MedicalXpress

Review highlights potential of cancer immunotherapy plus targeted therapy

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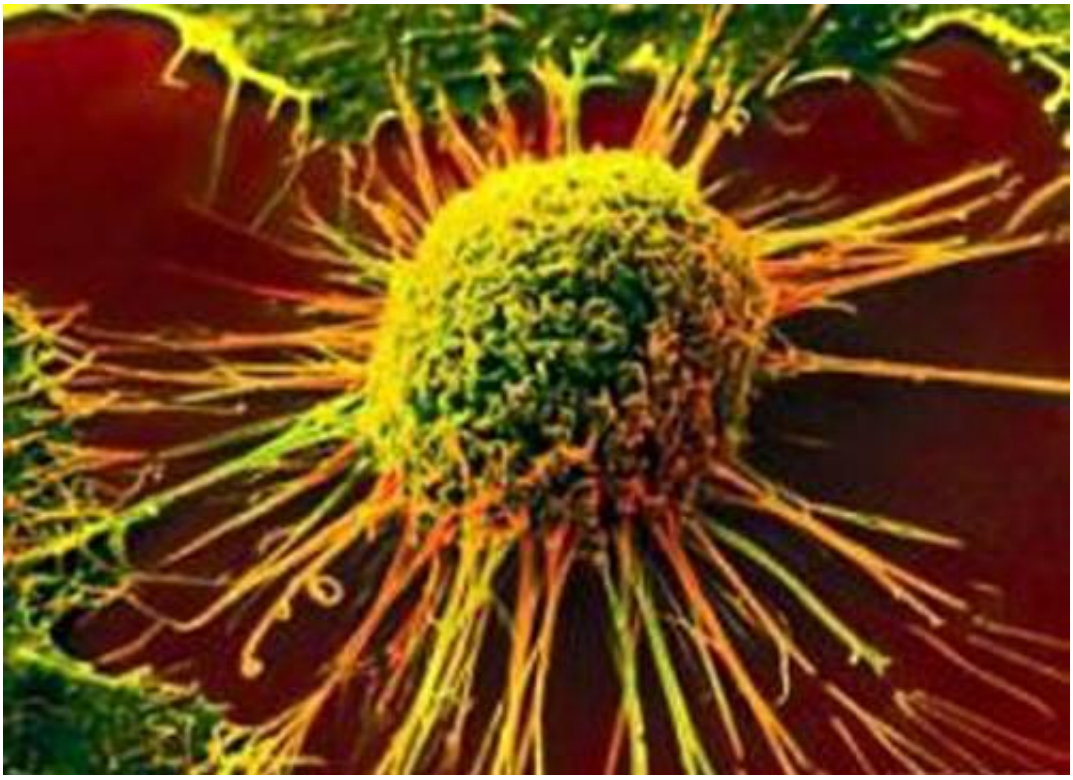


The prospect of combining genomically targeted therapies with drugs that free the immune system to attack cancer suggests "we are finally poised to deliver curative therapies to cancer patients," researchers at The University of Texas MD Anderson Cancer Center note in a review in the April 9 edition of *Cell*.

"To support this goal and accelerate these efforts, changes in directions of research support and funding may be required," co-authors Padmanee Sharma, M.D., Ph.D., professor of Genitourinary Medical Oncology and Immunology, and Jim Allison, Ph.D., chair of Immunology, said in the review.

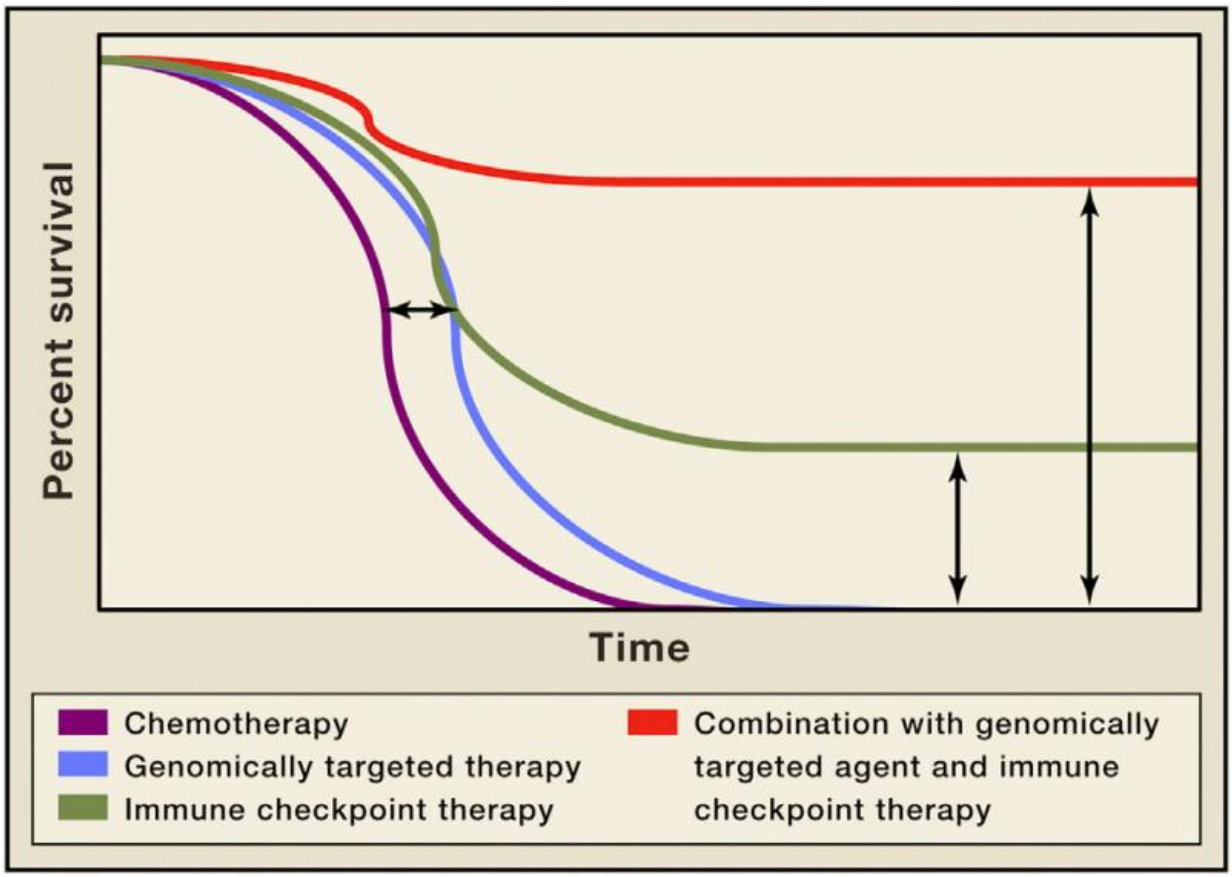
The review, titled "Immune Checkpoint Targeting in Cancer Therapy: Toward Combination Strategies with Curative Potential," covers the strengths and weaknesses of the two forms of therapy and notes how their combination could be particularly potent.

While individual researchers and pharmaceutical companies are studying and developing both types of drugs, a major initiative is needed to understand how both drug types might best work together, Sharma and Allison note.

"Without a major initiative, it will be harder to make progress because the groups focused on genomically targeted therapy and the checkpoint blockade researchers will largely stay in their own camps," Sharma said.

Targeted therapy: Frequent but short-lived responses

The molecular mechanisms involved in the development of cancer have been uncovered by extensive research over the past 30 years, culminating in The Cancer Genome Atlas, a National Institutes of Health project that identified and characterized many genetic mutations that fuel cancer.



A depiction of Kaplan-Meier survival curve with genomically targeted agents(blue line) as compared to standard therapies (purple line), indicating animprovement in median overall survival but lack of durable responses;improved median overall survival and durable responses in a fraction ofpatients treated with immune checkpoint therapy (green line); possibility forimproved median overall survival with durable responses for the majority ofpatients in the setting of combination treatment with genomically targetedagents and immune checkpoint therapy (red line). Credit: Sharma et al./*Cell* 2015

Drugs that hit a specific genomic defect that drives a patient's cancer provoke good initial responses in most patients, the review notes. For example, drugs that target a specific BRAF gene mutation commonly

found in melanoma shrink tumors in about half of patients with the mutation.

However, resistance almost always develops because tumors harbor multiple genomic defects capable of driving the disease after a targeted drug knocks down one driver. BRAF inhibitors prolonged median survival in clinical trials by about seven months.

Checkpoint blockade: Fewer but stronger results

Allison pioneered immune checkpoint blockade, an approach that treats the immune system, rather than the tumor directly, by blocking molecules on T cells that shut those attack cells down, protecting tumors from immune response.

The first such drug, called ipilimumab (Yervoy), developed out of Allison's basic science research, showed much lower response rates against advanced melanoma than those obtained with targeted drugs, but long-term follow-up found that 22 percent of those treated with Yervoy survived at least four years, unprecedented results for the disease. Importantly, those who survived three years have gone on to live up to 10 years and beyond.

Drugs that hit other immune checkpoints have been developed after Yervoy and show similar response rates in a variety of cancers.

Immunity is key to long-term responses

Knowing that the immune system is capable of recognizing distinctive features of cancer cells and launching a T cell attack against those tumor antigens, and that checkpoint blockade removes a roadblock to that attack, it's logical that these drugs should work against many tumor

types. But the impact varies across cancers.

"We need to understand why some patients don't respond to immunotherapy," Allison said. But in others, the response is dramatic, as evidenced by the long-term survival of the those melanoma patients.

The immune system is custom made to deal with the problem of genomic diversity of tumors, Allison said.

"T cells are specific; they recognize and attack tumor-specific antigens down to the peptide level. They remember those target antigens forever, so they can thwart recurrence," Allison said. "And finally, T cell response is adaptable, generating custom T cells to match multiple targets found in the genomic diversity of the tumor or generated by new mutations."

How combinations might work

There's a school of thought, Sharma notes, that combining multiple genomically targeted therapies might prove effective. However, evidence suggests that tumor genomic diversity might still defeat such combinations, and that it's axiomatic in oncology that side effects increase in number and intensity as more drugs are added to treatment.

Targeted therapies might act as effective cancer vaccines, killing tumor cells and releasing new target antigens for T cells to identify and associate with tumors. And they might vary in their ability to enhance or inhibit immune response, because little is known right now about how targeted agents affect the immune system, Sharma said.

Early efforts to combine approaches have yielded interesting results. One phase I trial of an immune checkpoint blockade drug combined with two established targeted therapies yielded 40-50 percent response

rates among patients with metastatic kidney cancer. Follow-up has not been long enough to determine durability of responses or impact on survival.

Two clinical trials combining Yervoy with two different BRAF inhibitors in melanoma illustrate potential issues for combination therapy. In one case, liver toxicity led to closure of the trial, while the other combination appears well-tolerated as the trial continues.

"This highlights that differences in drugs, doses and dosing schedule need to be evaluated as we develop combination therapies," Sharma said.

While checkpoint blockade drugs currently focus on blocking two checkpoint mechanisms, others have been identified by research, as well as molecules that stimulate immune response. These provide new targets for immunotherapy. Facing multitudes of possible drug combinations, more effective preclinical research could make the choosing of such combinations for clinical trials more precise.

The two investigators address such issues in their leadership roles of the immunotherapy platform for MD Anderson's Moon Shots Program. The program is designed to accelerate the conversion of scientific discoveries into clinical advances that significantly reduce cancer deaths.

Enhanced support for immunotherapy

Sharma and Allison close by noting that federal funding for cancer research has been "overwhelmingly directed toward genomically targeted therapies." While Allison's early research that led to Yervoy was funded by the National Cancer Institute, "since then, there have been no major initiatives to accelerate progress in this area."

They suggest allocating greater resources to research focused on immune

checkpoint therapies and targeted/immunotherapy combination therapies with "curative potential."

They conclude: "At this stage, it does not seem a stretch to say that increasing funding to combination therapies will be key to development of new, safe treatments that may prove to be curative for many patients with many types of cancer."

More information: *Cell*, Sharma, P. and Allison, J.P.: "Immune Checkpoint Targeting in Cancer Therapy: Toward Combination Strategies with Curative Potential"
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