



KeyPoints

MICRO-LEARNING FOR ONCOLOGISTS



RET fusion-positive NSCLC

Experts: Professor Benjamin Besse and Assistant Professor Mihaela Aldea, Institute Gustave Roussy (Paris, France)

MARCH 2024



3 slides, <5 mins

Funded independently by OncShare Ltd





DISEASE and DIAGNOSTICS

- RET fusions occur in 1–2% of patients with non-small cell lung cancer and should be screened for all patients with non-squamous histology and advanced disease^{1,2}
- Next-generation sequencing, specifically RNA sequencing, is the preferred method for molecular diagnosis; FISH or RT-PCR can be used for screening, but not IHC^{3,4}
- The most frequent fusion partner is KIF5B-RET, followed by CCDC6-RET; the fusion partner does not impact disease management⁵
- Co-mutations may occur, especially TP53 mutations⁵
- Patients have a median age of 63 years and mainly adenocarcinoma histology; ~60% are non-smokers⁵
- Frequent metastatic sites at diagnosis involve the lungs, bones and pleura; brain metastases are present in ~20% of cases at diagnosis of advanced disease⁵
- There is an increased risk of thromboembolic events in these patients⁶
- These tumours often exhibit low TMB and PD-L1 levels, described as “cold tumours”⁷





TREATMENT

- Specific RET inhibitors (RETi) show high response rates and durability, with notable intracranial efficacy; older multi-tyrosine kinase inhibitors offer limited benefits and greater toxicity⁸⁻¹¹
- The LIBRETTO-431 trial is the first to prove a progression-free survival benefit for a RET inhibitor in a Phase 3 randomised trial compared with first-line standard of care¹²
- Immunotherapy is generally ineffective, though a minority may respond⁵
- Using RETi in a real-world cohort has shown improved overall survival vs no RETi⁵
- Hypertension, liver enzyme elevation and digestive effects are frequent side effects of both currently licensed specific RETi; drug-specific frequent side effects include neutropenia for pralsetinib and oedema for selpercatinib⁸⁻¹⁰
- At progression after RETi, acquired/secondary RET mutations were detected in 14% of patients and potential off-target gene alterations (bypass resistance) were identified in 42%, but cannot usually be targeted¹³
- Platinum-based chemotherapy is currently the standard of care after RETi¹⁴



RET fusion-positive NSCLC

EMERGING



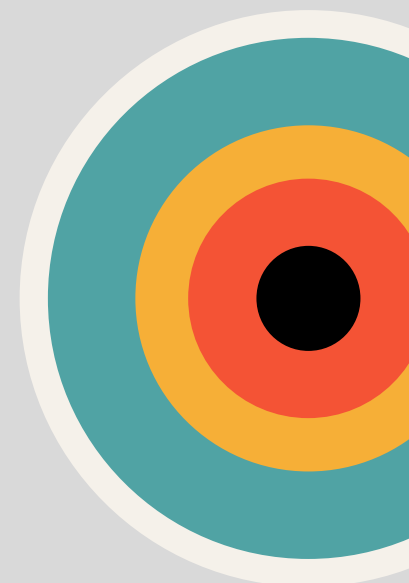
- Next-generation RET inhibitors, targeting secondary RET mutations, are currently in clinical trials, including LOXO-260, EP0031, TAS0953/HM06 and APS03118¹⁵⁻¹⁸
- These are designed to cover both solvent front mutations (RET p.G810X) occurring after existing selective inhibitors and gatekeeper mutations^{19,20}
- In the presence of an acquired bypass mechanism alteration, these treatments are less likely to be effective²¹
- As such, it would be helpful for other therapeutic drug classes such as ADCs to be tested in this setting – currently, no specific data on RET fusion-positive NSCLC are available
- In order to identify those rare patients who may benefit from PD-(L)1 inhibitors, predictive biomarkers would be needed⁷



References



1. [Singal G, et al. JAMA 2019;321:1391–1399](#)
2. [Wang R, et al. J Clin Oncol 2012;30:4352–4359](#)
3. [Furugaki K, et al. BMC Cancer 2019;19:301](#)
4. [Ju YS, et al. Genome Res 2012;22:436–445](#)
5. [Aldea M, et al. J Thorac Oncol 2023;18:576–586](#)
6. [Aldea M, et al. JAMA Oncol 2023;9:1583–1584](#)
7. [Offin M, et al. JCO Precis Oncol 2019;3:PO.18.00386](#)
8. [Gainor JF, et al. Lancet Oncol 2021;22:959–969](#)
9. [Griesinger F, et al. Ann Oncol 2022;33:1168–1178](#)
10. [Drilon A, et al. J Clin Oncol 2023;41:385–394](#)
11. [Desilets A, et al. Cancers \(Basel\) 2023;15:4146](#)
12. [Zhou C, et al. N Engl J Med 2023;389:1839–1850](#)
13. [Cooper AJ, et al. Poster presented at ASCO 2023 \(Abstract 9065\)](#)
14. National Comprehensive Cancer Network 2024. Available from: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450> (Accessed 19 January 2024)
15. NCT05241834. Updated 24 August 2023. Available from: <https://clinicaltrials.gov/study/NCT05241834> (Accessed 19 January 2024)
16. NCT05443126. Updated 10 January 2024. Available from: <https://clinicaltrials.gov/study/NCT05443126> (Accessed 19 January 2024)
17. NCT04683250. Updated 3 March 2023. Available from: <https://www.clinicaltrials.gov/study/NCT04683250> (Accessed 19 January 2024)
18. NCT05653869. Updated 15 June 2023. Available from: <https://clinicaltrials.gov/study/NCT05653869> (Accessed 19 January 2024)
19. [Solomon BJ, et al. J Thorac Oncol 2020;15:541–549](#)
20. [Subbiah V, et al. Ann Oncol 2021;32:261–268](#)
21. [Rosen EY, et al. Nat Commun 2022;13:1450](#)



Disclosures and funding



Specialising in the management of thoracic cancers, Professor Besse is Director of Clinical Research and Assistant Professor Aldea is a medical oncologist for the Thoracic Cancer and Precision Medicine Group at Gustave Roussy (Paris, France), one of the world's leading cancer hospitals.

All content in this KeyPoints post is based on the personal opinions of both doctors and does not represent the opinion of OncShare, Gustave Roussy or the funding organisation.

Disclosures

Professor Besse (past 2 years)

Advisory boards (to institution): AbbVie, BioNTech SE, Bristol Myers Squibb, Chugai Pharmaceutical, CureVac AG, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, PharmaMar, Regeneron, Sanofi-Aventis, Turning Point Therapeutics

Advisory (to institution): AbbVie, Eli Lilly, Ellipses Pharma Ltd, F. Hoffmann-La Roche Ltd, Genmab, Immunocore, Janssen, MSD, Ose Immunotherapeutics, Owkin, Taiho Oncology

Steering committee (to institution): AstraZeneca, BeiGene, Genmab, GlaxoSmithKline, Janssen, Ose Immunotherapeutics, PharmaMar, Roche-Genentech, Sanofi, Takeda

Speaker (to institution): AbbVie, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Hederax Dx, Janssen, MSD, Roche, Sanofi-Aventis, Springer Healthcare Ltd

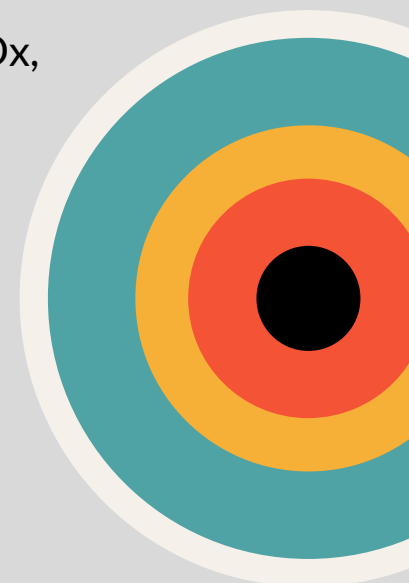
Assistant Professor Aldea

Funding for research from: Sandoz, Amgen, AstraZeneca

Consulting: Viatrix

Funding

Funding for this KeyPoints update came from OncShare Ltd.



About



OncShare

OncShare's mission is to utilise the power of social and digital media to spread important learning relating to precision oncology among as many oncologists as possible around the world, as quickly as possible.

Founded in the UK in 2023, OncShare recognises that precision oncology is ever-increasing in complexity and requires effective collaboration between all involved parties. To facilitate this, fast and efficient information sharing is vital, and this is our focus.

KeyPoints

A summary of the key points that oncologists need to know for a given biomarker/tumour type. Authored by experts, the simple concept behind *KeyPoints* is "if you, as the expert, had 5 minutes with a practising oncologist who is not as close to the developing science as you are, what would they need to know?"

Designed for consumption in 5 minutes or less, *KeyPoints* complements longer forms of independent medical education. References are included for those requiring further reading.

KeyPoints content is 100% independent medical education, funded directly by OncShare and/or by fully independent grants from the pharmaceutical industry.

Although not accredited, content is developed with a focus on accuracy, fairness and balance and aims to provide practical learning based on experts' experience, offering more than oncologists can get from guidelines alone.

As media is now globally accessible, *KeyPoints* is designed for a global audience, whilst recognising that practice can vary according to country, region and funding mechanism.