Pretreatment with TNF inhibitors may improve outcomes of combination cancer immunotherapy

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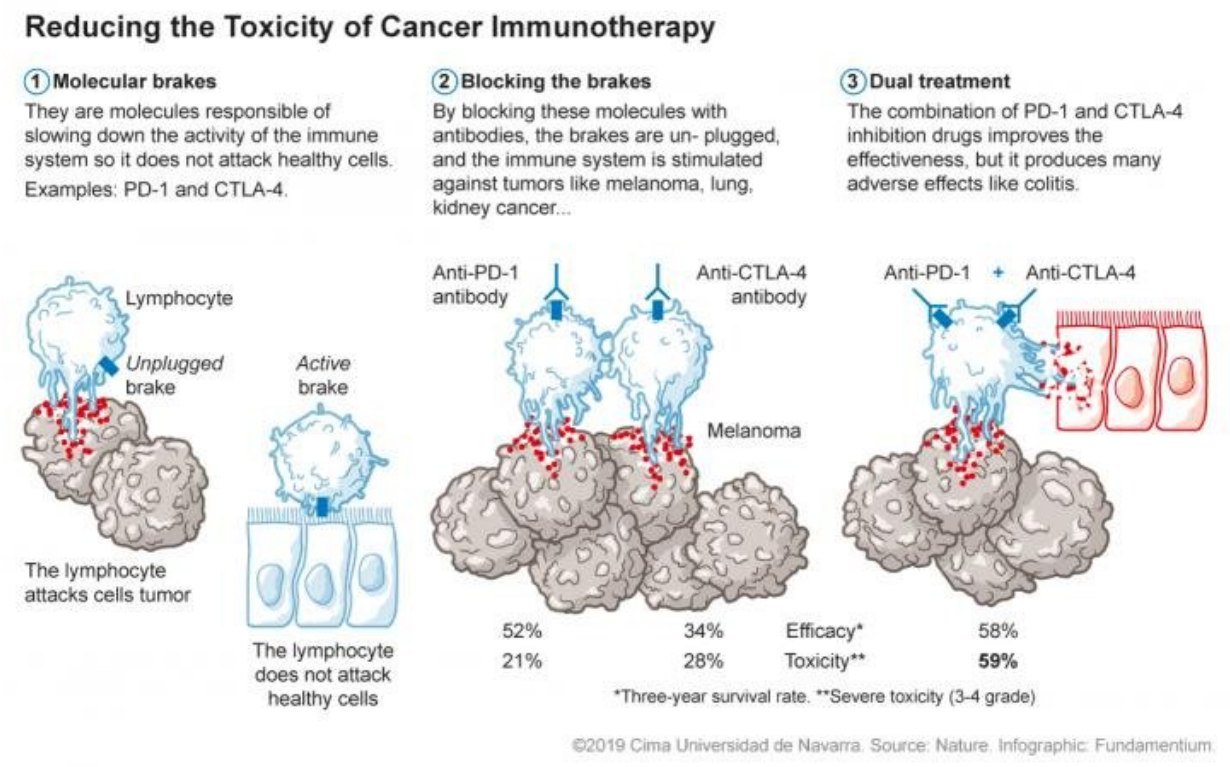
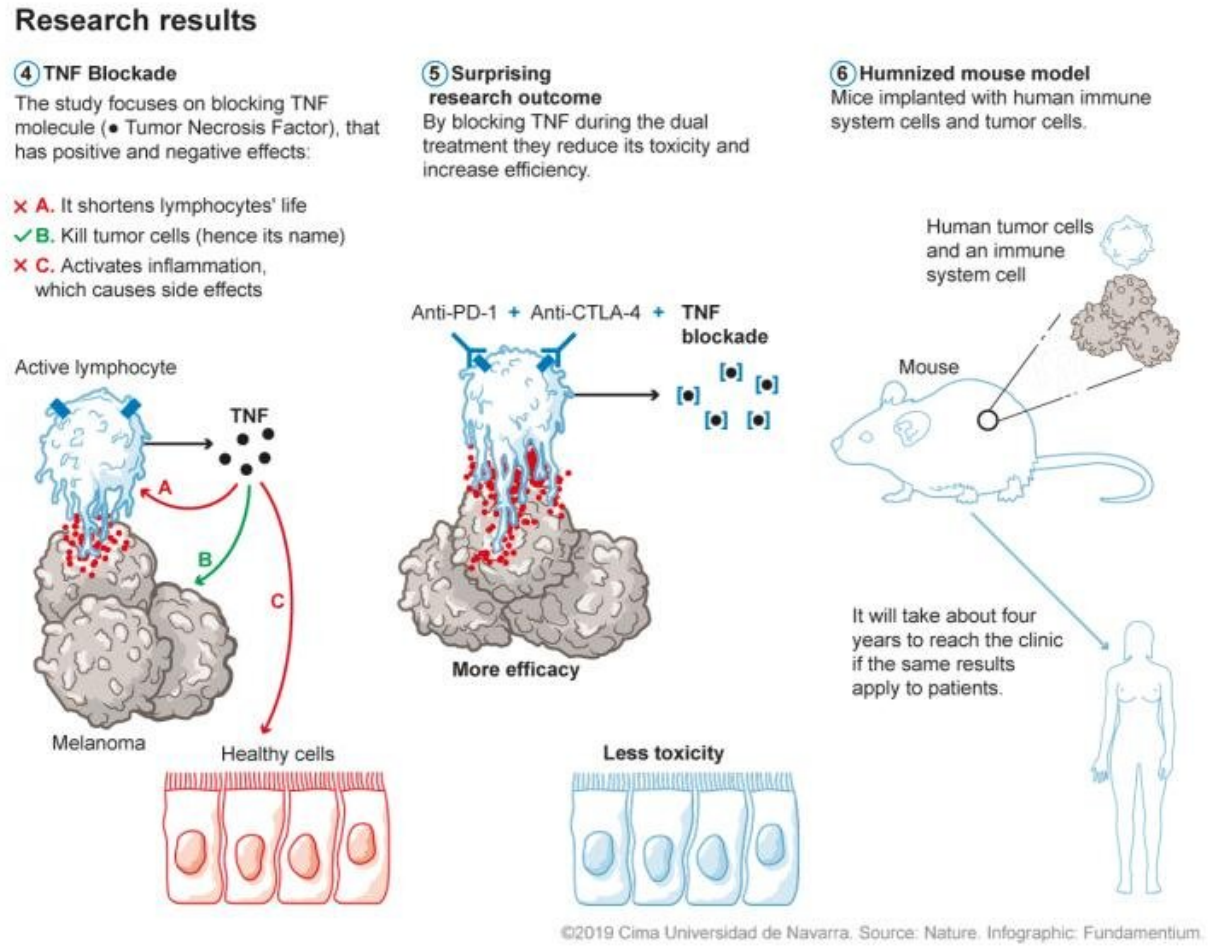


Study proposes a new therapeutic approach against cancer that dissociates efficacy and toxicity in the use of combined immunotherapy in animal models. This clinical strategy consists of blocking TNF protein while applying combination immunotherapy treatment (inhibition therapy of PD-1 and CTLA-4, other proteins that 'slow down' the immune response). Credit: Cima Universidad de Navarra

A collaborative experimental study led by researchers at Cima and Clinica Universidad de Navarra proposes a new therapeutic approach against cancer that dissociates efficacy and toxicity in the use of combined immunotherapy in animal models. This clinical strategy consists of blocking a protein involved in the regulation of the immune system (called tumor necrosis factor, TNF) while applying combination immunotherapy treatment (inhibition therapy of PD-1 and CTLA-4, other proteins that "slow down" the immune response). *Nature*, the leading international weekly journal of science, publishes this research in its latest issue.

"In this study, we have identified that the immunoregulatory function of TNF is dispensable and, to a certain extent, harmful to the antitumor activity of this combined immunotherapy," explains Dr. Ignacio Melero, a senior researcher at Cima and co-director of the Department of Immunology at Clinica Universidad de Navarra. "We have verified that the prophylactic blocking of TNF before applying immunotherapy avoids adverse effects and improves the response to treatment in these animal models. This allows us to adjust the doses of the medication better and thus achieve a more robust anti-tumor efficacy, "adds Dr. Pedro Berraondo, a researcher at Cima. Dr. Elisabeth Perez Ruiz, from Hospital Costa del Sol and first author of the work, highlights the usefulness of this approach "since in prevention context it means using what we already use in routine practice to treat the autoimmune adverse effects."

The next step pointed out by the experts, is to transfer this research to the clinic. According to Dr. Melero, "if we obtain the results of this study in patients, it will change the paradigm for treating cancer. However, despite these promising results in animal models, we must be very cautious about their interpretation, because we don't know with certainty if they will be reproduced in the patients that are included in the ongoing clinical trials or in those that are going to start soon."



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Novelty in anti-TNF treatment

Research in cancer treatment seeks to extend the benefits of

immunotherapy to a more significant number of patients. The latest advances in this field consist of uniting several of these treatments. Among them, "the combination of PD-1 and CTLA-4 inhibition drugs achieves remarkable efficacy against the most aggressive skin cancer (melanoma), kidney and lung cancer. However, 40% of patients suffer serious side effects," says Dr. Melero. "That is precisely why preventing them as achieved in this study is so important for the success of this combined immunotherapy," adds the expert.

PD-1 and CTLA-4 are a type of immune cells proteins (the T lymphocytes) responsible for preventing these cells from destroying other cells, such as cancer cells. Thus, they act as "brakes" in the control of the immune system. By inhibiting these molecules, the "brakes" are unplugged, and the defenses of the organism are stimulated.

The tumor necrosis factor (TNF) serves to mediate inflammation, induce the destruction of some tumor cells, and activate the white blood cells, the cells of the immune system. The blocking of this protein in immunotherapy is not new, but its prophylactic application in this anti-PD-1 and anti-CTLA-4 therapy is. "The clinical evidence is modest, but points to an excellent safety of TNF inhibition in advanced cancer patients," says Dr. Berraondo. "Our results in the laboratory along with previous clinical experience suggest conducting a clinical trial to test the safety and efficacy of this combined immunotherapy treatment. In fact, we are evaluating a potential clinical trial protocol to study the effect of prophylactic TNF blockade upon treatment with nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) in humans," adds the expert.

More information: Elisabeth Perez-Ruiz et al, Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy, *Nature* (2019). DOI: 10.1038/s41586-019-1162-y