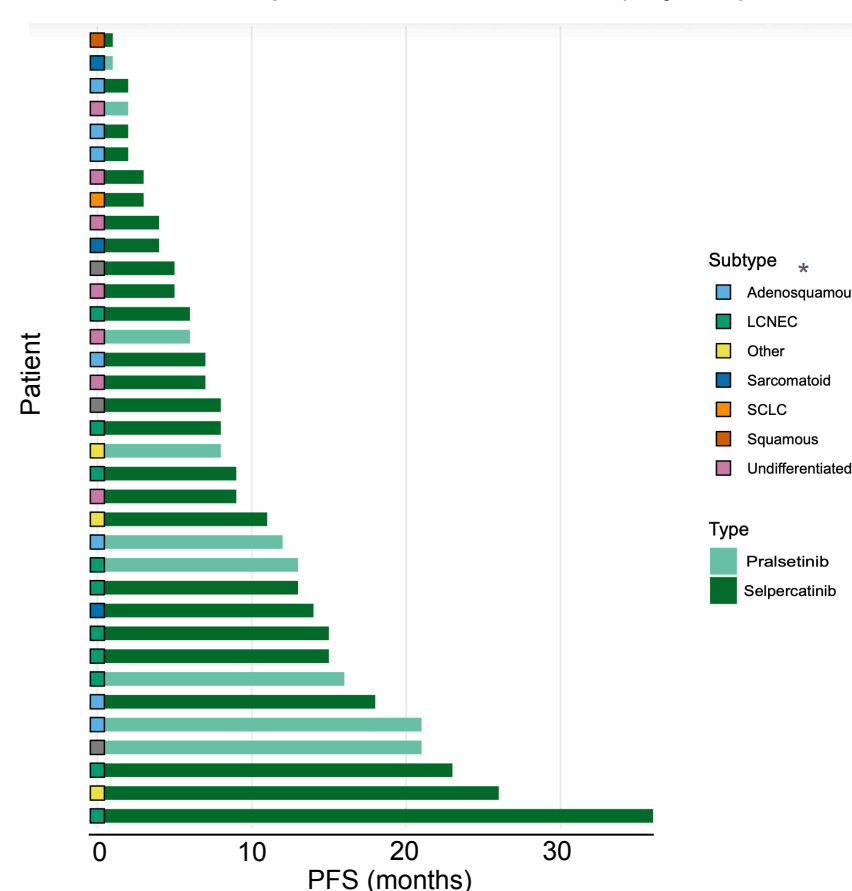


- Increased metabolic activity and enrichment of proliferative and oncogenic programs in non-LUAD (E2F signalling, MYC targets, PI3K/mTOR pathway, DNA repair)
- Upregulation of genes associated with stemness-related signaling and enhanced tumor proliferation, such as TUBB3 in non-LUAD

Outcomes with systemic therapies

	LUAD	non-LUAD	Interaction
SRI (first exposure, any line)	ORR: 73%	ORR: 56%	OR:0.46, 95%CI 0.22-0.96, p=0.05
mOS (95%CI)	34.5 (29.8-45.5)	19.0 (13.2-NA)	Multivariate analysis: HR 1.99 (1.25, 3.17), p=0.004
mPFS (95%CI)	19.22 (15.64-23.3)	8.94 (6.08-14.7)	Multivariate analysis: HR: 2.07 (1.29, 3.33), p=0.003
First line chemotherapy	ORR: 55%	ORR: 42%	OR: 0.60, 95%CI 0.26-1.38, p=0.32
mOS (95%CI)	44.6 (35-53.6)	16.3 (11.7-37.8)	Multivariate analysis: HR: 1.69 (1.06, 2.70), p=0.028
mPFS (95%CI)	7.6 (6.9-9.1)	5.19 (2.37-7.6)	Multivariate analysis: HR:2.24 (1.35, 3.73), p=0.002

PFS with SRI in patients with non-LUAD (any line)



LCNEC showed encouraging outcomes with SRI treatment (n=10):

- ORR: 80% vs 73% in LUAD;
 - mOS: 30.4 months (95% CI, 23-NA); HR vs LUAD: 0.90 (95% CI, 0.37-2.20; p=0.87)
- In contrast, LCNEC showed poor outcomes with first line chemotherapy (n=7).

CONCLUSIONS

RET+ non-LUAD NSCLC represents a rare but distinct entity with a biologically aggressive phenotype and poor prognosis.

Treatment with SRI provides objective responses, underscoring the importance of molecular screening in non-LUAD.

Survival outcomes for non-LUAD are shorter with both SRI treatment and first-line platinum-based chemotherapy. However, LCNEC may derive a similar survival benefit from SRI treatment as LUAD.

Clinico-biological characteristics and treatment outcomes in patients with RET+ lung cancer with non-LUAD histology

Arianna Marinello¹, Meghanne Lomibao², Julia C F Quintanilha³, Adeyelu Tolulope⁴, Maria Rosa Ghigna⁵, Daniela Miliziano¹, Rita Leporati⁶, Barliz Waissengrin⁷, Gheorghe Emilian Olteanu⁸, Isabelle Monnet⁹, Michael Duruisseaux¹⁰, Emilio Bria¹¹, Mariana Brandão¹², Florian Guisier¹³, Annarita Avanzo¹⁴, Francesco Cortiula¹⁵, Judith Raimbourg¹⁶, Marco Tagliamento¹⁷, Helena Bote-de Cabo¹⁸, Jamie Feng¹⁹, Andrea De Giglio²⁰, Massimiliano Cani^{21,1}, Francesca Colamartini^{22,1}, Fabrizio Citarella²³, Teresa Gorria²⁴, Anna Eisert²⁵, Patricia Iranzo²⁶, Colin R. Lindsay²⁷, Vladimir Lima²⁸, Amin H. Nassar²⁹, Nicolas Minatta³⁰, Alessio Cortellini³¹, Skyler Taylor³², Elizabeth Fabre³³, Ayesha Aijaz³⁴, Sophie Cousin³⁵, Katarzyna Szymczak³⁶, Alessandro Russo³⁷, Vincent Fallet³⁸, Hélène Doubre³⁹, Nicolas Girard⁴⁰, Philippe Rochigneux⁴¹, Jose Carlos Benitez⁴², Matteo Fila⁴³, Andrew Elliott⁴, Ole Gjoerup³, Julia K. Rotow⁴⁴, Alexander Drilon², Benjamin Besse^{1,45}, Mihaela Aldea^{1,45}

1. Department of Medical Oncology, Gustave Roussy, Villejuif, France; 2. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3. Foundation Medicine, Boston, Massachusetts; 4. Caris Life Sciences, Phoenix, Arizona, USA; 5. Biopathology Department, Gustave Roussy Cancer Campus, Villejuif, France; 6. Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 7. Department of Pathology, British Columbia Cancer Agency, Vancouver, BC, Canada; 8. Pneumology and Thoracic Oncology Department, Intercommunal Hospital of Créteil (CHI), Créteil, France; 9. Respiratory Department and Early Phase (EPSILYON), Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute, Lyon, France; 10. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; 11. Clinica di Oncologia, Università di Padova, Padova, Italy; 12. Clinica de Oncologia, Universidade de Lisboa, Lisboa, Portugal; 13. Normandie Univ, UNIROUEN, AIMS Lab QuantIF team, CHU Rouen, Department of Pneumology and Inserm CIC-CRB 1404, Rouen, France; 14. Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy; 15. Department of Oncology, University Hospital of Udine, Udine, Italy; 16. Institut de Cancérologie de l'Ouest, St Herblain, France; 17. Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; 18. Division of Medical Oncology, Princess Margaret Cancer Centre, University Health Network (UHN), Toronto, ON, Canada; 19. Department of Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; 20. Department of Oncology, University of Turin, S. Luigi Gonzaga Hospital, Orbassano, Turin, Italy; 21. Thoracic Oncology Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; 22. Medical Oncology Department, Hospital Clinic of Barcelona, Barcelona, Spain; 23. Department of Medical Oncology, University Hospital of Cologne, Cologne, Germany; 24. Medical Oncology Department, Vall d'Hebron Hospital Universitari/Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; 25. Department of Medical Oncology, A. C. Camargo Cancer Center, São Paulo, Brazil; 26. Division of Oncology, Yale University School of Medicine, New Haven, CT, USA; 27. Department of Medical Oncology, Hospital Italiano, Buenos Aires, Argentina; 28. Department of Medical Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy; 29. Department of Hematology-Oncology, Mayo Clinic Arizona, Phoenix, AZ, USA; 30. Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; 31. Department of Medical Oncology, Institut Bergonié, Bordeaux, France; 32. Department of Oncology and Radiotherapy and Early Phase Clinical Trials Center, University of Gdańsk, Gdańsk, Poland; 33. Department of Medical Oncology, Azienda Ospedaliera Papardo, Messina, Italy; 34. Department of Pneumology, Sorbonne Université, Paris, France; 35. Department of Pulmonary Medicine, Hôpital Foch, Suresnes, France; 36. Department of Medical Oncology, Institut Curie, Paris, France; 37. Department of Medical Oncology, Paoli-Calmettes Institute, Marseille, France; 38. Department of Medical Oncology, Virgen de la Victoria University Hospital, Biomedical Research Institute of Malaga (IBIMA plataforma BIONIA), Málaga, Spain; 39. Department of Medical Oncology, Gustave Roussy, Villejuif, France; 40. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 41. Paris-Saclay University, Kremlin-Bicêtre, France; 42. Department of Medical Oncology, Gustave Roussy, Villejuif, France; 43. Department of Medical Oncology, Gustave Roussy, Villejuif, France; 44. Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 45. Paris-Saclay University, Kremlin-Bicêtre, France

BACKGROUND

RET fusions occur in 1-2% of non-small cell lung cancer, predominantly in adenocarcinoma (LUAD), while ~7% present with non-adenocarcinoma (non-LUAD) histologies.

Data about the clinical and biological features of *RET*-rearranged (RET+) non-LUAD, their response to systemic treatment and prognosis are scarce.

This study aimed to characterize the clinical and biological features of RET+ non-LUAD and evaluate outcomes with selective RET inhibitors (SRI) and chemotherapy.

METHODS

We conducted a **multicenter international retrospective study** of RET+ patients from the RET-MAP registry.

The RET MAP registry is a world-wide registry enrolling patients from 52 Institutions, irrespective of stage or treatment.

Non-LUAD cases underwent **central pathological review**

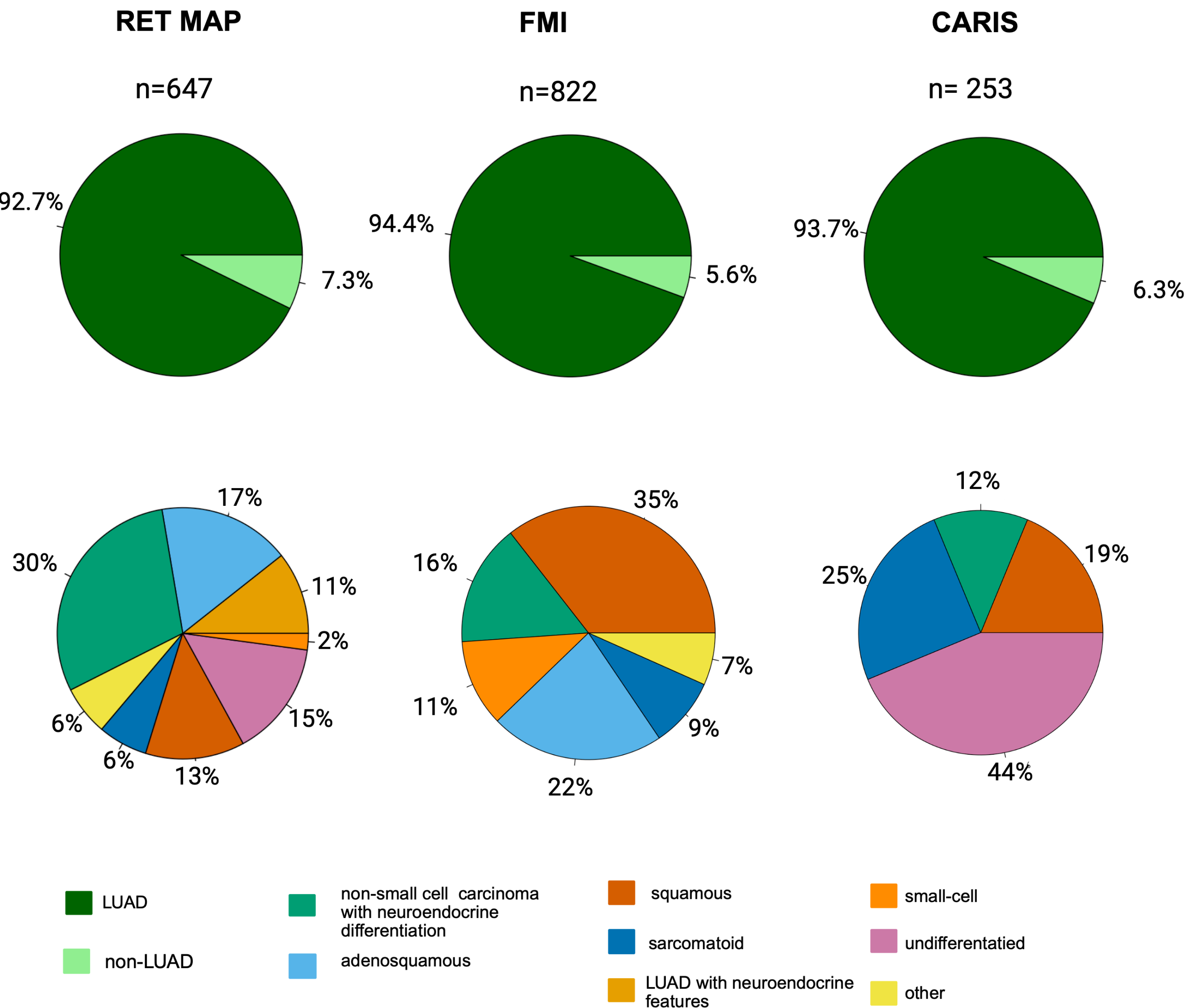
Clinical outcomes with SRI and first-line chemotherapy were assessed by overall response rate (ORR), progression-free survival (PFS), and overall survival (OS), calculated from treatment initiation.

Multivariable Cox proportional hazards models were adjusted for sex, *TP53* alterations, fusion partner, brain metastases, and line of treatment.

Genomic profiles of non-LUAD and LUAD cases were explored in independent Foundation Medicine (FMI) and CARIS cohorts.

Whole-transcriptome sequencing and pathway analyses performed in the Caris cohort.

RESULTS



Upregulation of genes associated with stemness-related signaling and enhanced tumor proliferation, such as *TUBB3* in non-LUAD

