A subset of patients with metastatic melanoma achieves clinical benefit from combination of immunotherapy and radiation therapy

San Antonio, October 19, 2015— Immunotherapy combined with palliative radiation therapy (RT) for a subset of patients with metastatic melanoma reduces the growth and spread of the cancer, according to research presented today at the American Society for Radiation Oncology’s (ASTRO’s) 57th Annual Meeting.

Although melanoma is not the most common type of skin cancer, it is the most serious type. Stage IV melanoma indicates that the cancer has metastasized and spread through lymph nodes to distant sites in the body and/or to the body's organs. The liver, lungs, bones and brain are areas most frequently affected by these metastatic lesions. Immunotherapy—the use of medicines to stimulate a patient’s own immune system to recognize and destroy cancer cells more effectively—can be combined with other cancer therapies to aid in the treatment of stage IV melanoma. Ipilimumab is an immunotherapy approved for use in melanoma patients.

This phase II clinical trial is one of the first prospective clinical trials to report results from the treatment of metastatic melanoma with the combination of RT and systemic immunotherapy.
study, 20 patients with stage IV melanoma were treated with palliative RT and intravenous ipilimumab (3mg/kg) every three weeks, for a total of four treatment cycles. RT was initiated to one or two sites of metastatic melanoma within five days of the initial immunotherapy treatment. All patients had at least one nonirradiated (untreated) site of metastasis that could be used for assessment of response to therapy.

Patients had blood drawn during and after treatment to determine if there was evidence of an immune response developing in response to the therapy. Baseline tumor imaging studies were completed prior to treatment, and follow-up assessments were completed two-to-four weeks following the fourth dose of immunotherapy, and every three months until disease progression was detected. Response Evaluation Criteria in Solid Tumors (RECIST) and Immune Response Criteria (IRC) guidelines were used to score responses based on tumor measurements.

At a median follow-up of 38 weeks, 11 patients (55 percent) had an initial response to therapy—including complete and partial responses, as well as stable disease (SD) (meaning the cancer had not grown or spread). A complete response (CR) means that all signs of the cancer have disappeared. A partial response (PR) indicates that the cancer responded to treatment but did not disappear. Of the 11 patients who responded to the immunotherapy, one patient (9.1 percent) had an ongoing systemic CR to the combination therapy at a median follow-up of 39 weeks. Three patients had a PR to therapy for a median of 38 weeks (range 26-52 weeks), and 5 patients had SD as best response for a median of 36 weeks (range 26-76 weeks). The nine other patients had progressive disease as defined by RECIST on the first treatment scan.

Additionally, an analysis of blood markers in a subset of patients identified immune markers that appeared to correlate with responses. This initial data suggests that immune response markers in the peripheral blood may have promise to help to distinguish responders from nonresponders in the future, for purposes of facilitating better patient selection for treatment and early detection of potentially meaningful immune responses to therapy.

“We were impressed that half of the patients appeared to have benefited from this combination therapy, many with durable responses to therapy,” said Susan Hiniker, MD, lead author.
of the study and instructor in the Department of Radiation Oncology at Stanford University School of Medicine. “Current data shows that three patients have had an ongoing complete response to therapy, which suggests that the combination of immunotherapy plus radiation can be extremely effective in a subset of patients. Our results suggest that local radiation therapy can be safely and effectively combined as a component of in situ tumor vaccine strategies with the new potent class of immunotherapy drugs that are revolutionizing the treatment of metastatic melanoma and other difficult-to-treat cancers. These data also suggest that radiation may potentiate the effects of this new class of immune-targeting medication and support the design of larger trials to further investigate potential synergy between radiotherapy and immunotherapy in the treatment of cancer.”

The abstract, “A Prospective Clinical Trial Combining Radiation Therapy With Systemic Immunotherapy in Metastatic Melanoma,” will be presented in detail during a scientific session at ASTRO’s 57th Annual Meeting at 4:45 p.m. Central time on Tuesday, October 20, 2015. To speak with Dr. Hiniker, please call Nancy Mayes in ASTRO’s Press Office at the Henry B. González Convention Center, in San Antonio on October 18 – 21, 2015 at 210-258-8104 or 210-258-8105, or email press@astro.org.

ASTRO’s 57th Annual Meeting, being held at the Henry B. González Convention Center in San Antonio, October 18-21, 2015, is the nation’s premier scientific meeting in radiation oncology. The 2015 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 D. Minsky, MD, FASTRO, a radiation oncologist specializing in gastrointestinal cancers, Professor of Radiation Oncology, and the Frank T. McGraw Memorial Chair at The University of Texas MD Anderson Cancer Center, Houston, the theme of the 2015 Meeting is “Technology Meets Patient Care.” Dr. Minsky’s Presidential Symposium, “Multidisciplinary Management of Esophageal and Rectal Cancers,” will feature Leonard L. Gunderson, MD, MS, FASTRO, and Joel E. Tepper, MD, FASTRO, to highlight imaging, staging, genomics and data mining approaches, as well as the latest
advances in esophageal and colorectal cancer treatment. ASTRO’s four-day scientific meeting includes presentation of more than 2,100 abstracts: five plenary papers, 351 oral presentations, 1,609 posters and 171 digital posters in more than 53 educational sessions and 26 scientific panels for 20 disease-site tracks. Three keynote speakers will address a range of topics including cancer biology in radiation oncology, the essential roles of a physician, and patient safety: Arul Chinnaiyan, MD, PhD, Professor and Director, Michigan Center for Translational Pathology; Francisco G. Cigarroa, MD, Past President and Chancellor, University of Texas; and Gerald B. Hickson, MD, Senior Vice President and Assistant Vice Chancellor, Vanderbilt University Medical Center.

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 who 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 three medical journals, International Journal of Radiation Oncology • Biology • Physics (www.redjournal.org), Practical Radiation Oncology (www.practicalradonc.org) and Advances in Radiation Oncology (www.advancesradonc.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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Purpose/Objective(s): Local radiation therapy (RT) in combination with systemic anti-CTLA-4 immunotherapy has the potential to enhance the induction of systemic antimelanoma immune responses. The primary objective of this trial was to assess the safety and efficacy of combining ipilimumab with RT in patients with stage IV melanoma. Secondary objectives included assessment of induction of antimelanoma immune responses using laboratory correlative studies.

Materials/Methods: In our prospective, Phase 2 clinical trial, 20 (14 men, 6 women, ages 18-83 years) evaluable patients with stage IV melanoma were treated with palliative RT and ipilimumab (3mg/kg) every 3 weeks for a total of 4 cycles. Palliative RT to 1-2 sites of disease was initiated within 5 days of the first dose of ipilimumab. Patients were required to have at least one nonirradiated metastasis measuring at least 1.5cm for assessment of response to therapy. Tumor imaging studies were obtained at baseline prior to treatment, 2-4 weeks following the fourth dose of ipilimumab, and every 3 months until disease progression. Both Response Evaluation Criteria in Solid Tumors (RECIST) and Immune Response Criteria (IRC) were used to assess tumor responses. Patients were monitored for safety, and laboratory immune response parameters were measured before and during the treatment period, including enumeration of major cell subsets, as well as myeloid-derived suppressor cells (MDSC), and antigen-specific T cell responses by intracellular cytokine staining.

Results: Of the 20 evaluable patients treated to date, 11 patients (55.0%) had an initial response to therapy, including complete and partial responses (CR, PR) as well as stable disease (SD) at median follow-up of 38 weeks. Of the responders, one patient (9.1%) had achieved an ongoing systemic CR to the combination therapy. Five patients (45.4%) have an ongoing PR and 5 additional patients (45.4%) initially had SD following treatment without progression for a median of 39 weeks (range 26-76 weeks). Nine patients had progressive disease by IRC on the first posttreatment scan. Combined treatment has been well tolerated with no unexpected toxicities, and no apparent exacerbation of either radiation or ipilimumab-associated toxicities. Analysis of the immune response data suggests that pro-inflammatory cytokines are elevated in responders (eg, MCP-1, MIG and IP-10), and that there may be a relationship between elevated CD8 activated T cells and response.

Conclusion: This is one of the first prospective clinical trials to report results from the treatment of metastatic melanoma with the combination of RT and systemic immunotherapy. Our results demonstrate that a subset of patients can achieve significant clinical benefit from this combination therapy, and that this in situ tumor vaccine strategy is a promising area for continued clinical investigation.