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KeyPoints

MICRO–LEARNING FOR ONCOLOGISTS

RET fusion-positive NSCLC

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

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3 slides, <5 mins

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RET fusion-positive NSCLC

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 management[5]
- Co-mutations may occur, especially TP53 mutations[5]
- Patients have a median age of 63 years and mainly adenocarcinoma histology; ~60% are non-smokers[5]
- Frequent metastatic sites at diagnosis involve the lungs, bones and pleura; brain metastases are present in ~20% of cases at diagnosis of advanced disease[5]
- There is an increased risk of thromboembolic events in these patients[6]
- These tumours often exhibit low TMB and PD-L1 levels, described as “cold tumours”[7]

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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 toxicity[8–11]
- 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 care[12]
- Immunotherapy is generally ineffective, though a minority may respond[5]
- Using RETi in a real-world cohort has shown improved overall survival vs no RETi[5]
- 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 selpercatinib[8–10]
- 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 targeted[13]
- Platinum-based chemotherapy is currently the standard of care after RETi[14]

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EMERGING

- Next-generation RET inhibitors, targeting secondary RET mutations, are currently in clinical trials, including LOXO-260, EP0031, TAS0953/HM06 and APS03118[15–18]
- 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 effective[21]
- 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 needed[7]

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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 Key*Points* 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)

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