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To interview Salvatore Siena, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896 (office) or 267-250-5441 (cell). For a photo of Siena, click here. Visit our newsroom.

Combination HER2-targeted Therapy Effective in Heavily Pretreated HER2-positive Colorectal Cancer Patients

WASHINGTON — 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.
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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.

This study was funded by Associazione Italiana per la Ricerca sul Cancro; Roche and Novartis provided study drugs free of charge. Siena is a clinical investigator and advisory board member for Amgen, Bayer, Celgene, Eli Lilly, Merck, Merrimack, Novartis, Roche, and Sanofi.

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Abstract: CT005

Presentation Session: CTSY01 - Precision Medicine Clinical Trials, Sunday, April 2, 12:45-3 p.m. ET, Ballroom C, Level 3

Title: Final results of the HERACLES trial in HER2-amplified colorectal cancer

Authors: Salvatore Siena¹, Andrea Sartore-Bianchi¹, Livio Trusolino², Cosimo Martino², Katia Bencardino¹, Sara Lonardi³, Vittorina Zagonel¹, Francesco Leone², Erika Martinelli⁴, Fortunato Ciardiello⁴, Patrizia Racca⁵, Alessio Amatu¹, Laura Palmeri¹, Emanuele Valtorta¹, Silvia Ghezzi¹, Angelo Vanzulli¹, Daniele Regge², Silvio Veronese¹, Alberto Bardelli², Silvia Marsoni². ¹Grande Ospedale Metropolitano Niguarda, Milano, Italy; ²Fondazione del Piemonte per l'Oncologia IRCCS, Candiolo (Torino), Italy; ³Istituto Oncologico Veneto - IRCCS, Padova, Italy; ⁴Seconda Università degli Studi di Napoli, Napoli, Italy; ⁵AOU Città della Salute e della Scienza di Torino, Torino, Italy

Background HER2 amplification is found in 5% of RAS wild type (RASWT) metastatic colorectal cancer (mCRC). Dual HER2 blockade with trastuzumab (T) and lapatinib (L), but not treatment with either drug alone, led to remarkable inhibition of tumor growth in patient-derived tumorgrafts of HER2-amplified mCRC. CRC-specific criteria for HER2 positivity by immunohistochemistry (IHC) and in situ hybridization (ISH) were defined retrospectively in 256 CRC paraffin embedded samples (HERACLES DGX criteria). The ensuing diagnostic algorithm was utilised to screen 1299 HER2-positive tumors for therapeutic targeting in patients in the HERACLES phase 2 trial.

Methods HERACLES was conducted at 4 Italian centres. Eligibility criteria were: RASWT exon 2, HER2 positivity, refractoriness to standard of care (including cetuximab or panitumumab), PS-ECOG ≤ 1, and measurable. HER2 positivity was defined by IHC and ISH according to HERACLES DGX criteria. Patients (PTS) received T i.v. at 4 mg/kg loading dose followed by 2 mg/kg weekly, and L p.o. at 1000 mg daily, until progression. The primary endpoint was the objective response rate, assessed by independent central review. Secondary endpoints were progression-free survival and safety. The study was 85% powered to detect an objective response rate of ≥30% with a one-sided alpha level of 0.05
Combination HER2-targeted Therapy Effective in Heavily Pretreated HER2-positive Colorectal Cancer Patients

Page 4 of 4

(EudraCT, number 2012-002128-33).

**Findings** Between August 27, 2012, and December 31, 2016, 69/1299 (5.3%) RASWT PTS were found HER2-positive. Of these, 33 were enrolled in HERACLES, and evaluable for response. At data cut-off (December 31, 2016), 10 (30.3%, 95% CI 17-47) of 33 heavily refractory PTS (median 5 prior regimens), achieved an objective response (2 complete and 8 a partial responses). 13 (39.3%, 95% CI 24-56) of 33 PTS had stable disease (SD) for a disease control rate of 70% (95% CI 52-82). Toxicity was mild with six (18%) of 33 PTS experiencing grade-3 side effects: fatigue (4), skin rash (1) elevated bilirubin (1). No drug-related SAEs were observed.

**Interpretation** HERACLES results prove that targeting HER2 is a successful therapeutic strategy in treatment-refractory HER2-positive mCRC patients, which can be easily implemented in clinical practice.

**Funding** Associazione Italiana Ricerca Cancro (AIRC), Fondazione Oncologia Niguarda Onlus and Roche.