Regorafenib, nivolumab, chemo combo found safe and effective for various cancers, heading to phase 3 trial

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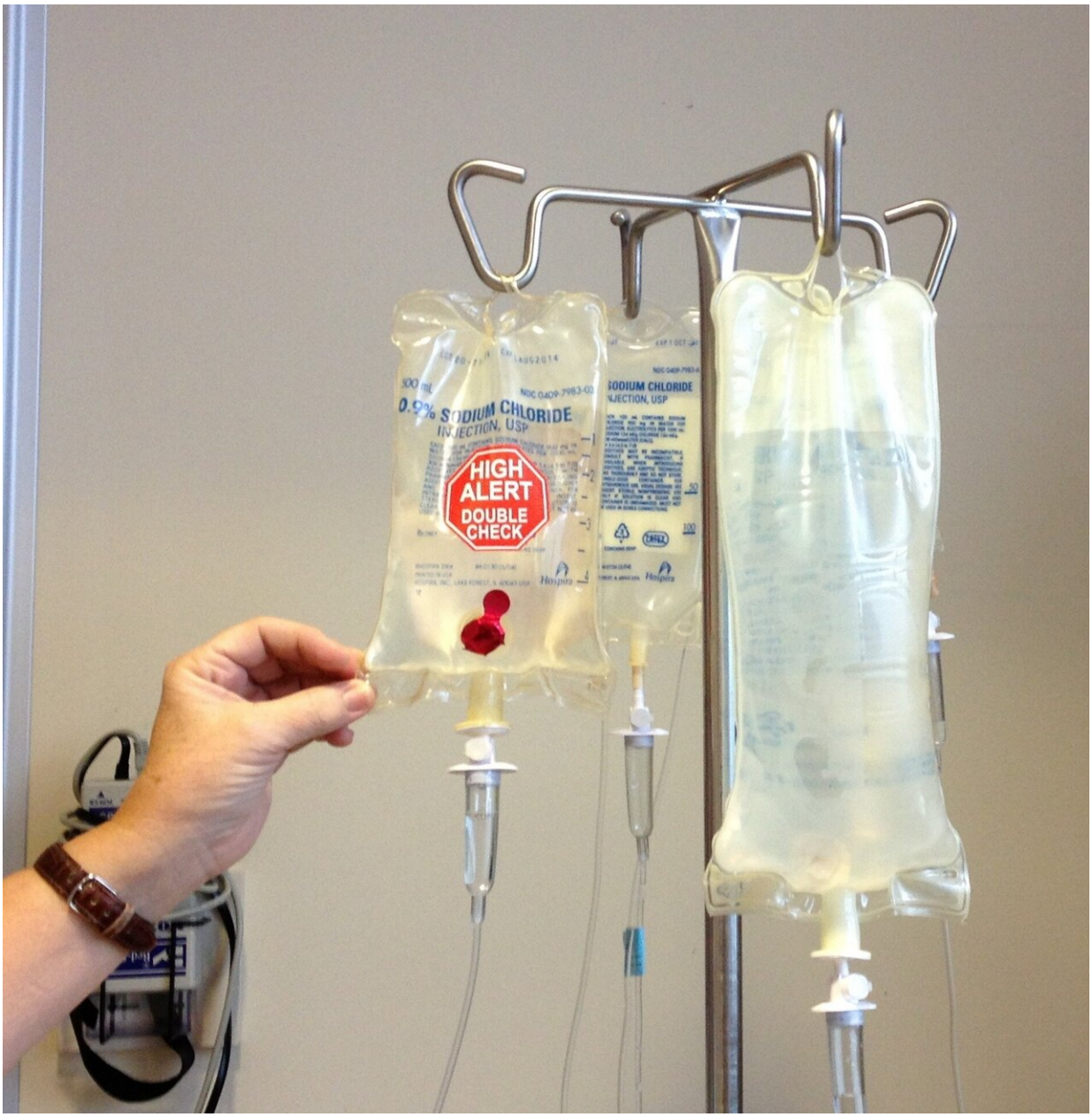

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Researchers at Memorial Sloan Kettering Cancer Center, New York, have concluded their phase 2 trial of chemotherapy in combination with the drugs nivolumab, and regorafenib.

The findings, "First-line regorafenib with nivolumab and chemotherapy in advanced oesophageal, gastric, or gastro-oesophageal junction cancer in the U.S.: a single-arm, single-centre, phase 2 trial," published in *The Lancet Oncology*, suggest that regorafenib and nivolumab with chemotherapy is safe and demonstrates some anti-tumor activity in patients with advanced oesophagogastric cancer. Based on these results, a randomized phase 3 clinical trial of the combination is planned.

In previous studies, each of the drugs has demonstrated potential effectiveness against oesophagogastric adenocarcinoma. Regorafenib has shown promise in improving outcomes in refractory oesophagogastric cancer, nivolumab (an anti-PD-1 antibody) has shown benefit in combination with chemotherapy, and chemotherapy itself is a standard treatment option. Combining these agents was expected to enhance the overall efficacy of the treatment, potentially providing better results.

Despite the initial benefits of immunotherapy (like nivolumab) and chemotherapy in treating oesophagogastric cancer, many patients eventually develop therapeutic resistance. The addition of regorafenib, which can modulate the tumor microenvironment and enhance immune responses was a strategic approach to potentially overcome or delay the development of resistance.

Nivolumab is an immune checkpoint inhibitor that can activate the patient's own immune system to target cancer cells. Regorafenib, in addition to its direct anti-tumor effects, can enhance the function of natural killer cells and $CD8^+$ T cells while inhibiting immunosuppressive factors produced by the tumor.

Oesophagogastric cancer is the second-leading cause of cancer-related deaths, resulting in approximately 1.3 million fatalities annually. Many patients are diagnosed with a metastatic form of disease, which is challenging to treat effectively as it spreads to various regions in the

body.

The trial was conducted at the Memorial Sloan Kettering Cancer Center with a final sample size of 35 patients. Participants received a combination treatment regimen, including FOLFOX chemotherapy, nivolumab, and oral regorafenib. The primary endpoint was 6-month progression-free survival, and safety was assessed in all patients who received at least one dose of any study treatment.

At the 6-month assessment, 25 of the 35 evaluable patients (71%) were progression-free, meeting the primary endpoint, an 18% improvement over historically derived control of 53%.

Follow up assessments conducted approximately 18 months later revealed the most common adverse event was fatigue (92% of patients). Serious adverse events occurred in 26% of patients, which were acute kidney injury (8%), hepatotoxicity (5%), sepsis (5%), dry skin, pruritus, or rash (3%), nausea (3%), and gastric perforation (3%). There were no treatment-related deaths.

More information: Samuel L Cytryn et al, First-line regorafenib with nivolumab and chemotherapy in advanced oesophageal, gastric, or gastro-oesophageal junction cancer in the USA: a single-arm, single-centre, phase 2 trial, *The Lancet Oncology* (2023). DOI: 10.1016/S1470-2045(23)00358-3

Kazuhiro Shiraishi et al, Combination immunotherapy in chemotherapy in gastric cancer, *The Lancet Oncology* (2023). DOI: 10.1016/S1470-2045(23)00404-7