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TARGETING CANCER CARE

News Release

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Immune response prognostic for prostate cancer survival, recurrence and response to radiation therapy

Findings indicate new avenue for personalized medicine and potentially inform use of immunotherapy treatments currently on the market for localized prostate cancer

SAN DIEGO, September 24, 2017 – A new study finds that immune response in prostate cancer may be able to forecast how patients will respond to radiation therapy, as well as their likelihood of disease recurrence and survival outcomes. The analysis of more than 9,000 prostate tumors also found evidence that PD-L2, not PD-L1, may provide a key route for targeted therapies, such as immunotherapy, to slow disease progression. Findings will be presented today at the 59th Annual Meeting of the American Society for Radiation Oncology (ASTRO).

"When the immune system responds to tumors, it sends specific types of immune cells directly to the tumor. Understanding this infiltration of immune cells allows researchers and oncologists to devise treatment strategies based on each patient's specific immune response and disease biology. Checkpoint inhibitors and other immunotherapies have been utilized to manage other solid tumors. Our work suggests that there may be a role for these innovative treatments in prostate cancer, as well," said Shuang (George) Zhao, MD, lead author of the study and a radiation oncology resident at the University of Michigan in Ann Arbor.

To better define the immune landscape of localized prostate cancer, researchers examined 9,393 tumor samples from men who underwent a radical prostatectomy, including 7,826 recently collected prospective tumor samples and 1,567 retrospectively obtained samples. Immune content in the tumor samples was identified using high-throughput computational analysis with specific immune-related genes. Gene expression profiling was conducted on a commercial clinical-grade platform, and gene selection was guided by the

published literature.

Clustering analysis of the 9,393 tissue samples identified a subset of patients with higher expression of immune-related pathways. This immune content score, which was predicted computationally, appeared to predict prostate cancer recurrence, metastasis and survival. Higher levels of the immune content score were associated with lower likelihood of survival, including freedom from disease progression (Hazard Ratio (HR) = 1.3, p = 0.0002), freedom from distant metastases (HR = 1.3, p = 0.0006), prostate cancer-specific survival (HR = 1.5, p = 0.0003) and overall survival (HR = 1.3, p = 0.006). Clinical outcomes were available for retrospective data only.

The immune content score also predicted response to radiation therapy following radical prostatectomy. On multivariate analysis, it interacted significantly (p = 0.017) with response to post-operative radiation therapy (PORT).

"Our analyses also found a potential interaction between immune content and radiation response, suggesting that combinations of radiation therapy and immunotherapies may be a treatment option worthy of further investigation," said Dr. Zhao.

Different types of immune cells were influential in different ways, indicating a complex interaction between immune cells and tumor cells. Specifically, higher levels of active macrophages and T-cells were prognostic for worse distant metastasis-free survival ($p < 0.05$), while active mast cells, NK cells and dendritic cells were associated with improved distant metastasis-free survival ($p < 0.05$). Individual cell types were examined from the genome-wide expression data using the CIBERSORT algorithm.

PD-L1, the target of several FDA-approved checkpoint inhibitors, was not associated with outcomes in this study, but PD-L2, which interacts with PD-1 similarly to PD-L1, was associated with worse treatment outcomes. Specifically, higher levels of PD-L2 were associated with greater likelihood for disease recurrence (HR = 1.17, p = 0.013), distant metastasis (HR = 1.25, p = 0.014) and prostate cancer death (HR = 1.45, p = 0.003).

"As immune checkpoint blockers have come to market, PD-L1 has received a great deal of attention—but it does not appear to be widely expressed in prostate cancer. PD-L2, however, was much more highly expressed in these tumor samples, and it also was associated with worse outcomes. The understudied PD-L2 ligand may be the better therapeutic target for patients with localized prostate cancer," said Dr. Zhao.

"The immune landscape of prostate cancer is highly complex. We need to develop treatment approaches that account for individual tumor and patient characteristics in order to prescribe the best treatments for each individual prostate cancer patient."

The abstract, "Novel associations between the immune landscape of prostate cancer and post-operative radiation response," 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. Zhao and/or outside experts in prostate cancer or immunotherapy combinations, 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
- News Briefing: Monday, September 25, 11:00 a.m. – 12:00 p.m. Pacific, San Diego Convention Center, room 24C, webcast: http://www.bit.do/astro17-2

Resources on Prostate Cancer and Radiation Therapy

- Digital brochure: Radiation Therapy for Prostate Cancer (Spanish version)
- Videos: Radiation Therapy for Prostate 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 3: Novel associations between the immune landscape of prostate cancer and post-operative radiation response

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Purpose/Objective(s): To investigate the immune landscape in localized prostate cancer (PCa) utilizing high-throughput genome-wide expression analysis.

Materials/Methods: Gene expression on a commercial clinical platform was used to analyze 7759 recently-collected prospective and 1567 retrospective prostatectomy samples with long term clinical outcomes. Hallmark pathways were obtained from the Molecular Signatures Database. Immune infiltrate/content in the tumor was estimated using immune cell-specific genes from the literature, and de-convoluted computationally with a published algorithm (Cibersort). Immune infiltrate was correlated to the published PORTOS score, which predicts benefit of distant metastases from post-operative radiation therapy (PORT). Development and validation of an integrated immune-PORTOS signature was performed using ridge-penalized Cox regression.

Results: Unsupervised hierarchical clustering of the hallmark pathways of 9326 PCa samples demonstrates an immune-related cluster of tumors. This immune cluster is correlated with estimated immune content score ($p<0.0001$). Increased immune content is associated with worse biochemical progression free survival (PFS) ($p=0.0002$, HR=1.3), distant metastasis free survival (DMFS) ($p=0.0006$, HR=1.3), PCa specific survival (PCSS) ($p=0.0003$, HR=1.5), and overall survival (OS) ($p=0.006$, HR=1.3). When de-convoluted into individual immune cell types, active macrophages and T-cells conferred significantly worse DMFS ($p<0.05$), while active mast cells and NK cells conferred significantly better DMFS ($p<0.05$), all consistent with the literature in PCa. A higher CTLA-4/T-cell ratio was associated with worse PFS, DMFS, and PCSS. Select immune cell types were also associated with predicted radiation response (PORTOS). We therefore added immune-related genes to PORTOS and found that immune-PORTOS improves the p-value and hazard ratio for PORT in the predicted responder group ($p<0.0001$, HR=0.04 vs. $p=0.002$, HR=0.15).

Conclusion: We identify a clear immune-related cluster in 9326 PCa samples. Immune content was associated with more aggressive clinical outcomes. We identified specific cell types correlated most with prognosis, which were all consistent with the literature. A high CTLA-4/T-cell ratio was associated with worse prognosis, which is particularly relevant as two recent phase III studies in metastatic PCa have demonstrated a PFS (but not OS) benefit for ipilimumab. This suggests that ipilimumab has an anti-tumor effect, but that patient selection is critical to maximize the benefit. Furthermore, the addition of immune genes to a previously developed predictor of radiation response improves the predictions of which patients have a systemic control benefit from radiation. These results illustrate the complex relationship between the immune system, PCa prognosis, and radiation treatment. Future work should focus on the clinical implications of radiation and immunotherapy in PCa.

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