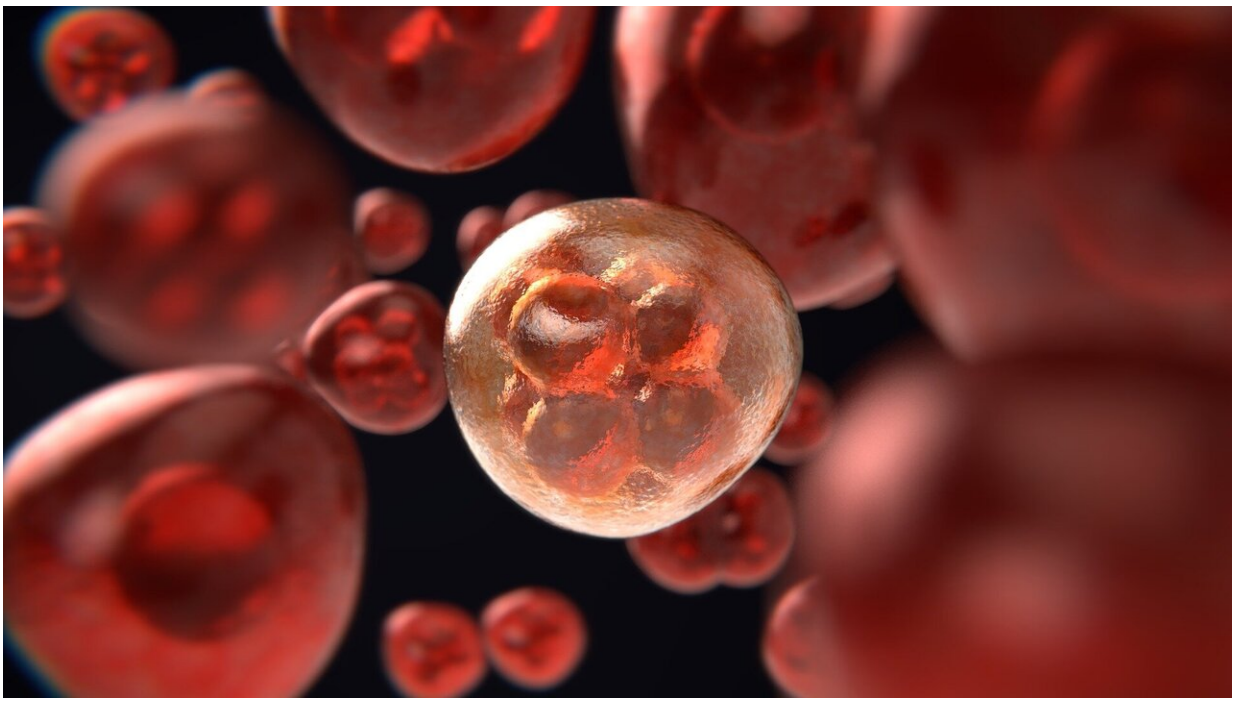
MedicalXpress

Combination therapies may improve outcomes due to independent, rather than synergistic or additive, drug action

January 19 2022



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Independent drug action, not synergy nor additivity, accounted for the clinical efficacy of nearly all examined combination therapies involving immune checkpoint inhibitors in clinical trials, according to results from a retrospective analysis.

The study was published in*Clinical Cancer Research*, a journal of the American Association of Cancer Research (AACR).

While immune checkpoint inhibition, a form of cancer immunotherapy, has greatly improved outcomes for certain patients, most patients still do not benefit from this treatment. Combining immune checkpoint inhibitors either with each other or with other cancer therapies has improved responses in many cases, leading to the approval of various combinations by the U.S. Food and Drug Administration. However, the underlying reason for the greater clinical efficacy of combination therapies compared with single-agent immune checkpoint inhibition remains understudied.

"Combination therapy dominates the treatment landscape for cancer," said Sorger. "There is, therefore, enormous interest in understanding why combination therapies work or don't work for patients, and in understanding how we can better design new combinations."

In this study, Sorger, Palmer, and colleagues, sought to determine whether the benefits of combination therapies were a result of drug synergy or if they were simply due to independent drug action, which Sorger described as "bet hedging."

The concept of independent drug action was first introduced by Emil Frei in 1961, and has long been understood to occur in chemotherapy combinations. Sorger, Palmer, and colleagues explained this concept, its historical context, and its contemporary applications in a recent review article published in *Cancer Discovery*, another journal of the AACR.

"Whereas a single drug might not be effective in killing every cancer cell in a heterogeneous tumor, drug combinations have the potential to kill different subset of cells, improving the likelihood and durability of response," they wrote. "The same reasoning also applies to inter-patient

heterogeneity: Any single therapy will not be effective in every patient but combination therapies provide patients with several opportunities for a clinically meaningful response." Thus, when a combination works through independent drug action, the benefit to an individual patient is attributed to only one of the drugs in the combination; the benefit over monotherapy is due to increasing the odds that the combination includes a drug that is effective for a given patient.

This mode of drug action contrasts with synergy, in which one drug enhances the clinical activity of another drug in the combination, and additivity, in which the clinical benefit is the sum of multiple drugs in the combination.

How the study was conducted

To determine whether independent drug action was behind the efficacy of oncology combination therapies, the researchers utilized a predictive model in a retrospective analysis of 13 clinical trials of immune checkpoint inhibitor combination therapies representing eight different cancer types.

"For each immunotherapy combination we examined, we used a probability model to calculate the expected progression-free survival distribution that would occur if the combination worked through independent drug action," explained Palmer. "This expected distribution from independent drug action was then compared to the actual trial result."

If the actual progression-free survival observed in the clinical trial was not different from the predicted benefit, then the authors concluded that the combination worked through independent drug action; if the actual progression-free survival was significantly greater than the prediction, then the combination benefit was due to synergy or additivity, he added.

Results

Their analyses found that the progression-free survival of patients receiving 12 of the 13 evaluated combinations was similar to or shorter than the predicted outcomes for independent drug action, suggesting that the benefit of these combinations were due to independent drug action rather than synergy or additivity.

In the phase III IMpower150 trial, patients with metastatic non-small cell lung cancer who received first-line treatment with the immune checkpoint inhibitor atezolizumab plus chemotherapy and bevacizumab had longer progression-free survival than would be expected by independent drug action, suggesting that this drug combination may have a synergistic or additive effect on clinical outcomes in this setting.

Author's comments

"Our study revealed that the efficacies of all but one of the combination therapies we analyzed occurred through independent drug action, and not through synergy or additivity," summarized Palmer.

"To be clear, we are not suggesting that these combinations are ineffective. We agree that the combinations are clinically effective; what we are proposing is that their effectiveness is through a different mechanism than was previously thought," said Sorger. "These findings have important implications for preclinical and clinical research."

Sorger suggested that instead of focusing on achieving drug synergy through interacting mechanisms, researchers should instead combine drugs that are known to have single-agent efficacy in a given disease context. "By combining two drugs that are each effective for some patients with a disease, we can increase the odds that a patient's cancer

will respond to one of the drugs," he explained.

Sorger added that the study's findings also indicate a need to better understand variability in treatment response among patients and to identify biomarkers that could accurately predict a patient's response to individual drugs in a combination. For combinations working by independent drug action, greater precision could yield substantial improvements in clinical outcomes even with existing drugs, a notion supported by preclinical research, he explained.

Furthermore, the propensity of independent drug action in combination therapies suggests that administering drugs sequentially, rather than together, might reduce toxicities without impacting clinical efficacy. However, Palmer adds that in a rapidly progressing cancer, it is often best to provide the greatest chance of tumor control upfront by using a simultaneous combination.

Study limitations

A limitation of the study is that it was a retrospective analysis with imputed data. An additional limitation was that only a subset of existing combination therapies could be analyzed by their predictive model due to the lack of data on monotherapy activity.

More information: Adam C. Palmer et al, Predictable Clinical Benefits without Evidence of Synergy in Trials of Combination Therapies with Immune-Checkpoint Inhibitors, *Clinical Cancer Research* (2022). DOI: 10.1158/1078-0432.CCR-21-2275

Provided by American Association for Cancer Research