Combined BRAF-targeted and Immunotherapy Shows Promise for Melanoma Treatment

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Oncogenic BRAF contributes to immune escape in melanoma.
MAPK pathway inhibition can release suppression.
BRAF inhibition improves T-cell immune response against cancer.

PHILADELPHIA - Combined targeted therapy against the BRAF/MAPK pathway with immunotherapy shows promise as a new therapeutic approach for the treatment of melanoma, according to results of a preclinical study published in *Cancer Research* [2], a journal of the American Association for Cancer Research.

"Our results provide preclinical evidence for the rational combination of BRAF-targeted therapy and immunotherapy in the treatment of this most dangerous type of skin cancer," said lead researcher Jennifer A. Wargo, M.D. [3], division of surgical oncology at Massachusetts General Hospital, Boston.

"By blocking the oncogenic BRAF, tumor antigen expression may be restored. This would make the melanoma tumors susceptible to strategies incorporating immunotherapy," she said.

Previous studies have shown that melanoma treatment with selective BRAF inhibitors are very effective and result in a high initial response rate, but the response is temporary. An alternative approach would be to combine other agents and extend the duration of treatment response.

Using biopsies of melanoma tumors, the researchers investigated the effects of mitogen-activated protein kinase (MAPK) pathway inhibition vs. selective inhibition of BRAF-V600E on T-cell function.

Inhibition of the MAPK pathway with a specific inhibitor of BRAF-V600E resulted in increased expression of antigens, which was associated with improved recognition by antigen-specific T-cell. T-cell function was not compromised after treatment with BRAF-V600E.

Mario Colombo, Ph.D. [4], director of molecular immunology at the Italian National Cancer Institute and senior editor for *Cancer Research*, said these results advance cancer research by offering new arguments to sustain the combination of selective targeted therapy with immunotherapy.

"This study shows the need for considering the effect of off-targeted drug therapy

on the many aspects of host immune response to make real the combination of chemo- and immunotherapy," Colombo said. "It also prompts the idea of performing vaccination in the attempt to eradicate the disease and prevent recurrence."

Several clinical trials are underway using agents that selectively inhibit BRAF-V600E in patients with metastatic melanoma. These studies have shown impressive response rates, though durability of response remains an issue, according to Wargo.

Results of this study provide a basis for combining this type of therapy with immunotherapy, with the goal of improving durability of responses.

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