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News Release

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Adding radiation to chemotherapy may dramatically improve survival for advanced-stage NSCLC patients

Randomized phase II trial finds progression-free survival expectancy nearly tripled with addition of consolidative stereotactic radiation therapy for limited metastatic disease

SAN DIEGO, September 24, 2017 – Combining radiation therapy with chemotherapy for patients with limited metastatic non-small cell lung cancer (NSCLC) may curb disease progression dramatically when compared to NSCLC patients who only receive chemotherapy, according to a new randomized phase II clinical trial reported today at the 59th Annual Meeting of the American Society for Radiation Oncology (ASTRO). Progression-free survival in the trial escalated from 3.5 months to 9.7 months with the addition of radiation therapy delivered to all the metastatic sites of lung cancer as well as the primary disease site. Treatment-related side effects were similar for the two treatment approaches.

Lung cancer claims the most cancer-specific deaths of any tumor type. Few existing treatments offer durable survival benefits for patients whose NSCLC has spread past the lungs, due in part to the aggressive nature of lung cancer and its propensity to progress, even following treatment. Research on metastatic colorectal cancer and sarcoma, however, suggests a potential benefit from adding local therapy—treatment directed specifically at the tumor cells—to the standard approach of systemic therapy. In these studies, adding radiation or/and surgery bolstered the ability of systemic therapies, such as chemotherapy, to control disease and improve survival in patients with few metastases.

"Even in the era of immunotherapy, there are not large numbers of metastatic NSCLC patients with durable responses to systemic therapy. In our trial, however, the addition of radiation therapy directed at

each of the cancerous areas greatly improved how patients responded to subsequent rounds of chemotherapy," said Puneeth Iyengar, MD, PhD, lead author of the study and an assistant professor of radiation oncology at the University of Texas Southwestern Medical Center in Dallas. "This finding suggests that local treatments, including radiation, could work in concert with chemotherapy to prolong the amount of time before recurrence occurs in patients with limited sites of metastatic NSCLC."

The study was a randomized phase II trial testing whether the addition of local treatment, in the form of consolidative radiation therapy, to the standard treatment of systemic therapy improved progression-free survival for patients with limited metastatic NSCLC. Eligible patients included those with stage IV disease, spread to six or fewer sites including the primary tumor site, and who responded at least partially to first-line/induction chemotherapy.

Patients were randomly assigned to receive either maintenance chemotherapy alone (15 patients) or a combination of stereotactic ablative radiotherapy (SAbR)—also known as stereotactic body radiation therapy or SBRT—to all sites of disease followed by maintenance chemotherapy (14 patients). Radiation to metastases was offered as a single fraction (to 21-27 Gray (Gy)), three fractions (to 26.5-33 Gy) or five fractions (to 30-37.5 Gy) of SAbR (regimens were biologically equivalent). Radiation to the primary disease site was delivered to a total dose of 45 Gy via SAbR where possible, or through 15 fractions of hypofractionated radiation therapy if the primary tumor was too central or involved mediastinal nodes. Maintenance chemotherapy was left to the discretion of the treating medical oncologists and consisted of pemetrexed, docetaxel, erlotinib or gemcitabine.

Twenty-nine patients were accrued between April 2014 and July 2016. The median patient age was 70 years (range 51-79 years) for the patients receiving maintenance chemotherapy only and 63.5 years (range 51-78) for the patients receiving SAbR to metastases followed by maintenance chemotherapy. Most patients were male (69%). Eighty-six percent of all patients had tumors with non-squamous histologies. Thirty-one lesions were treated with radiation in the 14 patients that received local therapy.

The median follow-up for this report was 9.6 months (range 2.4-30.2 months). Patient accrual was stopped ahead of schedule after an unplanned interim analysis found substantially improved survival rates in the arm receiving local therapy, matching similar findings in a parallel trial.

The interim analysis found a median progression-free survival rate of 9.7 months with consolidative radiation therapy followed by chemotherapy, versus 3.5 months for maintenance chemotherapy alone ($p = 0.01$; Hazard Ratio (HR) = 0.304, 95% CI 0.113-0.815). Survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test and Cox proportional hazard models.

Specifically, rates of local control and delay in distant metastases also favored the approach incorporating radiation with systemic therapy. In the arm with consolidative local therapy, there were no recurrences in original sites of gross disease versus seven failures in original sites of gross disease in the arm receiving only maintenance therapy. At the time of analysis, 10 of the 15 patients receiving maintenance chemotherapy-only had progressed, compared with four of the 14 patients also receiving radiation. None of the recurrences among the latter patients were in areas treated directly with radiation therapy.

Treatment-related side effects were similar between the two treatment arms, indicating that the addition of local therapy was well-tolerated by patients. There were no grade 5 toxicities attributable to study treatment. On the maintenance chemotherapy-only arm, there were two grade 3 and one grade 4 toxicities. On the SAbR plus maintenance chemotherapy arm, there was one grade 4 toxicity.

"These findings verify that progression-free survival for limited metastatic disease really is no different than it is for widely metastatic disease, suggesting that local therapy could play an important future role in survival outcomes," said Dr. Iyengar. "Moreover, the addition of consolidative radiation did not increase toxicity, which allowed patients to continue on to additional systemic therapy that is important to controlling aggressive metastatic disease."

Next steps for this research include a larger, randomized phase III trial to test progression-free survival, as well as overall survival. While results indicate a clear benefit of adding local therapy for the management of limited metastatic NSCLC, Dr. Iyengar stressed the need for confirmation in a larger prospective trial.

"There is a significant possibility that local therapy, such as consolidative radiation, may become an important part of the management of limited metastatic NSCLC patients, but this validation must take place in randomized phase III studies. Interested patients should seek more information about the ongoing NRG LU 002 and SARON trials."

The abstract, "Consolidative radiotherapy for limited metastatic non-small cell lung cancer (NSCLC): A randomized phase II trial," will be presented in detail during a news briefing and the Plenary Session at ASTRO's 59th Annual Meeting in San Diego (full details below). The study is also available beginning today in JAMA Oncology. To schedule an interview with Dr. Iyengar and/or outside experts in 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

- News Briefing: Sunday, September 24, 1:00 – 2:00 p.m. Pacific time, San Diego Convention Center, room 24C, webcast: http://www.bit.do/astro17-1
- Scientific Session: Plenary, Monday, September 25, 2:15 – 3:45 p.m. Pacific time, San Diego Convention Center, Ballroom 20

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)
- ASTRO's clinical practice statements and guidelines
- Additional brochures, videos and information on radiation therapy from ASTRO's patient site, RTAnswers.org

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-3: Consolidative radiotherapy for limited metastatic non-small cell lung cancer (NSCLC): A randomized phase II trial

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Purpose/Objective(s): Maintenance systemic therapy has shown statistically significant but modest benefits in progression free survival (PFS) and overall survival (OS) for patients with stage IV non-small cell lung cancer (NSCLC). This trial sought to determine if intervening with non-invasive, stereotactic body radiation therapy (SBRT) prior to maintenance chemotherapy in patients with limited metastatic NSCLC led to significant improvements in PFS.

Materials/Methods: Patients with stage IV NSCLC who achieved a partial response or stable disease to induction chemotherapy with six or fewer sites of limited metastatic disease (including primary) were randomized to maintenance chemotherapy or consolidative SBRT to all sites of disease followed by maintenance chemotherapy. The primary endpoint was PFS, with secondary endpoints including toxicity, local and distant tumor control, and patterns of failure.

Results: A total of 29 patients were enrolled from April 2014 to July 2016, with 14 patients in the SBRT plus maintenance chemotherapy arm and 15 patients in the maintenance chemotherapy alone arm. The trial was stopped to accrual early after an unplanned interim analysis found a significant improvement in PFS in the SBRT plus maintenance chemotherapy arm of 9.7 months versus 3.5 months in the maintenance chemotherapy alone arm (p=0.013). Toxicity was similar in both arms.. There were no in-field failures with fewer overall recurrences in the SBRT arm.

Conclusion: Consolidative SBRT prior to maintenance chemotherapy was beneficial, nearly tripling PFS in patients with limited metastatic NSCLC compared to maintenance chemotherapy alone, with no difference in toxicity. It is promising that a phase III study, based on this and other trials, has been activated by NRG (NRG LU 002, NCT03137771) to answer the benefit of local therapy on OS.

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