Researchers use dual drug strategy to advance melanoma treatment against resistance

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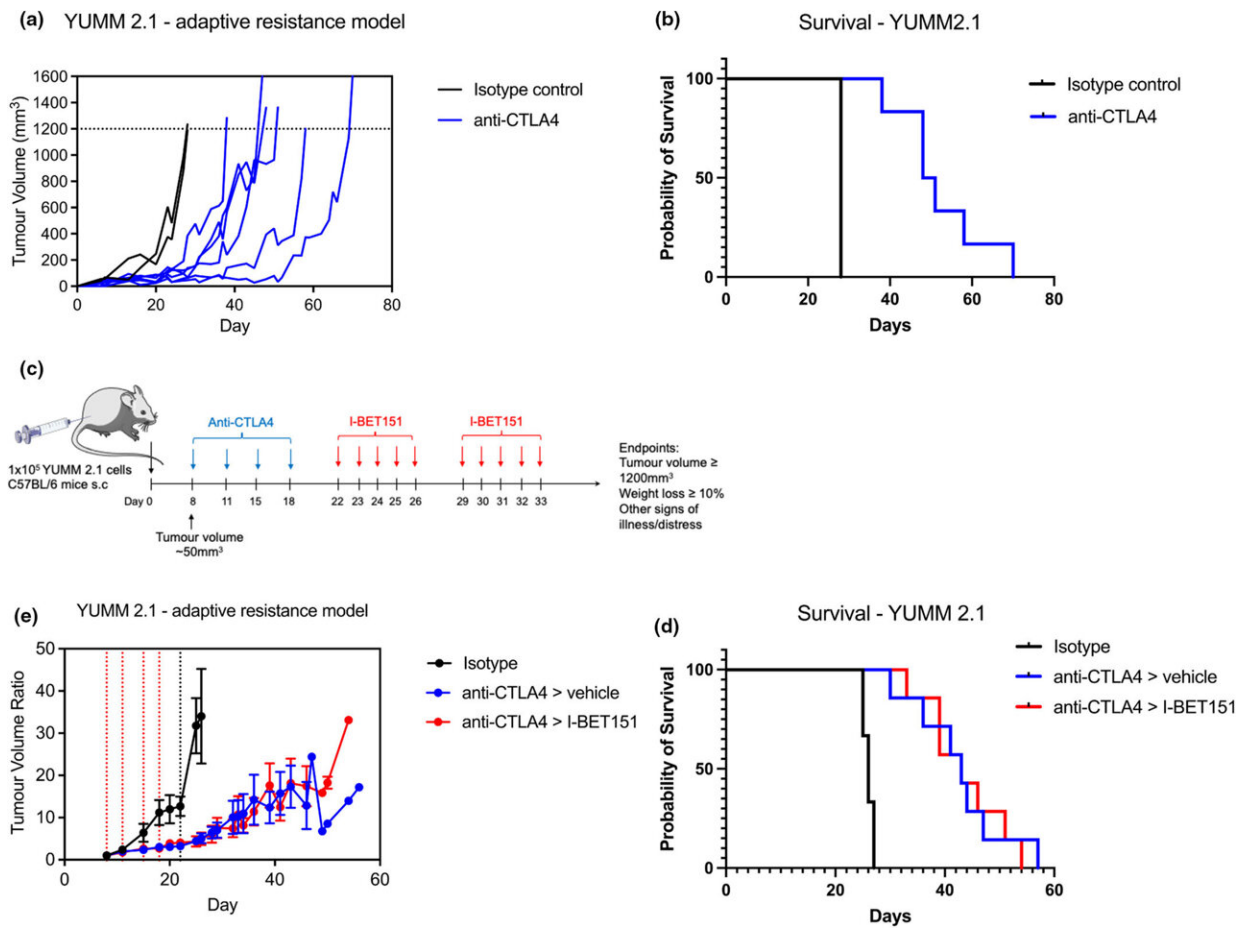

BET inhibition following anti-CTLA-4 is unable to prevent ICB acquired resistance in a melanoma mouse model. Pilot study showing anti-CTLA-4 response and relapse of YUMM2.1 tumors represented by tumor volume (a) or experimental endpoint survival (maximum tumor growth of 1200mm^3) (b).

Dosing schedule of anti-CTLA-4 followed by IBET151 treatment. Tumor volume ratios of isotype control, anti-CTLA-4 alone, or anti-CTLA-4 followed by IBET, endpoint survival (d). Red vertical lines indicate anti-CTLA-4 treatment whereas black indicates the start of IBET treatment. Credit: *Pigment Cell & Melanoma Research* (2024). DOI: 10.1111/pcmr.13174

Research conducted by the Centenary Institute has revealed a promising new approach to tackling melanoma, an aggressive form of skin cancer notorious for its resistance to conventional treatments.

Published in the journal *Pigment Cell & Melanoma Research*, the study identifies a new "dual drug" strategy that could redefine treatment options for patients facing immune checkpoint blockade resistance, a frequent challenge in melanoma treatment.

Immune checkpoint blockade (ICB) therapy, a form of immunotherapy, aids the immune system in identifying and attacking cancer cells by blocking proteins that hinder immune responses. However, overcoming patients' physical resistance to ICB therapy remains a significant obstacle in treating melanoma.

The study found that high levels of bromodomain and extra terminal (BET) proteins were linked to poorer survival and less effective ICB responses in people with melanoma. Additionally, in experiments involving mice, a combination of two drugs, BET inhibitor IBET151 and anti-CTLA-4, successfully overcame innate resistance to ICB, suggesting a new and promising treatment option for many melanoma patients.

Dr. Cindy Hsin-Yi Tseng, co-lead study author and researcher at the Centenary Institute's Center for Cancer Innovations said melanoma poses a significant clinical challenge.

"About half of all melanoma patients don't respond to immune checkpoint blockade therapy due to treatment resistance. Even those who initially respond positively may eventually lose that response, impacting their long-term survival," said Dr. Tseng.

"Our research not only sheds light on the reasons behind treatment resistance but also proposes a new drug combination for melanoma patients with innate resistance to this type of immunotherapy. This breakthrough brings renewed hope for improved treatments benefitting both patients and clinicians," she said.

More information: Hsin-Yi Tseng et al, BET inhibition sensitizes innate checkpoint inhibitor resistant melanoma to anti-CTLA-4 treatment, *Pigment Cell & Melanoma Research* (2024). DOI: 10.1111/pcmr.13174

Provided by Centenary Institute