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Targeted Therapy

Major Finding: *HER3* missense mutations can inhibit response of tumor cells to HER2-targeted therapies.

Concept: PI3K inhibitors recover response to HER2-targeted therapies in cells with mutated *HER2* and *HER3*.

Impact: Combined HER2 and PI3K inhibition may be a promising strategy in tumors with *HER2* and *HER3* mutations.

HER3 MUTATIONS AFFECT TUMOR RESPONSE TO HER2-TARGETED THERAPIES

Activating mutations in the receptor tyrosine kinase gene HER2 occur in a subset of breast and other cancers and are key biomarkers for the treatment of these tumors. They are often found alongside missense mutations affecting the related receptor HER3, with which HER2 can heterodimerize, but little is known about how these *HER3* mutations affect HER2 and the subsequent response to targeted therapies. Using computational modeling, Hanker, Brown, and colleagues predicted that the $HER3^{E928G}$ mutation would enhance kinase domain dimerization and increase HER2 activation compared with wild-type HER3. Co-immunoprecipitation experiments in cells engineered to express combinations of wild-type or mutant HER2 and HER3 revealed that the simultaneous presence of HER2 and HER3 mutants increased HER2/HER3 and PI3K activation in a ligand-independent manner. *In vitro* 3-D culture of nonmalignant breast epithelial cells transduced with combinations of *HER2* and *HER3* mutations showed increased invasion and growth compared with cells expressing only *HER2* mutations. Cells expressing the $HER2^{S310F}$ mutant were sensitive to HER2-targeting antibody treatments that inhibited dimerization and blocked phosphorylation of HER3 as well as downstream phosphorylation of AKT and S6. The introduction of $HER3^{E928G}$ reversed this response. *HER3* mutations influenced the response of HER2 wild-type and mutated cells and patient-derived organoids to the tyrosine kinase inhibitor neratinib, with simulations suggesting that the association of mutant HER3 with HER2 reduced the binding affinity of neratinib to HER2. Combining neratinib with the PI3K inhibitor alpelisib to treat cells expressing both HER2 and HER3 mutants blocked AKT and S6 phosphorylation more effectively than either single agent alone, also reducing growth and invasion in a 3-D culture model. RNAi knockdown experiments in colorectal cancer cells harboring somatic *HER2* and *HER3* mutations also showed that both regulate proliferation and PI3K activity, and that neratinib and alpelisib were required to block proliferation and growth of xenografts *in vivo*. The authors conclude that *HER3* mutations affect response to single-agent HER2-targeting TKIs and suggest that combination therapy with PI3K inhibitors may be a promising therapeutic strategy. ■

Hanker AB, Brown BP, Meiler J, Marín A, Jayanthan HS, Ye D, et al. Co-occurring gain-of-function mutations in HER2 and HER3 modulate HER2/HER3 activation, oncogenesis, and HER2 inhibitor sensitivity. Cancer Cell 2021;39:1099–114.

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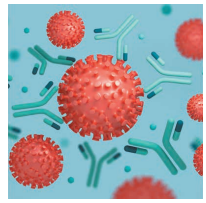
Immunology

Major Finding: Patients with tumors had low seropositivity rates after one vaccine dose but high rates after both doses.

Concept: Age, sex, and disease stage did not appear to affect seroconversion rates in patients with cancer.

Impact: BNT162b2 seems effective in patients with cancer but may require two doses to provide protection.

PATIENTS WITH SOLID TUMORS SEROCONVERT AFTER SARS-CoV-2 mRNA VACCINE



Some recent studies have concluded that cancer is a risk factor for severe or fatal COVID-19, and patients with cancer have been defined by many organizations as comprising a high-risk group to be prioritized for vaccination. Several SARS-CoV-2 vaccines have now shown safety and efficacy in phase III clinical trials; however, these studies did not assess the impact of cancer or anticancer treatment on these outcomes. To address this, Goshen-Lago and colleagues conducted a cohort study of the two-dose Pfizer–BioNTech SARS-CoV-2 mRNA vaccine (BNT162b2) enrolling 232 patients with solid tumors undergoing active anticancer treatment along with 261 healthcare workers, who served as control participants. Following the first vaccine dose, 29% of patients with cancer were seropositive for SARS-CoV-2 IgG, whereas 84% of control participants were seropositive at the same timepoint. Age was a factor affecting seropositivity after the first dose in control participants, with those under age 60 having a seropositivity rate of 94% compared with 80% for those aged 60 or older, but it was not a major factor among patients with cancer. Along with age, sex and disease stage were not found to be correlated with seropositivity after vaccination. Interestingly, IgG titers among those who were seropositive after the first dose did not differ between patients with cancer and control participants. Importantly, after the second vaccine dose, 86% of patients with cancer were seropositive, nearly reaching the seropositivity rate in the control participant group. The safety and tolerability profile for the vaccine was favorable in both groups, and adverse events (mainly injection site pain) were as expected based on previous studies. In summary, this work demonstrates that patients with solid tumors seroconvert following administration of the recommended two doses of the BNT162b2 vaccine despite having lower rates of seropositivity than control participants after a single dose; additionally, the vaccine appeared to be safe in this vulnerable group. Further research to determine whether these findings also apply to hematologic malignancies is warranted. ■

Goshen-Lago T, Waldhorn I, Holland R, Szwarcwort-Cohen M, Reiner-Benaim A, Shachor-Meyouhas Y, et al. Serologic status and toxic effects of the SARS-CoV-2 BNT162b2 vaccine in patients undergoing treatment for cancer. JAMA Oncol 2021 Jul 8 [Epub ahead of print].

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AACR American Association for Cancer Research

CANCER DISCOVERY

Patients with Solid Tumors Seroconvert after SARS-CoV-2 mRNA Vaccine

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