Combination HER2-targeted therapy effective in heavily pretreated HER2-positive colorectal cancer patients

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A combination of two HER2-targeted therapies, trastuzumab (Herceptin) and lapatinib (Tykerb), showed clinical benefit in patients with heavily pretreated HER2-positive metastatic colorectal cancer, according to final results from the phase II clinical trial HERACLES, presented here at the AACR Annual Meeting 2017, April 1-5.

"Amplification and mutations in the gene HER2 are found in 6-8 percent of RAS/RAF-wild type colorectal cancers [cancers in which the RAS/RAF genes are not altered]," said Salvatore Siena, MD, professor of medical oncology at Università degli Studi di Milano, and director of Niguarda Cancer Center at Grande Ospedale Metropolitano Niguarda in Milan, Italy. RAS/RAF-wild type colorectal cancers account for about 60 percent of colorectal cancers.

Extensive preclinical studies conducted by Livio Trusolino, MD, at Candiolo Cancer Institute and University of Turin, Italy, and by Siena and their teams in the past had demonstrated that shutting down the HER family of proteins through multiple mechanisms is necessary for effectiveness against HER2-positive colorectal cancer.

On the basis of these preclinical studies, Siena and colleagues initiated the HERACLES clinical trial with two cohorts of patients with heavily pretreated metastatic colorectal cancer: In cohort A (L+T), patients received a combination of trastuzumab, a monoclonal antibody that

targets HER2, and lapatinib, a HER1/HER2 tyrosine kinase inhibitor. In cohort B (P+T-DM1), patients received a combination of pertuzumab (Perjeta), another monoclonal antibody that targets HER2, and T-DM1 (Kadcyla), an antibody-drug conjugate that pairs trastuzumab with the cytotoxic drug emtansine.

"Final results from cohort A showed that the L+T combination resulted in a 70 percent clinical benefit with an overall objective response rate (ORR) of 30 percent. These are very positive results, bearing in mind that these patients had received an average of five previous treatments," Siena said. ORR was 50 percent in patients with tumors with highly amplified HER2, he noted.

Interim results from this portion of the clinical trial were published last year in *The Lancet Oncology*.

All patients in this trial had RAS-wild type tumors that were HER2-positive and refractory to standard of care treatments, including the EGFR inhibitors cetuximab (Erbitux) or panitumumab (Vectibix). At data cutoff (February 28, 2017), 10 of the 33 patients in cohort A achieved an objective response, which included two complete responses and eight partial responses; 13 had stable disease. Six patients experienced grade 3 adverse events.

The two patients who had a complete response continue to be disease-free for one and almost four years, respectively, since treatment initiation, according to Siena. "Both had tumors refractory to cetuximab and had become resistant to all standard chemotherapies. This means that HER2-targeted therapy can be a potential stand-alone, low-toxicity treatment approach for this patient population," he added.

"It is also clear from our results that HER2 amplification is both a positive predictor of response to anti-HER2 treatment and a negative

predictor of response to anti-EGFR therapy," Siena noted.

Historically, the response rate for metastatic colorectal cancer patients after second-line treatment is less than 5 percent with chemotherapy, and about 10 percent in unselected patients to 20 percent in RAS/RAF wild type patients with anti-EGFR therapy, Siena noted.

The team has enrolled 10 patients in cohort B, so far. Of the eight patients who received P+T-DM1 and are evaluable for response, seven had a clinical benefit (with tumor shrinkage); of those, two have already met the RECIST objective response criteria, Siena said.

"We believe that HERACLES demonstrated the efficacy of HER2-targeting because the right patients were selected for the right treatment," Siena said. "We suggest that oncologists determine HER2 status at diagnosis of metastatic disease in colorectal cancer patients, and collect information about anti-EGFR response in HER2-positive cases."

A limitation to the study is that the HER2-targeted therapy combinations were tested only against colorectal cancer tumors with HER2 amplifications but not against those with HER2 mutations, Siena noted.

More information: Andrea Sartore-Bianchi et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial, *The Lancet Oncology* (2016). DOI: 10.1016/S1470-2045(16)00150-9

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