RET-altered thyroid cancer: how selective inhibitors changed advanced disease

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Advanced thyroid cancers, particularly those driven by rearranged during transfection (RET) fusions or mutations, have historically presented a significant therapeutic challenge. Standard systemic therapies offered limited efficacy, leaving many patients with few viable options. The development of highly selective RET inhibitors has fundamentally altered this outlook, providing a targeted approach to a specific oncogenic driver.

KEY TAKEAWAYS

- The Pivot: Highly selective RET inhibitors offer a targeted therapeutic strategy for advanced RET-altered thyroid cancers, moving beyond conventional systemic treatments.
- The Data: These agents demonstrate substantial improvements in objective response rates and duration of response in patients with RET fusions or mutations.
- The Action: Clinicians should consider routine RET gene testing for patients with advanced thyroid cancer to identify those eligible for selective RET inhibitor therapy.

Thyroid cancer, while often indolent, can become aggressive and difficult to treat in its advanced forms. A subset of these aggressive thyroid cancers, including medullary thyroid cancer (MTC) and a proportion of differentiated thyroid cancers (DTC), are driven by alterations in the RET proto-oncogene. These alterations can manifest as RET fusions in DTC or specific RET mutations in MTC, leading to constitutive activation of the RET kinase pathway and uncontrolled cell proliferation. Identifying these specific genetic drivers is paramount for guiding treatment decisions, a concept increasingly central to modern oncology, as seen in targeted ADCs for advanced lung cancer.

Before the introduction of selective RET inhibitors, treatment options for advanced RET-altered thyroid cancer were largely limited to multi-kinase inhibitors (MKIs). While MKIs offered some benefit, their broad-spectrum activity often led to significant off-target toxicities, limiting their tolerability and overall clinical utility. This created a clear unmet need for more precise therapies that could specifically target the RET pathway with improved safety profiles.

The Mechanism of Selective RET Inhibition

RET is a receptor tyrosine kinase that plays a critical role in cell growth, differentiation, and survival. In normal physiological conditions, RET activation is tightly regulated. But in RET-altered thyroid cancers, fusions or mutations lead to ligand-independent activation of the kinase, driving oncogenesis. These alterations are distinct and require specific therapeutic approaches.

Selective RET inhibitors are small molecule drugs designed to potently and specifically inhibit the aberrant RET kinase activity. Unlike earlier MKIs, which target multiple kinases, these newer agents are engineered to have high selectivity

for RET. This precision aims to maximise anti-tumour efficacy while minimising off-target effects, thereby improving the therapeutic index for patients. The development mirrors similar advancements in other cancer types, where understanding specific genetic drivers has led to more effective and less toxic treatments.

Clinical Efficacy in RET-Altered Thyroid Cancer

The clinical development of selective RET inhibitors has focused on patients with advanced RET-fusion positive DTC and RET-mutant MTC. These patient populations often have limited treatment options and a poor prognosis with conventional therapies. The agents have demonstrated compelling efficacy across various measures in these settings.

In patients with RET-fusion positive DTC, selective RET inhibitors have shown substantial objective response rates. These responses are often durable, meaning patients experience a prolonged period of disease control. The agents have also demonstrated efficacy in patients who have previously progressed on MKIs, highlighting their potential to overcome resistance mechanisms associated with less selective treatments. This represents a significant step forward, offering a new standard of care for a challenging disease subset. For a deeper dive into oncology management, the Oxford Handbook of Oncology (4th ed) provides a concise reference.

Similarly, in patients with advanced RET-mutant MTC, selective RET inhibitors have delivered impressive clinical activity. MTC is notoriously difficult to treat, and the identification of specific RET mutations as drivers has opened new therapeutic avenues. The drugs have induced high response rates, including in patients with aggressive disease and those who have failed prior systemic therapies. This efficacy extends to both treatment-naive patients and those with prior exposure to MKIs, indicating broad applicability within the RET-mutant MTC population.

Safety and Tolerability Profiles

One of the key advantages of selective RET inhibitors over older MKIs is their improved safety and tolerability profile. While all systemic cancer therapies carry the risk of adverse events, the selectivity of these agents generally translates to a more manageable toxicity spectrum. Common adverse events include fatigue, gastrointestinal disturbances, and hypertension, which are typically low-grade and manageable with supportive care or dose modifications.

But clinicians must remain vigilant for specific adverse events that, while less common, can be more serious.

These may include hepatotoxicity, QT prolongation, and haemorrhagic events. Regular monitoring of liver function, electrocardiograms, and coagulation parameters is essential to ensure patient safety. The improved tolerability compared to MKIs means more patients can remain on treatment for longer durations, potentially translating to sustained clinical benefit. This careful balance of efficacy and safety is a constant consideration in oncology, as seen in discussions around intensified blockade for prostate cancer.

Identifying Eligible Patients

The success of selective RET inhibitors hinges entirely on accurate patient selection. This requires comprehensive genomic profiling to identify RET fusions in DTC or specific RET mutations in MTC. Next-generation sequencing (NGS) is the preferred method for detecting these alterations, as it can simultaneously identify multiple genomic aberrations and provide a detailed molecular landscape of the tumour. Tissue biopsy remains the gold standard for obtaining tumour material, but liquid biopsies (circulating tumour DNA) are also emerging as a valuable tool, particularly in cases where tissue is limited or inaccessible.

The importance of early and accurate RET testing cannot be overstated. Patients with advanced thyroid cancer should

undergo genomic profiling at diagnosis or at the time of disease progression to determine their eligibility for these targeted therapies. Delaying testing can mean missing a critical window for effective treatment, particularly given the aggressive nature of some RET-altered thyroid cancers. This proactive approach to molecular diagnostics is becoming standard practice across many tumour types, reflecting a broader shift towards precision medicine in oncology.

Challenges and Future Directions

Despite the significant advances, challenges remain. Resistance to selective RET inhibitors can develop over time, often through the emergence of on-target secondary mutations or activation of bypass pathways. Understanding these resistance mechanisms is crucial for developing subsequent therapeutic strategies, such as next-generation RET inhibitors or combination therapies, as the ability to maintain long-term disease control is at stake. Research is ongoing to identify biomarkers that predict response or resistance, which could further refine patient selection and treatment sequencing.

Another area of ongoing investigation is the role of selective RET inhibitors in earlier disease settings or in combination with other modalities, such as chemotherapy or immunotherapy. While current approvals are primarily for advanced disease, exploring their utility in adjuvant or neoadjuvant settings could potentially improve long-term outcomes for a broader range of patients. The field continues to evolve rapidly, with new data constantly informing clinical practice. The journey from understanding a genetic alteration to developing a highly effective targeted therapy highlights the power of precision oncology in transforming patient care.

The open-label design of many initial studies is an obvious caveat, but the magnitude of response observed in these heavily pre-treated populations is compelling. The trials were not powered to detect differences in rare subgroups, and that gap matters for clinicians managing complex cases. Whether benefits extend to patients with less advanced disease remains unclear, requiring further investigation. The next trials need to show how these agents perform in combination with other therapies, and how to manage resistance when it inevitably emerges.

> **CLINICAL IMPLICATIONS**
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> The arrival of selective RET inhibitors has fundamentally reshaped the management of advanced RET-altered thyroid cancer. For too long, these patients faced limited options and the often-debilitating side effects of broad-spectrum multi-kinase inhibitors. Now, we have agents that specifically target the oncogenic driver, delivering impressive response rates with a far more tolerable safety profile.
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> This shift mandates a change in clinical practice: routine and comprehensive genomic profiling for all patients with advanced thyroid cancer is no longer optional. Identifying RET fusions or mutations early means patients can access therapies that offer genuine disease control, potentially extending their lives and improving their quality of life. The era of 'one size fits all' systemic therapy for these specific thyroid cancers is definitively over.
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> But the industry must continue to invest in understanding resistance mechanisms. As with many targeted therapies, patients eventually progress. The next wave of research needs to focus on second-generation inhibitors or rational combination strategies to maintain long-term disease control. For clinicians, this means staying abreast of evolving resistance patterns and new therapeutic approaches as they emerge.
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> The success of these inhibitors also reinforces the broader principle of precision oncology. When we understand the molecular underpinnings of a cancer, we can develop highly effective treatments. This

> approach should serve as a blueprint for other difficult-to-treat cancers where specific drivers can be identified and targeted.

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