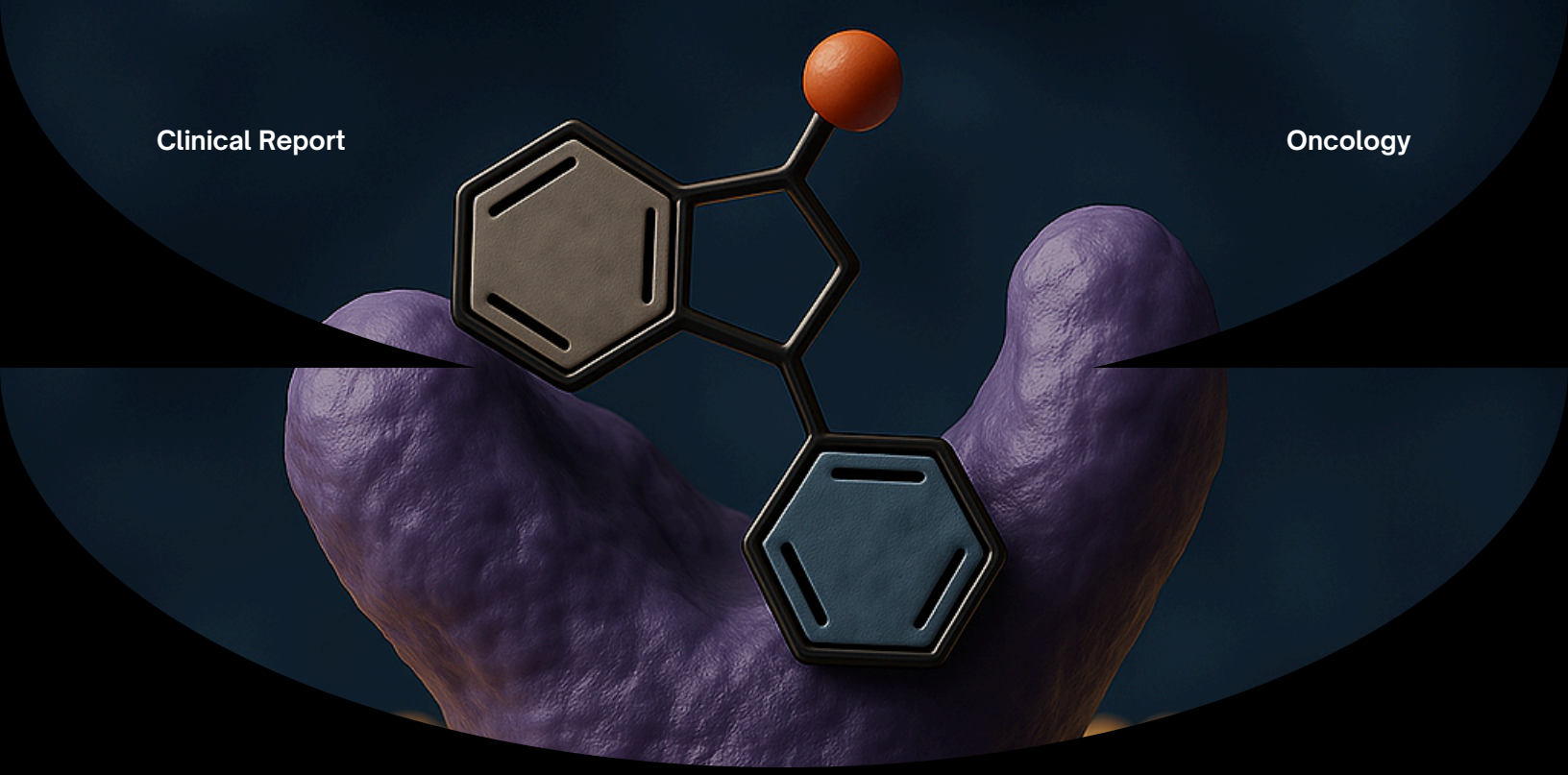

Combo - therapy

shows benefit in treating metastatic colorectal cancer

by Cliff Dominy PhD

A Phase 3 clinical trial has shown that adding a new tumour inhibitor to established immunotherapy meaningfully improves outcomes in patients with metastatic colorectal adenocarcinoma. This two-pronged approach may offer better treatment options to individuals with the immunotherapy-resistant form of the disease.

The STELLAR-303 results were presented at the 2025 European Society for Medical Oncology (ESMO) conference in Berlin, and simultaneously published in *The Lancet*.

An international team, led by US-based researchers, showed that their new kinase inhibitor zanzalintinib (Exelix Inc, California) when combined with monoclonal antibody atezolizumab, extends overall survival and reduces mortality risk in patients with drug-resistant colorectal cancer. The results were consistent across several clinical subgroups and were independent of genetic mutation status, liver metastases, prior therapy, or geographic location.

A new approach

The dual-therapy approach targeted tumor progression on two fronts:

- zanzalintinib; a small-molecule tyrosine kinase inhibitor - disrupts tumor growth signaling.
- atezolizumab; a monoclonal antibody - blocks PD-L1-mediated immune evasion.

Regorafenib, a broad-spectrum kinase inhibitor and current standard of care for colorectal cancer, served as the control arm in the trial.

Zanzalintinib (XL092) is a next-generation tyrosine kinase inhibitor developed by US-based Exelixis Inc. It targets several growth factors involved in tumour development. These targets have been implicated in tumor growth, angiogenesis, and immune evasion. By suppressing tumour growth, zanzalintinib may enhance the effectiveness of immune checkpoint inhibitors like atezolizumab.

Atezolizumab (Tecentriq), a monoclonal antibody made by Genentech, which targets the PD-L1 checkpoint inhibitor - a key player in tumour development. It was first approved by the U.S. Food and Drug Administration (FDA) in 2016 for the treatment of urothelial carcinoma. It has subsequently been approved for multiple cancers, including non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, and triple-negative breast cancer.

Regorafenib (Stivarga®), developed by Bayer, is an oral small molecule drug that inhibits multiple protein kinases involved in tumor growth, angiogenesis, metastasis, and immune evasion. It shuts down many of the targets that zanzalintinib, the test drug, is effective against. Approved for metastatic colorectal cancer (2012), gastrointestinal stromal tumors (2017), and hepatocellular carcinoma (2017), regorafenib offers a broad-spectrum approach to slowing disease progression in patients who have exhausted other treatment options and quickly established itself as the standard of care in this group.

STELLAR-303 was a global multicenter, open-label study that enrolled 901 adults from 16 countries with refractory metastatic colorectal adenocarcinoma. The primary endpoints were overall survival in the whole group and the subgroup that had not developed liver-metastases. Secondary outcomes included progression-free survival, objective response rate, and duration of response.

"STELLAR-303 is the first Phase 3 immunotherapy-based trial to show improved overall survival over standard care in microsatellite-stable colorectal cancer," Anwaar Saeed, MD,

Modest but meaningful results

The results reported one of the trial's primary endpoints - showing a 20% reduction in the risk of death in the intention-to-treat population.

Overall survival reached 10.9 months for patients receiving the dual therapy versus 9.4 months for those on regorafenib - the control arm. One- and two-year survival rates were 46% and 20%, respectively, compared with 38% and 10% in the controls.

The team presented preliminary data for the second primary endpoint - overall survival in the subgroup without liver metastases. The data showed preliminary overall survival numbers of 15.9 months vs. 12.8 months in the control group.

Side effects one can live with

Severe adverse events were reported by 59% of the dual-therapy participants and 37% of the controls. The most commonly reported side effects were hypertension (15% vs 9%), diarrhea (6% vs 2%), fatigue (6% vs 2%), and proteinuria (6% vs 2%). Of note, palmar-plantar erythrodysesthesia, or hand-foot syndrome, a common debilitating reaction to regorafenib was lower (16% vs 50%) in the therapy group.

The disease

Colorectal cancer is the second leading cause of cancer death in the United States, with about 154,000 new cases and 53,000 deaths expected every year. Approximately 95% of metastatic colorectal cancer cases are microsatellite stable (MSS), meaning they do not accumulate genetic mutations and can be very difficult to treat. Life expectancy for this group is between 6 and 9 months, highlighting the clinical importance of exploring these new therapeutic approaches.

Lead author J. Randolph Hecht, MD, of UCLA's Jonsson Comprehensive Cancer Center, in The Lancet article noted, "This approach opens a new therapeutic avenue for non–MSI-high colorectal cancer." Non–MSI high colorectal cancers are the genetically stable MSS tumours that are resistant to standard immunotherapies.

The way forward

The STELLAR-303 results join a growing list of dual therapies, which combine a small drug growth inhibitor with immunotherapy to deliver superior results compared to either approach alone. Exelixis hopes to submit a new drug application to the FDA by the end of 2025.

"These findings strengthen our belief that zanzalintinib, in combination with immune checkpoint blockade, has the potential to transform the treatment landscape for metastatic colorectal cancer," said Dana T. Aftab, PhD, Executive Vice President of Research and Development at Exelixis. "Our next steps focus on regulatory submission and expanding exploration across additional solid tumor types."

Reference

Hecht JR, Park YS, Tabernero J, et al. Zanzalintinib plus atezolizumab versus regorafenib in refractory colorectal cancer (STELLAR-303): a randomised, open-label, phase 3 trial. Lancet. 2025;406(10265):online only