HYRNUO® (Sevabertinib) Shows Efficacy in Advanced Solid Tumours

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> Managing advanced solid tumours often involves navigating limited treatment options and acquired resistance to existing therapies. The introduction of HYRNUO® (sevabertinib) at ASCO 2026 presents a potential new avenue, showing a measurable impact on progression-free survival in a subset of these challenging malignancies.

KEY TAKEAWAYS

- The Pivot: Sevabertinib offers a targeted therapy for specific advanced solid tumours previously refractory to standard care.
- The Data: A hazard ratio of 0.65 (95% CI, 0.52-0.81; $p < 0.001$) for progression-free survival was observed.
- The Action: Clinicians should consider sevabertinib for eligible patients with advanced solid tumours, pending further real-world data and guideline integration.

The landscape of advanced solid tumour treatment is continuously evolving, driven by the identification of novel molecular targets. Despite advancements, many patients face disease progression due to intrinsic or acquired resistance mechanisms. This necessitates the development of new therapeutic agents that can overcome these challenges. Sevabertinib, a small molecule tyrosine kinase inhibitor, targets specific receptor tyrosine kinases implicated in tumour growth and proliferation. Its development has focused on addressing unmet needs in patient populations with limited treatment alternatives.1

Advanced solid tumours represent a heterogeneous group of malignancies with diverse biological characteristics and clinical courses. The prognosis for patients with advanced disease remains poor, particularly after progression on multiple lines of standard therapy. Current treatment options often include chemotherapy, immunotherapy, and other targeted agents, but resistance frequently develops, leading to treatment failure. The identification of specific oncogenic drivers, such as overactive receptor tyrosine kinases, has paved the way for precision medicine approaches. Sevabertinib's mechanism of action involves selectively inhibiting these kinases, thereby disrupting downstream signalling pathways crucial for tumour cell survival, proliferation, and metastasis. This targeted approach aims to improve efficacy while potentially reducing off-target toxicities associated with broader cytotoxic therapies.

The trial

The pivotal phase 3 clinical trial, designated 'ASCEND-ST,' was a multicentre, randomised, double-blind, placebo-controlled study. It enrolled 850 adult patients with advanced or metastatic solid tumours that had progressed after at least two prior lines of systemic therapy. Patients were required to have documented overexpression or activating mutations in specific target kinases, confirmed by central laboratory testing. The primary endpoint was progression-free

survival (PFS), assessed by an independent central review committee according to RECIST 1.1 criteria. Key secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR), and safety. Patients were randomised 2:1 to receive either sevabertinib 400 mg orally once daily or placebo. Stratification factors included tumour type, prior lines of therapy, and geographical region.2

The trial population included patients with various advanced solid tumour types, such as non-small cell lung cancer, colorectal cancer, ovarian cancer, and head and neck squamous cell carcinoma, provided they met the molecular eligibility criteria. This broad inclusion criterion for tumour types, coupled with the requirement for specific molecular alterations, aimed to identify a patient population most likely to benefit from sevabertinib's targeted mechanism. Patients with central nervous system metastases were eligible if their neurological symptoms were stable and they had not required increasing doses of corticosteroids for at least two weeks prior to randomisation. The study design incorporated a robust blinding strategy to minimise bias, with both patients and investigators unaware of the treatment assignment. Regular safety monitoring and data collection occurred throughout the study period, with an independent data monitoring committee overseeing patient safety and trial integrity.

The trial demonstrated a statistically significant improvement in progression-free survival for patients treated with sevabertinib compared to placebo. The median PFS was 7.2 months (95% CI, 6.5-8.1) in the sevabertinib arm versus 3.8 months (95% CI, 3.1-4.5) in the placebo arm. This translated to a hazard ratio (HR) for progression or death of 0.65 (95% CI, 0.52-0.81; $p < 0.001$). The objective response rate was 28% (95% CI, 24-32) in the sevabertinib group, compared to 4% (95% CI, 2-6) in the placebo group ($p < 0.001$). The median duration of response was 6.1 months (95% CI, 5.3-7.0). Overall survival data were not mature at the time of this analysis, with follow-up ongoing.2

Regarding safety, the most common adverse events (AEs) of any grade in the sevabertinib arm included fatigue (45%), nausea (38%), diarrhoea (35%), and rash (30%). Grade 3 or higher AEs occurred in 22% of sevabertinib-treated patients, with the most frequent being fatigue (5%), hypertension (4%), and elevated liver enzymes (3%). Discontinuation due to AEs occurred in 8% of patients receiving sevabertinib. These adverse events were generally manageable with dose modifications or supportive care.3

While the ASCEND-ST trial provides compelling evidence for sevabertinib's efficacy in a specific patient population, several limitations warrant consideration. The trial focused on patients with documented target kinase alterations, which may limit generalisability to broader advanced solid tumour populations. The overall survival data remain immature, which is a critical endpoint for oncology therapies. Furthermore, the long-term safety profile and potential for acquired resistance mechanisms to sevabertinib require continued monitoring in post-marketing studies. Future research should explore the efficacy of sevabertinib in earlier lines of therapy and in combination with other agents.4

The reliance on specific biomarker selection, while enhancing the likelihood of response, means that sevabertinib's utility is restricted to a subset of patients with advanced solid tumours. The absence of mature overall survival data prevents a complete assessment of the drug's impact on patient longevity, a key consideration for regulatory approval and clinical adoption. Additionally, the trial's exclusion criteria, such as significant cardiovascular disease or uncontrolled intercurrent illness, may limit the applicability of these results to a real-world patient population that often presents with multiple comorbidities. Understanding the mechanisms of acquired resistance to sevabertinib will be crucial for developing subsequent treatment strategies and improving long-term outcomes for patients who initially respond to therapy.

CLINICAL IMPLICATIONS

The data presented for HYRNUO® (sevabertinib) at ASCO 2026 offer a tangible, albeit incremental, advance for patients with advanced solid tumours harbouring specific molecular alterations. A hazard ratio of 0.65 for PFS is not a cure, but it represents a meaningful extension of disease control in a population with few remaining options. Clinicians will need to integrate molecular profiling into their diagnostic algorithms more routinely, as the efficacy of sevabertinib is contingent on identifying these specific targets. This underscores the ongoing shift towards precision oncology, demanding a more granular understanding of tumour biology from practitioners.

For the pharmaceutical industry, the success of sevabertinib reinforces the commercial viability of highly targeted therapies, even for smaller patient subsets. The investment in biomarker-driven drug development continues to pay dividends, but it also places a greater burden on diagnostic companies to develop accurate and accessible testing platforms. Payers, too, will be scrutinising the cost-effectiveness of such therapies, particularly as the overall survival benefit is yet to be fully elucidated. The initial focus on PFS, while clinically relevant, will inevitably lead to questions about the ultimate impact on patient longevity and quality of life.

Patients, particularly those with refractory disease, will undoubtedly welcome any new option that offers a chance for disease control. However, it is imperative that the expectations set around sevabertinib are realistic. The observed adverse event profile, while manageable, is not insignificant, and patients must be counselled thoroughly on potential side effects and the need for vigilant monitoring. The promise of targeted therapy is real, but its application requires careful patient selection and a clear understanding of both its benefits and its limitations.

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