PEAK Study Shows Novel Agent Improves PFS in Advanced GIST

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Advanced gastrointestinal stromal tumors (GIST) present a significant challenge in oncology, particularly following resistance to standard tyrosine kinase inhibitors. The PEAK study, presented at ASCO 2026, investigated a novel agent in this refractory setting, showing a statistically significant improvement in progression-free survival (PFS) compared to current standard of care.

KEY TAKEAWAYS

- The Pivot: A novel therapeutic agent offers a new treatment option for advanced GIST patients who have progressed on prior therapies.
- The Data: The PEAK study reported a hazard ratio for progression-free survival of 0.68 (95% CI, 0.57-0.81; $p < 0.001$).
- The Action: Clinicians should consider this agent for eligible patients with advanced GIST who have exhausted established treatment lines.

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract, typically driven by mutations in KIT or PDGFRA. While imatinib revolutionized GIST treatment, resistance inevitably develops, necessitating subsequent lines of therapy such as sunitinib and regorafenib. For patients progressing beyond these established agents, treatment options become increasingly limited, highlighting an unmet clinical need for effective and tolerable therapies.1 The incidence of GIST is estimated to be around 10-15 cases per million per year, with the majority of cases diagnosed in older adults, typically between 50 and 70 years of age. Approximately 80% of GISTs harbor activating mutations in KIT, while 5-10% have mutations in PDGFRA. These mutations lead to constitutive activation of receptor tyrosine kinases, driving tumor cell proliferation and survival. The PEAK study aimed to address this by evaluating a novel small molecule tyrosine kinase inhibitor, designed to target a broader spectrum of GIST-associated mutations, in patients with advanced GIST who had progressed on at least two prior lines of therapy.2

The PEAK Study Design and Findings

The PEAK study was a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial. It enrolled 350 patients with unresectable or metastatic GIST who had previously received and progressed on imatinib and at least one other approved tyrosine kinase inhibitor. Patients were randomized 2:1 to receive either the novel agent (233 patients) or placebo (117 patients), both in combination with best supportive care. Eligibility criteria included an ECOG performance status of 0-2, adequate organ function, and measurable disease according to RECIST 1.1. Patients with known primary resistance to imatinib due to specific KIT or PDGFRA mutations (e.g., KIT exon 9 or PDGFRA D842V) were not

excluded if they had received prior standard therapies. The novel agent's mechanism of action involves potent inhibition of multiple kinases implicated in GIST pathogenesis, including wild-type and mutant forms of KIT and PDGFRA, offering a potential advantage in overcoming resistance mechanisms. The primary endpoint was progression-free survival (PFS), assessed by independent central review according to modified RECIST 1.1 criteria. Key secondary endpoints included overall survival (OS), objective response rate (ORR), and safety.3

The trial demonstrated a statistically significant improvement in the primary endpoint of PFS. The median PFS was 6.2 months (95% CI, 5.5-7.1) in the novel agent arm compared to 2.8 months (95% CI, 2.1-3.4) in the placebo arm. This translated to a hazard ratio (HR) for progression or death of 0.68 (95% CI, 0.57-0.81; $p < 0.001$). The objective response rate was 18.5% (95% CI, 13.8-24.1) in the novel agent arm versus 1.7% (95% CI, 0.2-6.0) in the placebo arm ($p < 0.001$). While overall survival data were not mature at the time of this presentation, an early trend favored the novel agent.4

Regarding safety, the novel agent exhibited a manageable toxicity profile. The most common treatment-emergent adverse events (TEAEs) of any grade in the novel agent arm included fatigue (45%), nausea (38%), diarrhea (35%), and hand-foot skin reaction (30%). Grade 3 or higher TEAEs occurred in 32% of patients receiving the novel agent, with hypertension (8%), fatigue (6%), and hand-foot skin reaction (5%) being the most frequent. Discontinuations due to TEAEs occurred in 12% of patients in the novel agent arm compared to 3% in the placebo arm. No new or unexpected safety signals were identified. These adverse events are generally consistent with the known toxicity profiles of other tyrosine kinase inhibitors used in GIST, suggesting that the novel agent's safety profile is predictable and manageable with appropriate supportive care.5

The PEAK study provides evidence for the efficacy and safety of this novel agent in advanced GIST patients who have exhausted prior lines of therapy. While the PFS benefit is statistically significant, the absolute gain in median PFS is modest, reflecting the aggressive nature of refractory GIST. Further follow-up for overall survival is ongoing and will be critical for a comprehensive assessment of the agent's clinical utility. The study population was well-defined, focusing on a challenging patient group. However, the generalizability to patients with fewer prior lines of therapy or specific rare GIST mutations not well-represented in this cohort remains to be fully elucidated. For instance, the study did not specifically stratify patients by specific secondary resistance mutations, which could influence treatment response. Future research may explore combination strategies or earlier integration into treatment algorithms.6

CLINICAL IMPLICATIONS

The PEAK study's findings offer a tangible, albeit incremental, advance for patients with advanced GIST who have few remaining options. A median PFS gain of 3.4 months, while statistically significant, underscores the persistent challenge of managing highly refractory disease. Clinicians will need to carefully balance this modest benefit against the observed toxicity profile, particularly for patients with compromised performance status. This agent will likely find its niche as a fourth-line or later therapy, extending the treatment continuum for a population desperately in need of any effective intervention.

From an industry perspective, the development of targeted therapies for rare cancers like GIST, even with modest effect sizes, remains commercially viable due to orphan drug designations and premium pricing. The pharmaceutical company behind this novel agent will undoubtedly seek expedited approval, positioning it as a critical addition to the GIST armamentarium. However, the cost-effectiveness in relation to the absolute PFS

> gain will warrant scrutiny from payers and health technology assessment bodies, especially as more agents compete in this space.
> For patients, the prospect of an additional treatment option, even one that extends progression-free survival by a few months, can be profoundly meaningful. It offers more time, potentially with maintained quality of life, before disease progression necessitates a shift to palliative care. Patient advocacy groups will likely champion access to this therapy, emphasizing the dire prognosis in the absence of new treatments. The onus will be on prescribers to clearly communicate the realistic expectations of this therapy, ensuring patients understand both the benefits and the potential for adverse events.

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