Radiation-immunotherapy combination can slow tumor growth for some patients with metastatic late-stage cancer

Phase II trial finds at least 30 percent of patients experienced favorable response after treatment

SAN DIEGO, September 24, 2017 – A new study involving patients with stage IV cancer finds that treatment with radiation therapy and immunotherapy can halt the growth of tumors by stimulating the body’s immune system to attack the cancer. In the phase II trial, patients with end-stage cancer that had spread to the lungs or liver demonstrated a favorable response to the combined treatment. Between 30 and 60 percent of the patients, depending on the treatment arm, found that their cancer stopped spreading. Findings will be presented today at the 59th Annual Meeting of the American Society for Radiation Oncology (ASTRO).

“This combination of immunotherapy and radiation therapy was safe and well-tolerated by patients with late-stage cancers. We were surprised that a large percentage of patients achieved stable disease several months after treatment—meaning that while their tumors didn’t shrink, they did stop growing,” said James Welsh, MD, lead author of the study and an associate professor of radiation oncology at The University of Texas MD Anderson Cancer Center in Houston.

“It appears that the radiation helped turn the tumor into a vaccine to stimulate an immune response. This heightened immune response was able to keep the tumors stable. Longer follow-up is needed to determine if this benefit of stable disease will endure over time.”

One hundred patients were enrolled in a phase II trial examining a combination of high-dose radiation therapy plus immunotherapy for patients with various types of stage IV cancers. Eligible patients included those with metastatic disease that was resistant to standard therapies, with one or more lesions in the liver or lung that was/were amenable to stereotactic radiation and one or more additional metastases not touching the
lung or liver lesion. The majority of patients (55%) had adenocarcinomas, while 13 percent had squamous cell carcinomas and the remaining 32 percent had various other histologies.

All patients received four cycles of ipilimumab (3 mg/kg every three weeks) and stereotactic body radiation therapy (SBRT) to the site(s) of metastasis in either the liver or the lungs. Radiation therapy was given either concurrently with or sequentially to immunotherapy. Concurrent radiation began on day two of the first immunotherapy cycle, to a total dose of 50 Gray (Gy) delivered in four fractions. Sequential radiation was given one week after the second immunotherapy cycle to a total radiation dose of 50 Gy delivered in four fractions, or 60 Gy in 10 fractions for larger lung or liver metastases—typically, those larger than four centimeters. Patients were enrolled in a nonrandomized fashion into one of the five treatment cohorts: concurrent lung, sequential 50-Gy lung, concurrent liver, sequential 50-Gy liver, and sequential 60-Gy liver or lung. There were 20 patients in each treatment arm.

Stable disease was achieved for half of the patients in the sequential 50-Gy lung cohort, 45 percent of the concurrent-lung group, 35 percent of the concurrent liver group and 30 percent of the sequential 50-Gy liver group. Sixty percent of patients in the larger-lesion, higher-dose radiation group demonstrated a favorable response to treatment.

The median progression-free survival (PFS) for all patients following radiation therapy combined with immunotherapy was five months (95% CI = 2.7-7.2 months). Median overall survival (OS) was 12 months (95% CI = 9.3-14.6 months). Patients who received sequential radiation to lung metastases rather than to liver metastases had better PFS (p = 0.055, 95% CI = 3.7-6.4) and OS (p = 0.059, CI = 7.9-20.0). No differences were found between the concurrent lung or liver groups for progression-free (p = 0.2) or overall (p = 0.3) survival.

There were no complete responses to treatment, but a partial response was found for three patients who received SBRT concurrently with ipilimumab, including two patients (10%) on the concurrent lung arm and one patient (5%) on the concurrent liver arm. No patients in the sequential radiation groups experienced a partial response.

“A small percentage of patients experienced a potential abscopal effect, where tumors that were not irradiated became smaller after we treated different sites with radiation,” explained Dr. Welsh. “For example, one patient with anaplastic thyroid cancer—one of the deadliest types of cancer—experienced a reduction in the primary tumor after we irradiated a lung metastasis. This patient had controlled disease for more than 13 months.”

Lesions from non-small cell lung cancer (NSCLC) were most responsive to the combined treatment; two thirds of these patients had a favorable response (partial response or stable disease) following SBRT plus
immunotherapy. Response to treatment was scored using immune-related criteria (irRC). Partial response represented a 50 percent or greater decrease in tumor size. Progressive disease represented a 25 percent increase in tumor size. Stable disease responses included those that did not fall into complete, partial or progressive response categories.

No patients experienced Grade 4 or 5 treatment-related side effects. Twenty-seven patients experienced Grade 3 toxicities related to immunotherapy, including colitis (8 patients), diarrhea (7 patients), rash (4 patients), elevation of liver enzymes (3 patients), hypophysitis (3 patients), elevation of bilirubin (1 patient) and intestinal obstruction (1 patient). Two patients experienced Grade 3 toxicities related to combination therapy, including one patient with an increase in liver enzymes and one patient with pneumonitis. Side effects were evaluated using the Common Terminology Criteria for Adverse Events, version 4.0.

“We found that the addition of SBRT for patients who are on immunotherapy to be safe and well-tolerated, meaning that radiation oncologists can feel confident continuing immunotherapy for most patients when adding SBRT to lung or liver metastases. In fact, there may be additional benefit from combining the therapies in terms of improved disease control. Follow-up research in larger clinical trials is needed to determine which types of tumors and patients will respond best to this immunotherapy-radiation approach,” said Dr. Welsh.

The abstract, “Phase II 5-arm trial of ipilimumab plus lung or liver stereotactic radiation for patients with advanced malignancies,” will be presented in detail during a news briefing and the clinical trials session at ASTRO’s 59th Annual Meeting in San Diego (full details below). To schedule an interview with Dr. Welsh and/or outside experts in immunotherapy and lung cancer, contact ASTRO’s media relations team on-site at the San Diego Convention Center September 24 through 27, by phone at 703-286-1600 or by email at press@astro.org.

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**ATTRIBUTION TO THE AMERICAN SOCIETY OF RADIATION ONCOLOGY (ASTRO) ANNUAL MEETING REQUESTED IN ALL COVERAGE.**

This news release contains additional and/or updated information from the study author(s). Full original abstract and author disclosures available on the final page of this release.

**Study Presentation Details**

- Scientific Session: Clinical Trials, Sunday, September 24, 3:15 – 4:45 p.m. Pacific time, San Diego Convention Center, Ballroom 20
Additional Information on Radiation Therapy and Immunotherapy

- **Immunology Primer**, by Heather McGee, MD, PhD
- **Radiation Oncology and Immunotherapy Primer**, by Michelle Kim, MD

Resources on Lung Cancer and Radiation Therapy

- Digital brochure: **Radiation Therapy for Lung Cancer (Spanish version)**
- Videos: **Radiation Therapy for Lung Cancer (Spanish version)**, **An Introduction to Radiation Therapy (Spanish version)**
- Additional brochures, videos and information on radiation therapy from ASTRO’s patient site, RTAnswers.org
- ASTRO’s clinical practice statements and guidelines

ABOUT ASTRO’S ANNUAL MEETING

ASTRO’s 59th Annual Meeting, the world’s largest scientific meeting in radiation oncology, will be held September 24-27, 2017, at the San Diego Convention Center. The 2017 Annual Meeting is expected to attract more than 11,000 attendees from across the globe, including oncologists from all disciplines and members of the entire radiation oncology team. More than 2,800 abstracts sharing results from clinical trials and other research studies will be presented in conjunction with educational sessions and keynote addresses that underscore the meeting’s theme, “The Healing Art and Science of Radiation Oncology.” Led by ASTRO President Brian Kavanagh, MD, MPH, FASTRO, the 2017 meeting will feature keynote addresses from Richard D. Zane, MD, FAAEM, Chief Innovation Officer for the University of Colorado Health System; Lucy Kalanithi, MD, FACP, widow of Paul Kalanithi, MD, the best-selling author of “When Breath Becomes Air,” with Heather Wakelee, MD, Paul’s oncologist; and Vinay K. Prasad, MD, MPH, an assistant professor of medicine at the Oregon Health & Science University. During the four-day meeting, more than 200 exhibitors will demonstrate cutting-edge technology and medical device innovations for radiation oncology. Visit us online for more information about ASTRO’s 59th Annual Meeting or press opportunities at the meeting.

ABOUT ASTRO

The American Society for Radiation Oncology (ASTRO) is the world’s largest radiation oncology society, 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. 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, RT Answers (www.rtanswers.org); and created the Radiation Oncology Institute (www.roinstitute.org), a nonprofit 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 and follow us on our blog, Facebook and Twitter.
Abstract LBA-5: Phase II 5-arm trial of ipilimumab plus lung or liver stereotactic radiation for patients with advanced malignancies

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Purpose/Objective(s): We present early toxicity and efficacy findings from a phase II trial that combines CTLA4 blockade (ipilimumab) with stereotactic ablative radiation therapy (SABR) targeting metastatic lung or liver lesions in patients with solid tumors.

Materials/Methods: Patients with metastatic disease refractory to standard therapies with ≥1 lung or liver lesion amenable to SABR and ≥1 additional non-contiguous lesion were enrolled in a nonrandomized fashion. All patients were to receive ipilimumab (3 mg/kg every 3 weeks for 4 cycles) plus radiation given either concomitantly (SABR started on day 2 of cycle 1) or sequentially (SABR given 1 week after the 2nd dose of Ipilimumab). The 5 treatment groups were as follows: concomitant liver 50 Gy, concomitant lung 50 Gy, sequential liver 50 Gy, sequential lung 50 Gy, and sequential 60 Gy (lung or liver for larger lesions). 50 Gy was given in 4 fractions and 60 Gy was given in 10 fractions. Toxicity was scored per the Common Terminology Criteria for Adverse Events v4.0 and were evaluated by medical and radiation oncologists. Disease response was scored per the immune-related response criteria (irRC) by an experienced radiologist. Best responses were reported as complete response (CR), partial response (PR; size decrease ≥50%), progressive disease (PD; size increase ≥25%), or stable disease (SD; not meeting criteria for PR/CR or PD). The Kaplan-Meier method and log-rank tests were used to assess progression-free survival (PFS) and overall survival (OS).

Results: Among 100 patients (20 in each treatment group), the most common primary histologies were adenocarcinoma (n=55) and squamous cell (n=13) carcinomas. No grade 4-5 toxicity was observed; 27 grade 3 toxicities were related to ipilimumab (colitis [n=8], diarrhea [n=7], liver enzyme elevation [n=3], bilirubin elevation [n=1], intestinal obstruction [n=1], hypophysitis [n=3], and rash [n=4]). Two grade 3 toxicities were attributed to combined ipilimumab plus SABR: liver enzyme increase (1%) and pneumonitis (1%). The concurrent and sequential lung groups had 45% and 50% of SD, and 10% and 0% PR, respectively. The concurrent and sequential liver groups showed 35% and 30% of SD, and 5% and 0% PR, respectively. Within the sequential 60 Gy group, 60% showed a favorable response. Lesions from non-small cell lung cancer had the highest rate of clinical benefit (SD + PR) at 67%. There was no CR to report. Median PFS time for all patients was 5 months (95% confidence interval [CI] 2.7–7.2) and median OS time was 12 months (95% CI 9.3–14.6). At 12 months, PFS and OS were better for the sequential lung group than for the sequential liver group (PFS p=0.055, CI= 3.7–6.4; OS p=0.059, CI=7.9–20). However, no differences in PFS (p=0.2) or OS (p=0.3) were found between the concurrent lung and liver groups.

Conclusion: These data suggest that combinations of ipilimumab and SABR have acceptable toxicity profiles and sequential treatment may provide significant clinical benefits in terms of response and survival, warranting further evaluation.

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