Blood test for vascular endothelial growth factor-A (VEGF-A) and transforming growth factor-β1 (TGF-β1) prior to treatment could help determine tailored treatment options for esophageal cancer patients

San Francisco, September 14, 2014—A blood test may be beneficial in indicating neoadjuvant treatment regimens for patients with esophageal squamous cell carcinoma (ESCC), according to research presented today at the American Society for Radiation Oncology's (ASTRO's) 56th Annual Meeting. Results of a nine-year study of patients undergoing concurrent chemotherapy and radiotherapy (CCRT) for esophageal cancer show that levels of two proteins found in the body, vascular endothelial growth factor-A (VEGF-A) and transforming growth factor-β1 (TGF-β1), indicate patients' pathological response and disease-free survival rates.

In order for a cancer to metastasize, the growth of a new network of blood vessels is necessary. This process of forming new blood vessels is called angiogenesis. Tumor angiogenesis is the proliferation of a network of blood vessels that penetrates into cancerous growths, supplying nutrients and oxygen, and removing waste products. VEGF-A plays a crucial role in facilitating tumors to form their supplying vessels needed for growth and metastasis.

TGF-β1 contributes to tumor invasion and systemic tumor spread, and overexpression of TGF-β1 has

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Page **1** of **5**

been reported as a negative predictor in esophageal cancer.

This study evaluated serum (blood) samples of 103 total patients with esophageal squamous cell carcinoma (ESCC) from 2004 to 2013. All patients received preoperative CCRT (taxane-/5-fluorouracil-based chemotherapy and 40 Gy dose of radiation therapy) prior to esophagectomy (surgical removal of a part of the esophagus).

Serum samples were collected from patients before and within one month of completion of CCRT. Researchers first used a proximity ligation assay (PLA) technique to screen for 15 serum biomarkers in 79 patients to evaluate the biomarkers' association with pathological tumor regression on surgery and survival. (A biomarker is a measurable indicator of disease state and can serve as a parameter to measure the progress of disease or the effects of treatment.)

The biomarkers significantly associated with pathological response (PathR) and survival rates were further analyzed by traditional enzyme-linked, immunosorbent assay (ELISA), a wet-lab test that uses antibodies and color change to identify a substance, to confirm initial biomarker findings by PLA in the total group of 103 patients. Associations between serum levels of biomarkers and clinical factors correlating with PathR, disease-free survival (DFS) and overall survival (OS) were evaluated by the Analysis Of Variance (ANOVA) and log-rank tests.

Researchers found that patients with high VEGF-A were less likely to achieve complete tumor regression (a decrease in the size of a tumor or in the extent of cancer in the body), and that the survival rates were lower among patients who had high VEGF-A and high TGF-β1 levels before treatment. With a median follow-up of 33.7 months, the median DFS for the entire patient group was 21.9 months, and the median OS was 42.3 months. Following CCRT, 38 patients (37 percent) had complete tumor disappearance, 44 (43 percent) had minimal disease, and 21 (20 percent) had gross residual tumor at the time of their surgery.

On ELISA, both pre- and post-CCRT VEGF-A levels were significantly correlated with PathR (p=0.042 and 0.019, respectively). Patients with pre-treatment VEGF-A of less than 250 pg/ml were more likely to have pathologically complete response after CCRT (57.1 percent, or 20/35) compared to patients with VEGF-A of more than 250 pg/ml (26.5 percent or 18/68, p=0.002).

Patients with high pre-CCRT VEGF-A/TGF-β1 levels (≥ median) had significantly worse median DFS compared to those with lower levels, and worse median OS (19.2 months vs. 46.2 months, p=0.07). On multivariate analysis, PathR (p<0.05) and pre-CCRT high levels (≥median) of both VEGF-A and TGF-β1 (p<0.05) were independent factors for DFS, while only PathR (p<0.05) was a factor for OS.

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Page **2** of **5**

"Through the utilization of a specific blood test of serum biomarkers, we could potentially predict if a patient will have a favorable pathological response and outcome before radiotherapy," said senior study author Jason Cheng, MD, division chief of radiation oncology at National Taiwan University Hospital, and professor at National Taiwan University College of Medicine in Taipei, Taiwan. "Treatment could be tailored for patients in order to achieve better outcomes and/or fewer side effects. Our study showed that the serum levels of VEGF-A and TGF-β1 were significant only before treatment. This would allow us to individualize the neoadjuvant treatment regimens based on the pre-treatment serum levels of VEGF-A and TGF-β1."

The abstract, "Serum Vascular Endothelial Growth Factor-A and Transforming Growth Factor-β1 Can Predict Pathological Response and Disease-Free Survival of Esophageal Cancer Patients Treated with Neoadjuvant Chemoradiotherapy Followed by Esophagectomy," will be presented in detail during a scientific session at ASTRO's 56th Annual Meeting at 1:15 p.m. Pacific time on Sunday, September 14, 2014. To speak with Dr. Cheng, please call Michelle Kirkwood on September 14 – 17, 2014, in the ASTRO Press Office at the Moscone Center in San Francisco Center at 415-978-3503 or 415-978-3504, or email michellek@astro.org.

ASTRO's 56th Annual Meeting, to be held at the Moscone Center in San Francisco, September 14-17, 2014, is the nation's premier scientific meeting in radiation oncology. The 2014 Annual Meeting is expected to attract more than 11,000 attendees including oncologists from all disciplines, medical physicists, dosimetrists, radiation therapists, radiation oncology nurses and nurse practitioners, biologists, physician assistants, practice administrators, industry representatives and other health care professionals from around the world. Led by ASTRO President Bruce G. Haffty, MD, FASTRO, a radiation oncologist specializing in breast cancer, the theme of the 2014 Meeting is "Targeting Cancer: Technology and Biology," and the Presidential Symposium, "Local-regional Management of Breast Cancer: A Changing Paradigm," will feature Jay R. Harris, MD, FASTRO, and Thomas A. Buchholz, MD, FASTRO, to highlight recent practice-changing, landmark studies and current developments in the local-regional management of breast cancer. ASTRO's four-day scientific meeting includes presentation of up to four plenary papers, 360 oral presentations, 1,862 posters and 144 digital posters in more than 50 educational sessions and scientific panels for 20 disease-site tracks. Three keynote speakers will address a range of topics including oncologic imaging, biology and targeting in oncology, and human error and safety concerns: Hedvig Hricak, MD, PhD, Chair of the Department of Radiology and the Carroll and Milton Petrie Chair at Memorial Sloan Kettering Cancer Center; Frank McCormick, PhD, FRS, DSc (hon), Professor Emeritus and the David A. Wood Distinguished Professor of Tumor Biology and Cancer Research of the University of California at San Francisco Helen Diller Family

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Page **3** of **5**

Comprehensive Cancer Center; and Sidney Dekker, PhD, MA, MSc, Professor and Director of the Safety Science Innovation Lab at Griffith University, Brisbane, Australia.

ABOUT ASTRO

ASTRO is the premier radiation oncology society in the world, with more than 10,000 members who are physicians, nurses, biologists, physicists, radiation therapists, dosimetrists and other health care professionals that specialize in treating patients with radiation therapies. As the leading organization in radiation oncology, the Society is dedicated to improving patient care through professional education and training, support for clinical practice and health policy standards, advancement of science and research, and advocacy. ASTRO publishes two medical journals, International Journal of Radiation Oncology • Biology • Physics (www.redjournal.org) and Practical Radiation Oncology (www.practicalradonc.org); developed and maintains an extensive patient website, www.rtanswers.org; and created the Radiation Oncology Institute (www.roinstitute.org), a non-profit foundation to support research and education efforts around the world that enhance and confirm the critical role of radiation therapy in improving cancer treatment. To learn more about ASTRO, visit www.astro.org.

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Page **4** of **5**

2014 American Society for Radiation Oncology (ASTRO) 56th Annual Meeting
News Briefing, Tuesday, September 16, 2014, 2:00 p.m. Pacific time

Scientific Session: Sunday, September 14, 2014, 1:15 – 2:45 p.m. PT, the Moscone Center

10   **Serum Vascular Endothelial Growth Factor-A and Transforming Growth Factor-*β*1 Can Predict Pathological Response and Disease-Free Survival of Esophageal Cancer Patients Treated with Neoadjuvant Chemoradiotherapy Followed by Esophagectomy**

Author Block: Y. Chiang[1], J. Cheng[1,2], M. Graber[3], F. Hsu[1], C. Tsai[1], J. Lee[4], D. Chang[3], A. Koong[3], *[1]Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan, [2]Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan, [3]Stanford University, Stanford, CA, CA, [4]Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan*

Purpose/Objective(s): This study is aimed to identify serum biomarkers that predict treatment response and survival by screening proximity ligation assay (PLA) and verified enzyme-linked immunosorbent assay (ELISA) for patients with esophageal squamous cell carcinoma (ESCC) undergoing neoadjuvant concurrent chemoradiotherapy (CCRT) followed by esophagectomy.

Materials/Methods: One hundred and three patients with ESCC receiving CCRT consisting of taxane-/5-fluorouracil-based chemotherapy and 40Gy radiotherapy followed by surgery were prospectively enrolled. Serum samples were collected before and within 1 month after completion of CCRT. With the use of PLA, 15 biomarkers were simultaneously analyzed in the initial 79 patients. The biomarkers significantly associated with pathological response (PathR)/survival were verified by ELISA in an expanded group of 103 patients. Associations between serum levels of biomarkers and clinical factors correlating with PathR, disease-free survival (DFS), and overall survival (OS) were evaluated by ANOVA and log-rank tests.

Results: Following CCRT, 38 patients had pathologically complete response (37%), 44 microscopic (43%), and 21 macroscopic residual disease (20%). With a median follow-up of 33.7 months, the median DFS and OS were 21.9 months and 42.3 months, respectively. Among the 15 biomarkers screened by PLA, vascular endothelial growth factor-A (VEGF-A) and transforming growth factor-β1 (TGF-β1) were significantly associated with PathR and/or DFS. These biomarkers were further analyzed by ELISA to confirm initial biomarker findings by PLA. On ELISA, both pre- and post-CCRT VEGF-A levels were significantly correlated with PathR (p=0.042 and 0.019, respectively). Patients with pre-treatment VEGF-A less than 250 pg/ml were more likely to have pathologically complete response after CCRT than VEGF-A more than 250 pg/ml (20/35 vs. 18/68, p=0.002). Patients with high pre-CCRT VEGF-A/TGF-β1 levels (≥median) had significantly worse median DFS (9.7 months vs. 42.9 months, p=0.009) and worse median OS (19.2 months vs. 46.2 months, p=0.07). On multivariate analysis, PathR (p<0.05) and pre-CCRT high levels (≥median) of both VEGF-A and TGF-β1 (p<0.05) were independent factors for DFS, while only PathR (p<0.05) was for OS.

Conclusions: Pre-/post-CCRT serum VEGF-A may be used to predict PathR. Overall, ESCC patients with pre-treatment high serum VEGF-A and TGF-β1 had worse DFS.

Author Disclosure Block: **Y. Chiang:** None. **J. Cheng:** None. **M. Graber:** None. **F. Hsu:** None. **C. Tsai:** None. **J. Lee:** None. **D. Chang:** None. **A. Koong:** None.

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Page **5** of **5**