Drug treatment could improve effectiveness of immunotherapy for cancer patients

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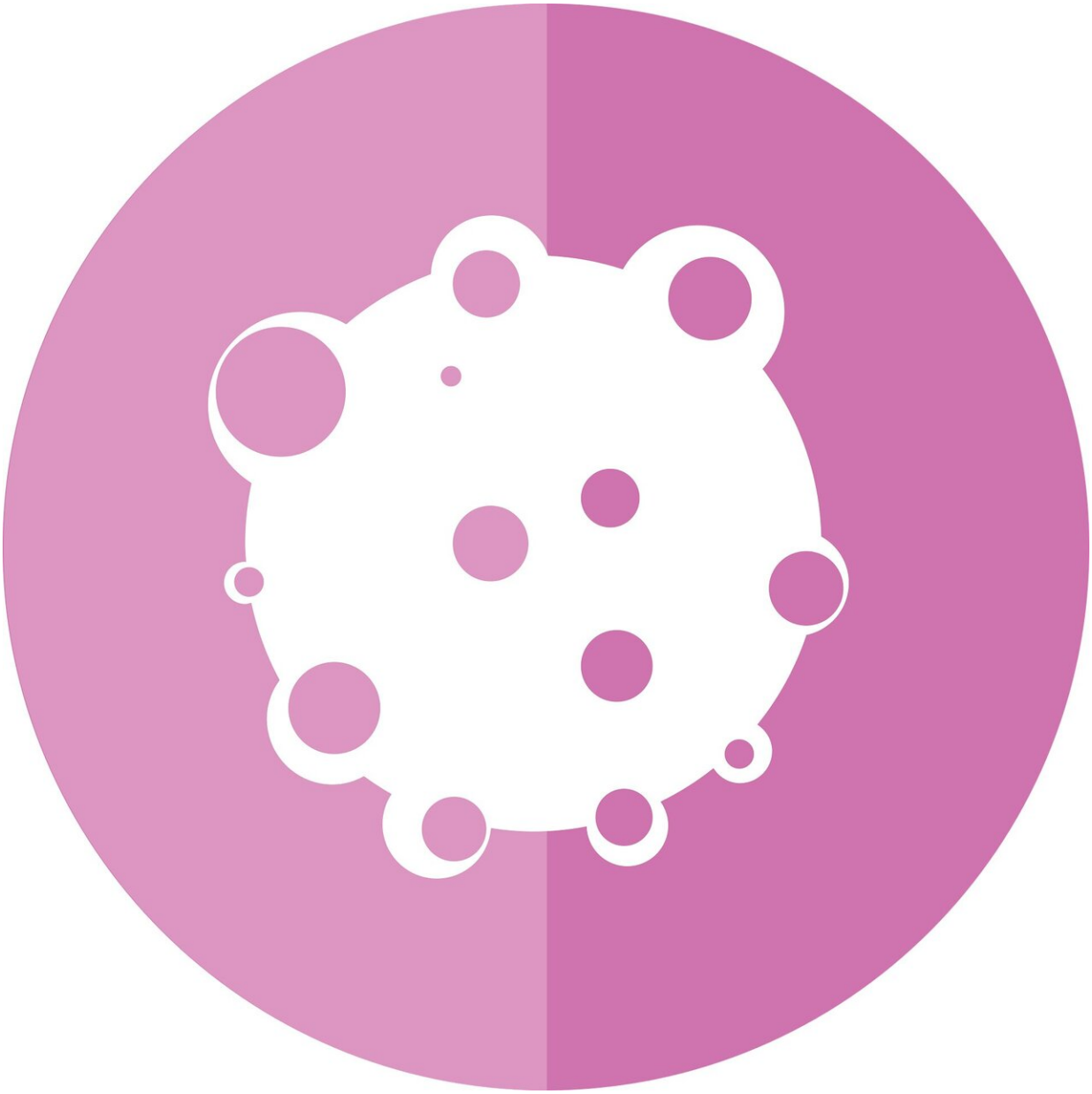

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While immunotherapy—a form of treatment that uses the body's immune system to recognize, attack and kill tumor cells—has given hope to people across the globe, it fails in a significant proportion of cancer patients.

However, a new study published in the Nature journal *Cell Death Discovery* on Monday, July 6, suggests that blocking the tumor-promoting protein MDM2 could bolster immunotherapy's effectiveness.

"Immunotherapy has been one of the biggest breakthroughs in biomedical science and medicine of the last two decades," said Dr. Wafik El-Deiry, a professor of pathology and laboratory medicine and associate dean for oncologic sciences at Brown University. "But it has limitations."

Some people's tumors respond to immunotherapy initially and then relapse. Other patients experience pseudoprogression, where tumors appear to grow before eventually shrinking. And a third group—between 5% and 29% of patients—experience hyperprogression, which means that immunotherapy actually worsens their tumor growth.

El-Deiry hopes that blocking MDM2, either through gene-silencing or the MDM2-inhibiting drug AMG-232, could be especially helpful for people with hyperprogression.

Various studies have found that when the MDM2 gene is amplified—meaning that cells contain too many copies of the gene—or when the MDM2 protein is overexpressed because the gene is not being regulated properly, tumor cells tend to grow more quickly and are more

resistant to immunotherapy. Researchers are still investigating exactly why this accelerated growth and resistance occur, but studies suggest that MDM2 can help tumors grow and evade the immune system through a variety of mechanisms. For example, MDM2 appears to inactivate the tumor-suppressor gene p53 and prevent immune cells from killing tumor cells, and it is also associated with higher levels of a tumor-promoting inflammatory protein called interleukin-6 (IL-6).

In their study, El-Deiry and his colleagues treated cell lines of MDM2-overexpressing ovarian cancer cells with the therapeutic AMG-232. The data show that AMG-232 allowed immune cells to kill the tumor cells much more efficiently and reduced levels of IL-6. These results suggest that MDM2 inhibitors could be combined with immunotherapy to enhance its effectiveness.

This study follows the recent launch of the Cancer Center at Brown University, where El-Deiry serves as inaugural director. The center builds on Brown's growing focus on translational science—the practice of ensuring that breakthroughs in basic research are advanced to the point where they can make a meaningful medical difference for patients, and that urgent scientific questions identified in the clinic or among patient populations become research priorities in the lab. Faculty at the new center will take a broad-spectrum approach to research, from working to understand how cancer develops, grows and metastasizes, to developing new therapeutics for patients in a personalized way that addresses their needs ranging from risk through survivorship.

For this specific finding, El-Deiry hopes the study will lead to a clinical trial so the research team can further evaluate the safety and effectiveness of this novel treatment. With MDM2 amplification and overexpression implicated in a variety of cancers, he believes that AMG-232 (or similar drugs, including those that block both MDM2 and a related protein, MDMX) could be widely applicable—and it could

even benefit immunotherapy patients whose tumors have normal MDM2 levels.

"We think this might be a good approach to treat patients whose tumors are predicted to undergo hyperprogression, but I would say our results show that targeting MDM2 in combination with immunotherapy works well even if MDM2 is not amplified or overexpressed," El-Deiry said. "It's tapping into a vulnerability within tumors to help immunotherapy work better."

In addition to El-Deiry, other Brown University authors on the study were Ilyas Sahin, Shengliang Zhang, Arunasalam Navaraj, Lanlan Zhou, Don Dizon and Howard Safran. The study was supported by the Mencoff Family endowed professorship at Brown.

This news story was authored by contributing science writer Kerry Benson.

More information: Ilyas Sahin et al, AMG-232 sensitizes high MDM2-expressing tumor cells to T-cell-mediated killing, *Cell Death Discovery* (2020). DOI: 10.1038/s41420-020-0292-1 Ilyas Sahin et al. AMG-232 sensitizes high MDM2-expressing tumor cells to T-cell-mediated killing, *Cell Death Discovery* (2020). DOI: 10.1038/s41420-020-0292-1

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