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TARGETED THERAPY

Leveraging ADCC to enhance anti-HER2 therapy

Outcomes of patients with HER2+ breast or gastroesophageal cancer are greatly improved with standard anti-HER2 antibody therapies, principally trastuzumab; however, resistance and disease relapse are common. The results of a first-in-human phase I study of a novel anti-HER2 antibody, margetuximab, indicate that enhanced immune-system engagement via antibody-dependent cell-mediated cytotoxicity (ADCC) might further improve outcomes.

ADCC is triggered by the binding of antibodies to Fc receptors on immune effector cells. As lead author Yung-Jue Bang explains, "retrospective data have revealed unfavourable outcomes of trastuzumab treatment in patients expressing low-affinity alleles of the CD16A and CD32A Fc receptors, suggesting a role for ADCC in the antitumour activity of this agent; notably, most people are heterozygous or homozygous for these low-affinity isoforms." He adds, "margetuximab has been Fc-modified to bind all allelic forms of CD16A and CD32A with increased affinity and, thus, to have greater potential to induce ADCC."

Margetuximab was evaluated in 66 patients with HER2+ breast or gastric cancer. A maximum tolerated dose was not reached and the drug was well tolerated, with mostly grade ≤2 adverse events, each at a frequency of <24%. Importantly, Bang emphasizes, "margetuximab, as a monotherapy, was active in these patients, two-thirds of whom had received prior anti-HER2 therapy." Among 60 response-evaluable patients, the partial response and disease-stabilization rates were 12% and 50%, respectively; 23 of 30 women with breast cancer (78%) had tumour shrinkage, some for >30 weeks.

Margetuximab is currently in phase II and phase III testing, in combination with an anti-PD-1 antibody for the second-line treatment of patients with HER2+ gastroesophageal cancer, and in women with heavily pretreated HER2+ metastatic breast cancer, respectively. Bang concludes, "we hope that margetuximab will overcome failures with trastuzumab, owing to its potential to enhance ADCC while retaining antagonistic activity on HER2."

David Killock

"margetuximab …was active in these patients, two-thirds of whom had received prior anti-HER2 therapy"

ORIGINAL ARTICLE Bang, Y. J. *et al.* First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors. *Ann. Oncol.* http://dx.doi.org/10.1093/annonc/mdx002 (2017)