Novel immunotherapy agent safe, shows promise against high-risk prostate cancers

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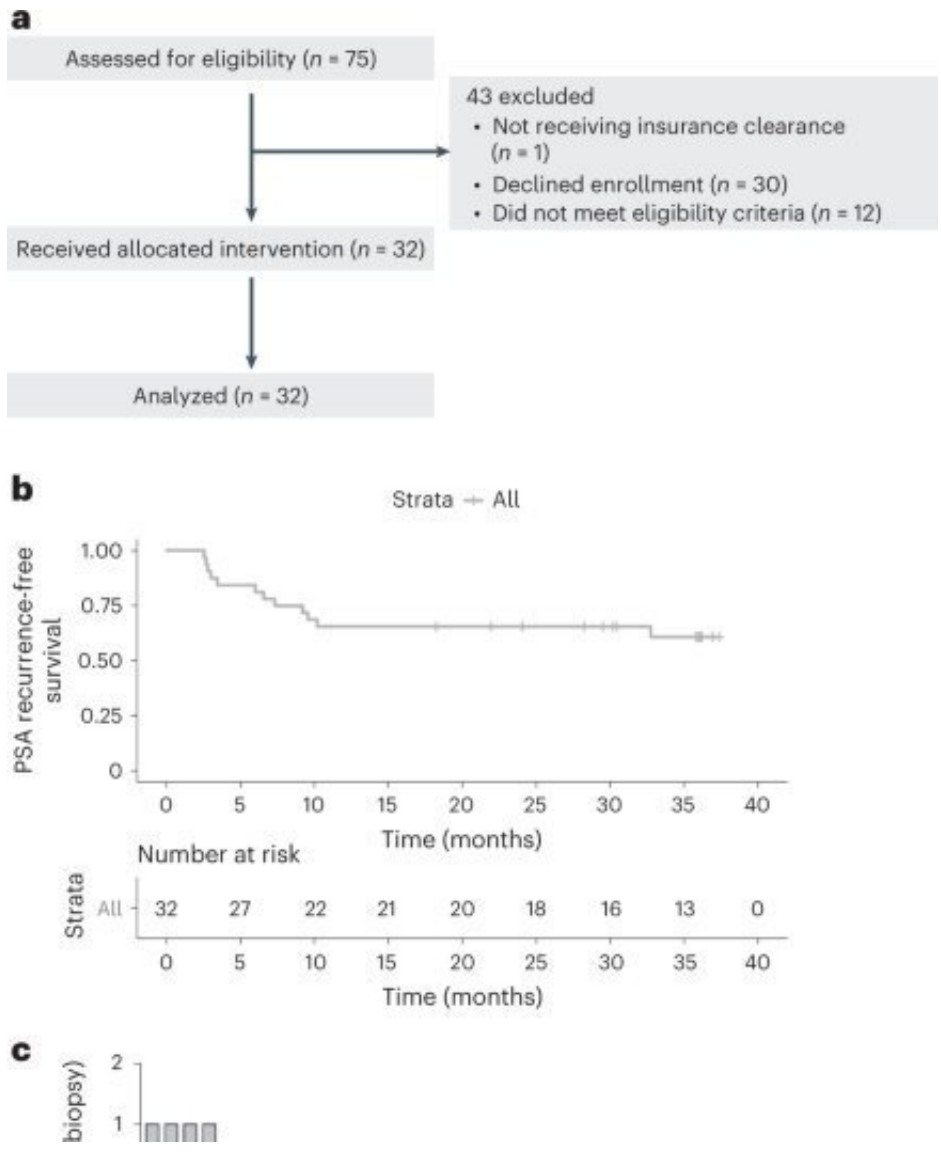

Patient consort diagram and efficacy outcomes in the neoadjuvant treatment of patients with PCa using enoblituzumab. Credit: *Nature Medicine* (2023). DOI: 10.1038/s41591-023-02284-w

A new drug, a monoclonal antibody known as enoblituzumab, is safe in men with aggressive prostate cancer and may induce clinical activity against cancer throughout the body, according to a phase 2 study led by investigators at the Johns Hopkins Kimmel Cancer Center and its Bloomberg~Kimmel Institute for Cancer Immunotherapy. If confirmed in additional studies, enoblituzumab could become the first promising antibody-based immunotherapy agent against prostate cancer.

In a clinical trial, 32 men with high-risk or very high-risk prostate cancers who were scheduled for prostate cancer surgery were treated with six weekly infusions of enoblituzumab prior to surgery, and were followed for an average of 30 months thereafter.

Twenty-one patients, or 66%, had an undetectable prostate-specific antigen (PSA) level 12 months following surgery, suggesting that there was no sign of residual disease. Additionally, the drug was well-tolerated overall; no patients had any surgical delays or medical complications during or after the operation.

A description of the work was published in the journal *Nature Medicine*.

If enoblituzumab continues to perform well in further larger randomized studies, it could represent a new pathway for immunotherapy against multiple cancers, and the first one that may have a role for prostate cancer, says lead study author and cancer immunology researcher Eugene Shenderov, M.D., Ph.D., assistant professor of oncology at the Johns Hopkins University School of Medicine.

Other existing antibody-based immunotherapy drugs have targeted immune checkpoints, natural on/off switches mediating immune responses, such as CTLA-4, PD-1 and LAG-3. Cancer cells hijack these

checkpoints, turning off the immune response to cancer. "Drugs that block these checkpoints have had success in other types of cancers, including lung cancer and melanoma, but not in prostate cancer," says Shenderov.

Enoblituzumab works by binding to a protein called B7-H3 that is overexpressed on prostate cancer cells and believed to impede the immune system's ability to attack cancer cells. The new therapy could pack a one-two punch against cancer, Shenderov says, by blocking B7-H3's inhibition of the immune system's recognition and elimination of cancer cells, and also triggering a process called antibody-dependent cellular cytoxicity (ADCC), which leads to tumor cell destruction by activating additional immune cells such as macrophages and natural killer cells.

"Enoblituzumab appears safe and seems to activate the immune system in a way that involves both T-cells and myeloid cells," Shenderov says.

"What this means is if these results can be replicated in a larger, randomized study, it opens the possibility that combining this therapy with local, curative-intent therapies like surgical prostate removal or radiation therapy, would allow this drug to potentially kill micrometastatic disease hiding elsewhere in the body, and therefore prevent a significant number of men from experiencing recurring disease. That could be a paradigm shift in prostate cancer."

The median age of study participants was 64 (age range 48–74). About half (47%) had a PSA greater than 10 ng/mL at diagnosis, which is abnormally high, and 50% had Gleason grade group 5 at biopsy, meaning they had highly aggressive disease. Patients were enrolled from February 2017 through June 2019. Enoblituzumab was confirmed to penetrate into prostate tumors and to bind to B7-H3 in the vast majority of participants, according to prostate samples studied after surgery.

Side effects of enoblituzumab were generally mild and included fatigue, neurological symptoms such as headache or dizziness, and flu-like or cold symptoms. One patient developed inflammation of the heart (myocarditis), which fully resolved with steroid treatment, and is a known side effect of other immune checkpoint drugs.

Beyond safety and anti-tumor activity based on PSA dropping to undetectable levels, investigators also looked for changes in the tumor microenvironment before and after enoblituzumab treatment. They found increased markers of cytotoxicity after treatment, consistent with the concept that the immune system was activated against tumor cells. The tumors showed increased infiltration with granulocytes, leukocytes and effector T-cells, and there was roughly a doubling of the density of cytotoxic T cells after treatment.

"The findings are exciting but exploratory, and need to be confirmed in larger study cohorts," cautions senior study author Emmanuel S. Antonarakis, M.D., the Clark Endowed Professor of Medicine and director of GU Oncology for the University of Minnesota Masonic Cancer Center. Antonarakis was the senior investigator of the study while he was at the Johns Hopkins Kimmel Cancer Center.

"However, these results in high-risk prostate cancer patients, and the broader need for immunotherapeutic strategies with efficacy in prostate cancers, provide justification to further develop multipronged approaches that include targeting B7-H3 to optimize antitumor activity in prostate cancers and other solid malignancies," he says.

Investigators are now planning a larger, randomized trial of enoblituzumab in newly diagnosed prostate cancer patients to assess clinical activity of the drug compared to current standards of care.

More information: Eugene Shenderov et al, Neoadjuvant

enoblituzumab in localized prostate cancer: a single-arm, phase 2 trial, *Nature Medicine* (2023). DOI: 10.1038/s41591-023-02284-w