CANCER DRUG PAIRINGS

Among the first cancer drug combinations were mixtures of several chemotherapies that resulted in better and longer-lasting responses than individual drugs could deliver. Then came targeted therapies and immunotherapies, which were combined with chemotherapies and with each other to increase the proportion of patients who respond and the duration of those responses. While many cancer drug combinations were discovered by empirically testing opportunistic and random pairings, others were based on biological hypotheses that one drug could complement the other. Below are a few of the strategies behind recently successful and still investigational combos.

**DROUBLING UP ON TARGETED THERAPY**

Codistributing two targeted agents that work on different targets within the same signaling pathway is a way to stave off cancer resistance. Combining two targeted agents that block molecules within different pathways is another common strategy.

In 2014, the FDA approved the first combination: dabrafenib, a B-raf inhibitor, plus trametinib, a MEK inhibitor, for advanced melanoma. The two drugs target different molecules within the Ras signaling pathway.

The combination of lenvatinib, an anti-VEGF oral drug, and everolimus, an oral mTOR inhibitor, was approved by the FDA for renal cell carcinoma in 2016. The drugs target two separate but cancer-linked signaling pathways that support tumor growth.

**IMMUNOTHERAPY-CHEMOTHERAPY, RADIATION, OR TARGETED THERAPY**

As chemotherapy, radiation, or targeted therapies kill cancer cells, neoantigens are released, helping the immune system recognize tumor cells. These therapies also minimize tumor burden, buying time for the immune system to act. Simultaneously, checkpoint inhibitors ramp up the immune response.

In 2017, the FDA approved the combination of the chemotherapies pemetrexed and carboplatin, plus the checkpoint inhibitor pembrolizumab, for advanced lung cancer.

**CHECKPOINT INHIBITOR PLUS A CELL-BASED THERAPY**

Also seen as a way to target different pathways to amplify the immune response and potentially overcome resistance.

**CHECKPOINT INHIBITOR PLUS A VIRAL VACCINE**

A vaccine, in theory, should increase the presentation of cancer neoantigens to the immune system, bolstering the immune system’s response to a checkpoint inhibitor.

**CHECKPOINT INHIBITOR PLUS A CELL-BASED THERAPY**

The cancer vaccine talimogene laherparepvec, a genetically engineered modified virus, was used to sensitize the animals to an anti-PD-1 antibody. And when the combination was coupled with tumor resection, up to 90 percent of the animals had zero evidence of disease. A version of the Maraba virus expressing the neoantigen MAGE-A3 is currently being tested in a Phase 2 targets the B-raf protein itself, while trametinib targets MEK, a downstream kinase. The combination decreased the risk of death from melanoma by 31 percent compared with dabrafenib alone and was approved by the FDA in January 2014. Recently, researchers at the Netherlands Cancer Institute uncovered two distinct populations of cells within drug-resistant melanomas. One consisted of cells expressing low levels of AXL, a receptor tyrosine kinase, and sensitive to B-raf and MEK inhibitors. The second population expressed high levels of AXL, was resistant to a B-raf plus MEK inhibitor combination, but was sensitive to a novel drug called an antibody-drug conjugate that binds to AXL on the surface of the tumor cells. The team showed that a triple combination targeting both cell populations was more effective than the standard combination, resulting in durable responses in patient-derived xenografts from resistant melanomas.

Sometimes the logic behind a potential drug combo is not as simple as targeting the pathways inside tumor cells. When it comes to immune checkpoint therapies, which don’t target the tumor cells directly but rather the immune system, clinical studies have revealed that patients are most responsive if they have already started to mount an antitumor response. Thus, some researchers are now looking to layer additional drugs on top of an immunotherapy to transform a nonresponsive immune system to a tumor-responsive one.

Earlier this year, for example, researchers at the University of Ottawa found they could slow tumor growth in mouse models of triple-negative breast cancer that are typically unresponsive to an immune checkpoint therapy by treating them with a Maraba rhabdovirus that sensitized the animals to an anti-PD-1 antibody. And when the combination was coupled with tumor resection, up to 90 percent of the animals had zero evidence of disease. A version of the Maraba virus expressing the neoantigen MAGE-A3 is currently being tested in a Phase 2 clinical trial.

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