Assessment of Clinical Activity of PD-1 Checkpoint Inhibitor Combination Therapies Reported in Clinical Trials

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Abstract

IMPORTANCE Because cancer drugs given in combination have the potential for increased tumor-cell killing, finding the best combination partners for programmed cell death 1 (PD-1) checkpoint inhibitors could improve clinical outcomes for patients with cancer.

OBJECTIVE To identify optimal strategies for combining PD-1 immune checkpoint inhibitors with other cancer therapies.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study compiled 319 results from 98 clinical trials testing PD-1 pathway inhibitors alone or in combination with other agents among 24,915 patients with metastatic cancer. All clinical trials had a primary completion date before September 16, 2018. Data analysis was conducted from November 2018 to August 2019.

EXPOSURES Patients with metastatic cancer were treated with PD-1 immune checkpoint inhibitors alone or with other cancer therapies.

MAIN OUTCOMES AND MEASURES Clinical activity was measured as objective response rates (ORRs). Combination measures included fold change from monotherapy to combination ORR, comparison of observed combination ORRs with estimated combination ORRs based on independent additivity, and a computational model to assess clinical synergy. To assess whether the ORRs of various combinations may be greater than the independent contribution of each agent, a Bliss independent activity model was used to analyze observed combination ORRs, and a Z score, measuring the difference between observed and calculated ORRs, was generated.

RESULTS In 319 results from 98 clinical trials among 24,915 patients, ORRs for monotherapy were compared with combination data by indication and line of therapy, demonstrating an increased ORR in 105 of 127 results (82.7%) where ORRs were available for both PD-1 pathway inhibitor monotherapy and combination therapy. A few combinations showed increases above the Bliss-estimated activity, possibly identifying limited clinical synergy. The mean (SD) Z score for all trials was 0.0430 (0.0243). The mean (SD) Z score was 0.0923 (0.0628) for platinum chemotherapy regimen combinations, 0.0547 (0.0821) for vascular endothelial growth factor or vascular endothelial growth factor receptor tyrosine kinase inhibitor combinations, 0.0893 (0.086) for indoleamine 2,3-dioxygenase inhibitor combinations, and 0.0558 (0.0849) for cytotoxic T-lymphocyte-associated protein 4 inhibitor combinations.

CONCLUSIONS AND RELEVANCE In this cross-sectional study, most combination trials showed the expected benefit of combining 2 active anticancer agents, but few combination trials showed clinical synergy according to the Bliss independent activity model.

Key Points

Question What therapies are best combined with programmed cell death 1 (PD-1) checkpoint inhibitors to improve outcomes for patients with cancer who do not respond to PD-1 pathway inhibitor monotherapy?

Findings This cross-sectional study of 98 clinical trials, which included 24,915 patients with metastatic cancer, compared objective response rates of PD-1 checkpoint immunotherapies used alone and in combination. Most combinations succeeded, given that the fold change from monotherapy ORR to combination ORR increased in 82.7% of trials. The highest observed Z score was for trials testing the combination of PD-1 checkpoint inhibitors and platinum-containing chemotherapy regimens.

Meaning In this study, higher combination ORRs were found for chemotherapies; however, all classes of cancer agents could be successfully combined with PD-1 checkpoint inhibitors.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.
Introduction

Advances in immunotherapy are changing treatment paradigms for most cancers. When given in combination, cancer drugs have the potential to increase tumor-cell killing. Therefore, following the success of programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) agents as monotherapies, research is turning to identifying effective combinations. Historically, the rationale for combining therapies has been that using 2 effective drugs with independent mechanisms of action would decrease the likelihood that resistant cancer cells could develop, a strategy that addresses clonal heterogeneity. DeVita and others have shown that agents active by any mechanism in shrinking tumors combine successfully. The activity of cancer treatments is defined by the US Food and Drug Administration (FDA) by using the overall response rate (ORR) in clinical trials, where the ORR is defined as the "proportion of patients with tumor size reduction of a predefined amount for a minimum time period." Clinicians have long sought to find combinations of drugs that might achieve synergy, defined as more than an additive effect. This has been such a key aspiration across all medical fields that a consensus conference in Saariselkä, Finland, determined that a mathematical definition of synergy requires comparison with the Bliss independence model. The Bliss model posits that the combination of 2 agents with independent activities will be estimated by the following equation:

\[ Y_{ab,P} = Y_a + Y_b - Y_a \times Y_b \]

In contrast, coincident with rapid advances in our understanding of the immune system, more than 550 references to checkpoint inhibition in PubMed invoked synergy in the absence of mathematic testing. For example, combinations based on the cancer immunity cycle have been proposed to identify synergy. This search for synergy differs from the historical approach to cancer therapies for 2 main reasons. First, immunologically targeted combination agents have similar, not independent, mechanisms of action. Second, the monotherapy activity of 1 combination partner is not strictly required, based on the premise that synergy will uncover anticancer activity that was unseen as monotherapy. We will refer to this approach to developing combinations as the search for immunologic synergy.

Combinations based on both independent action and immunologic synergy can be found in the more than 3000 clinical trials involving immunotherapies. Optimal combinations could yield more than independently additive effects, which we are calling clinical synergy. It is not at all clear whether immunologic synergy can lead to clinical synergy. This association was tested by Palmer and Sorger, who evaluated data from the combination of ipilimumab and nivolumab in patients with melanoma to show that combination progression-free survival and combination best overall response curves were no greater than the sum expected from each individual agent, as estimated by independence. They concluded that this combination presented no evidence for clinical synergy. Thus, the claimed immunologic synergy for ipilimumab plus nivolumab did not result in clinical synergy.

To enable a rigorous analysis of cancer therapy combination strategy, we compiled and systematically evaluated studies that reported ORRs for clinical combinations involving PD-1 pathway checkpoint inhibitors. We systematically reviewed clinical trials reporting ORRs for PD-1 pathway checkpoint combinations treating advanced metastatic cancers. We then compared the degree to which combination activity could be attributed to the independent activity of each agent vs mathematically greater activity that would be consistent with clinical synergy.
Methods

Per the Office of Scientific and Technical Information Clearance at Merck and Co, this study did not require institutional review board approval because it did not involve direct experimentation among patients. All collected studies were reported on ClinicalTrials.gov and adhered to appropriate standards for ethical research. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Design, Participants, and Data Sources

Clinical trials involving approved PD-1 or PD-L1 immune checkpoint inhibitors (ie, atezolizumab, avelumab, cemiplimab, durvalumab, nivolumab, or pembrolizumab) with results posted before September 16, 2018, were identified by a search at ClinicalTrials.gov. We assessed all trials listed as having a primary completion date before that date. We excluded trials as follows: (1) trials with 9 or fewer subjects, (2) terminated trials, (3) withdrawn trials, (4) trials in which combinations were not administered concurrently, (5) combination trials in biomarker-selected populations, (6) trials that included patients who had undergone prior PD-1 therapies, and (7) trials among patients with stage 1 to 3 diseases. Data entries were cross-checked by at least 2 of the audit team (E.V.S., M.J.C., M.F.C., and M.E.M) for the database.

Additional clinical trials whose results were not yet posted at ClinicalTrials.gov were identified through a systematic review of abstracts presented at major oncology meetings (ie, American Society of Clinical Oncology, American Association for Cancer Research, Gastrointestinal Cancers Symposium, Genitourinary Cancers Symposium, American Society of Clinical Oncology-Society for Immunotherapy of Cancer Immuno-Oncology Symposium, American Society of Hematology, European Hematology Association, European Society for Medical Oncology, San Antonio Breast Cancer Symposium, Society of Gynecologic Oncology, Society for Immunotherapy of Cancer, Targeted Anticancer Therapies, and World Conference on Lung Cancer). Data from additional studies were identified in PubMed using the search terms clinical trial, combination, or therapy with PD-1 pathway inhibitor names. The cross-sectional study sample size was determined by these combined searches.

Data were compiled in a tabular-formatted flat database (eTable 1 in the Supplement). Where results were available from both the literature and at ClinicalTrials.gov, we preferentially recorded literature-reported data. This database was compared with an annotated database (Beacon-Intelligence) to verify completeness. Taken together, these approaches identified all clinical trials involving PD-1 pathway inhibitors that reported ORRs at ClinicalTrials.gov, in articles, or at meeting presentations before the cutoff date.

Variables

We identified ORRs for combination agents or combination regimens in meeting abstracts and/or by a literature search in PubMed. Each member of the audit team (E.V.S., M.J.C., M.F.C., and M.E.M.) independently identified combination agent and regimen data.

Monotherapy ORRs were compiled and summarized by indication, line of therapy, and biomarker selection (eTable 2 in the Supplement). Where more than 1 PD-1 pathway inhibitor was tested in a line of therapy and indication, a consensus monotherapy ORR was calculated by a patient-number weighted mean of available monotherapy data. Where only 1 PD-1 pathway inhibitor was tested in a line of therapy and indication, it was recorded as such.

Combination regimens were classified by mechanism as proposed in previous reviews of cancer immunotherapies.2,12 Orthogonal combinations included radiotherapy, chemotherapy, and targeted therapies. Combinations based on immune synergy hypotheses included agents addressing innate immunity, adaptive immunity, and the tumor microenvironment. Classifications were assigned by consensus among 3 of us (E.V.S, G.A.B, and E.M.P).
Statistical Analysis

The fold change from monotherapy to combination activity was calculated in the database by division when both values were available. Individual values were plotted in a column plot using Excel Office 365 (Microsoft Corp). Histograms assessing the aggregate data, together with calculation of normal curve parameters, was performed in SigmaPlot version 14.0 (Systat Software).

A calculated combination ORR based on the Bliss independent activity model9 for each combination was recorded as $Y_{ab,P} = Y_a + Y_b - Y_a \times Y_b$, in which $Y_{ab,P}$ indicates the estimated proportion of patients responding to agents in combination, $Y_a$ indicates the observed proportion responding to agent or regimen 1, and $Y_b$ indicates the observed proportion responding to agent or regimen 2.

Observed ORRs were compared with Bliss-estimated ORRs using a linear regression plot in Prism version 8 (GraphPad), together with best fit calculations. The difference between the observed ORR and the Bliss-estimated ORR was calculated as a measure of clinical synergy using the following equation:

$$Z = \text{ORR} - (Y_a + Y_b - Y_a \times Y_b),$$

in which the Z score was defined as the difference between the observed ORR for a combination and the estimated combination ORR according to the Bliss equation. Because the Z score measures deviation from additivity, it constitutes a measure of clinical synergy. Individual values were plotted in a column plot using Excel Office 365 (Microsoft Corp). Histograms assessing the aggregate data as well as descriptive statistics were performed in SigmaPlot (Systat Software).

For platinum chemotherapies, vascular endothelial growth factor or vascular endothelial growth factor receptor (VEGF/R) inhibitors, indoleamine 2,3-dioxygenase (IDO) inhibitors, and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitors, all measures were determined for individual combinations and plotted using SigmaPlot (Systat Software). No tests of statistical significance were conducted, and therefore, no prespecified level of statistical significance was set.

Results

We identified 98 trials, which included 24,915 patients with metastatic cancer, involving PD-1 or PD-L1 inhibitors for inclusion in our cross-sectional study. We first evaluated ClinicalTrials.gov for trials with a primary completion date before September 16, 2018, and identified 111 trials. Of these, 70 (63.1%) had accompanying results on ClinicalTrials.gov, and of those, 54 (77.1%) also reported data in an article or at a scientific congress. A search of publications and scientific congress abstracts yielded an additional 28 trials reporting ORRs.

A total of 319 unique trial results were identified within these 98 trials, which were compiled in a master file of results for PD-1 pathway inhibitors (eTable 1 in the Supplement). Clinical activity was assessed as the ORR for each indication and line of therapy.

Cancer drugs are generally developed through a sequence of tests starting in late-line therapies, among patients with no available treatment options. These are then advanced in line of therapy as their potential advantages over current standards of care are established. Consequently, monotherapy responses as well as combination responses to PD-1 and PD-L1 therapies were considered by indication and line of therapy (Figure 1). Figure 1 shows monotherapy ORRs for 46 indications, categorized by line of therapy and enrichment for expression of PD-L1.

To assess potential combination benefit, the fold change from monotherapy response to combination therapy response was determined by dividing the ORR of combination therapy by the ORR of monotherapy using data from the same indication and line of therapy in biomarker-unselected populations (Figure 2A; eTable 3 in the Supplement). To compare combination results for orthogonal combinations (ie, chemotherapy and targeted therapies) with combinations chosen for potential immune synergy (ie, adaptive immunity, innate immunity, and the tumor microenvironment), results were plotted according to combination-regimen classes.

A frequency plot of fold change data is shown for the total combination data set in Figure 2B, comparing combination therapy with PD-1 monotherapy. This plot shows a skewed normal
Figure 1. Plot of the Objective Response Rates (ORRs) for Various Programmed Cell Death 1 Pathway Inhibitors Tested as Monotherapies

The ORRs shown were for any programmed cell death 1 pathway inhibitor where tested or for the mean of all those tested for a given indication and line of therapy. Various biomarkers and cut points were used in these trials; the details of each trial can be found in eTable 2 in the Supplement. BC indicates breast cancer; CLL, chronic lymphocytic leukemia; CRC, colorectal carcinoma; DLBCL, diffuse large B-cell lymphoma; ER, estrogen receptor; FL, follicular lymphoma; GBM, glioblastoma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; MSI, microsatellite instable; MSI-H, microsatellite instable–high; MSS, microsatellite stable; NHL, non-Hodgkin lymphoma; NSCLC, non–small cell lung cancer; NPC, nasopharyngeal cancer; PMBCL, primary mediastinal B-cell lymphoma; RCC, renal cell carcinoma; rrPMBCL, relapsed or refractory primary mediastinal B-cell lymphoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; STS, soft-tissue sarcoma; and TNBC, triple-negative breast cancer.
distribution, with a mean (SD) fold increase of 2.06 (0.33) from monotherapy to combination therapy. The median fold change was 1.72 (95% CI, 1.45-1.97), and 105 of 127 results (82.7%) had a fold change greater than 1.0. A frequency plot of fold change data is shown for the total combination data set in Figure 2C, comparing the ORRs of combination therapies with those of the combining agents or regimens (eg, IDO inhibitors). The fold change in activity from combination regimen to combination therapy also followed a skewed normal distribution with a mean (SD) fold increase of 2.40 (0.35). The median fold change was 1.82 (95% CI, 1.52-2.18), and 81 of 95 results (85.3%) where ORRs were available for the combining regimen as monotherapy and combination therapy had a fold change greater than 1.0.

The Bliss independent action model⁹ is shown diagrammatically in Figure 3A and B. Using the Bliss independent action model, we calculated the predicted ORR for the 100 trials (90.1%) in which the ORRs for PD-1 pathway monotherapy and the combination agent or regimen were known. A regression plot comparing the actual observed ORR with the Bliss predicted ORR is shown in Figure 3C. The slope of the nonlinear regression was 1.073 (95% CI, 1.00-1.14; $R^2 = 0.675$).
Differences between observed ORRs and Bliss-estimated ORRs were calculated and shown as a frequency plot (Figure 3D). The plot fits a normal distribution (Shapiro-Wilk \( P = .83 \)). The mean \( Z \) score contribution was 0.043 (95% CI, 0.019-0.67). Because this calculation measures additional activity, greater than estimated additive independent contributions, it offers a measure of clinical synergy.

To compare orthogonal combinations (ie, chemotherapy and targeted therapies) with immune synergy combinations (ie, the tumor microenvironment, adaptive immunity, and innate immunity), the \( Z \) score was plotted as a measure of clinical synergy for all combinations in which the monotherapy ORR for the PD-1 checkpoint inhibitor and the combination regimen components were available (Figure 4; eTable 4 in the Supplement). The mean \( Z \) score as a measure of clinical synergy for the therapeutic categories was 0.0763 (95% CI, 0.0242 to 0.1284) for chemotherapies, 0.0249 (95% CI, −0.0147 to 0.0645) for targeted therapies, 0.0755 (95% CI, −0.0076 to 0.1596) for tumor microenvironment therapies, 0.0232 (95% CI, −0.0386 to 0.0850) for adaptive immune therapies, and 0.0704 (95% CI, −0.0348 to 0.1756) for innate immune therapies.

As previously reviewed,12 4 types of combination regimens accounted for most available trial data. Combination results for these 4 regimens are shown in Figure 5, which displays results for platinum-containing chemotherapy regimens, VEGF/R inhibitors, IDO inhibitors, and CTLA-4 inhibitors (eTable 5 in the Supplement). The largest distances between the Bliss estimated ORR and the observed ORR were seen for patients with nonsquamous cell lung cancer receiving platinum-containing chemotherapy with pembrolizumab (\( Z \) score, 0.28),14 patients with renal cell carcinoma receiving axitinib plus pembrolizumab (\( Z \) score, 0.35),15 and patients with renal cell carcinoma...
receiving lenvatinib plus pembrolizumab (Z score, 0.28).16 The mean (SD) Z score for all trials was 0.0430 (0.0243). The mean (SD) Z score above the Bliss calculated contribution to combination activity as a measure of clinical synergy was 0.0923 (0.0628) for platinum chemotherapy regimen combinations, 0.0547 (0.0821) for VEGF/R tyrosine kinase inhibitor combinations, 0.0893 (0.086) for IDO inhibitor combinations, and 0.0558 (0.0849) for CTLA-4 inhibitor combinations. This plot offers a systematic approach to understanding PD-1 pathway combination success based on objective mathematic principles.

Discussion

The data compiled here demonstrated that most combination trials involving PD-1 or PD-L1 immune checkpoint inhibitors resulted in ORRs greater than expected from the PD-1 monotherapy associated with those inhibitors (Figure 2). This occurred across a broad range of indications, mechanisms, and classes of compounds. This is a key finding because it implies that PD-1 inhibitors will continue to evolve as a central part of combinations with all types of anticancer agents.

We compared 2 approaches to developing PD-1 combinations: combinations using independent orthogonal agents following historic paradigms vs combinations based on immune synergy hypotheses. Figure 2 shows that, while both strategies increase antitumor activity in a large proportion of clinical trials, more chemotherapies and targeted therapies showed higher fold increases than immune strategies.

Both historically10 and as agreed in consensus conferences,8 the Bliss equation9 is widely accepted as a valid measure of independent additivity. We applied the Bliss equation to all clinical trials in which component monotherapy ORRs were available (Figure 3). Figure 3C showed that the Bliss equation explained observed combination ORRs in nearly all the PD-1 checkpoint inhibitor clinical trials studied. Furthermore, the frequency plot of the same data (Figure 3D) showed that the average deviation from this model was 0.

Clinicians will likely choose to use therapies with the highest observed ORRs regardless of the approach used to identify the combination. Figure 5 provides the observed ORRs for key combinations. However, as future combinations are designed, those developing clinical trials need to consider strategies that achieve the best antitumor effects. Consequently, we adapted the Bliss equation to identify clinical synergy (ie, the Z score). While the measure of clinical synergy in the

Figure 4. Programmed Cell Death 1 Checkpoint Pathway Combination Regimens Activity With Estimated Combination Outcome

Trials on the x-axis are identified in eTable 4 in the Supplement. Orthogonal combinations (ie, chemotherapies and targeted therapies) vs immune synergy combinations (ie, the tumor microenvironment [TME], adaptive immunity, and innate immunity) are shown.
Figure 5. Combination Dynamics of Combinations

A. PD-1 pathway inhibitors plus platinum chemotherapy

B. PD-1 pathway inhibitors plus VEGF and VEGFR inhibitors

C. PD-1 pathway inhibitors plus IDO inhibitors

D. PD-1 pathway inhibitors plus CTLA-4 inhibitors

Columns indicate the observed objective response rate (ORR) for the combination therapies. Squares indicate the monotherapy ORRs for the identified programmed cell death 1 (PD-1) checkpoint inhibitors; triangles, the monotherapy ORR for the identified combination agent; and orange lines, the Bliss estimated ORR. Whiskers indicate SEs, which were not reported in all trials. The distance between the line and column represents the Z score, which can be positive or negative. The columns, squares, triangles, and orange lines all use the y-axis ORR scale. Individual trials are identified on the x-axis and in eTable 5 in the Supplement. CTLA-4 indicates cytotoxic T-lymphocyte-associated protein 4; IDO, indoleamine 2,3-dioxygenase; VEGF, vascular endothelial growth factor; and VEGFR, vascular endothelial growth factor receptor.
compiled PD-1 combination trials was 0, clinicians will likely choose those combinations with the best ORRs. Consequently, agents with a higher \( Z \) score, if accompanied by a higher observed ORR, may benefit patients the most. Figure 4 provides the \( Z \) score for 100 combinations to show that clinical synergy can be achieved by any of the combination mechanisms reviewed here; it was not associated with immune synergy. In fact, the greatest \( Z \) score seen was for the most orthogonal class, ie, chemotherapies. It is important to note that the \( Z \) score contribution for all combinations was not the major component of response. That is, while the y-axis in Figure 2 spans a range of 0.125- to 16-fold increases in overall efficacy, the y-axis in Figure 4 spans increments from 1.3-fold decreases to 1.4-fold increases in clinical synergy.

Previous reviews of the PD-1 checkpoint inhibitor landscape have shown that 4 types of compounds are tested in most PD-1 combination trials.\(^{17}\) Figure 5 provides specific data on available observed combination ORRs for the most commonly tested combinations of platinum chemotherapies, VEGF/R agents, and IDO and CTLA-4 inhibitor combinations. By plotting the observed ORR, the monotherapy ORRs, and the Bliss additive calculation, each combination can be dissected to understand how combination efficacy was achieved. Where the PD-1 monotherapy efficacy was the same as the Bliss calculation, the combination agent had no monotherapy efficacy. In this case, the combination would depend entirely on clinical synergy to achieve an increased ORR. The difference between the observed ORR and the Bliss prediction (ie, \( Z \) score) is the difference between the orange line and the ORR column. The most effective therapies, with the highest observed ORRs, were platinum chemotherapy and VEGF/R combinations; these therapies benefited from both independent additivity and clinical synergy—an unexpected finding for those advocating immune synergy.

**Limitations**

This study has limitations. The major limitation is its dependence on phase 1 trial data. Objective response rates do not always translate to the registration end points (ie, progression-free survival and overall survival) tested in phase 3 trials. During clinical development, the ORR in an initial phase 1 or phase 2 clinical trial is likely to be the first and most commonly reported efficacy end point. Consequently, an analysis of early phase ORRs provides the broadest and earliest data set for cross-sectional studies. As noted by the FDA, the ORR is the efficacy measure most appropriate for assessing clinical activity in single-arm phase 1 trials. However, this cross-sectional survey will need further validation in future randomized phase 3 studies.

To consider whether our data set largely based on phase 1 studies might be validated in the future, we listed combination regimens combining PD-1 pathway inhibitors approved by the FDA (eTable 6 in the Supplement). This table shows the registration potential for PD-1 pathway inhibitor combinations using chemotherapies, targeted therapies, and CTLA-4 inhibitors. Currently, all these FDA-labeled combinations show contributions from both independent activity and clinical synergy. All approved regimens combine 2 active agents, so they benefit first from independent additivity. The observation that active drugs combine most successfully is consistent with a long-understood finding in cancer drug development; the monotherapy ORR for new agents remains the best predictor of eventual approval by regulatory agencies.\(^{18-20}\)

In contrast, and illustrating the need for future phase 3 validations, the 2018 phase 3 trial outcome for a PD-1 checkpoint inhibitor plus IDO inhibitor\(^{21}\) offers a caution that lack of monotherapy activity may present special challenges in moving to a phase 3 trial. As shown in Figure 5, the proposed combination benefit of epacadostat plus pembrolizumab was entirely dependent on a proposed clinical synergy based on immune synergy. A 2018 phase 3 trial of the pembrolizumab-epacadostat combination failed to achieve its primary end points of increased overall survival or progression-free survival.\(^{21}\) While \( Z \) score for the IDO combinations was substantial (\( Z = 0.0893 \)), this mechanism failed in a phase 3 trial.
Conclusions

This study showed that most clinical combinations including PD-1 or PD-L1 inhibitors demonstrated more clinical activity than the monotherapy activity of the checkpoint inhibitor alone. Most of this can be attributed to the independent contribution of the combination components. This clinical snapshot should add value to decisions about advancing immunotherapy combinations in the clinic. It highlights platinum compound-containing agents as benefitting from both independent and clinical synergy, and it identifies angiogenesis inhibition as an additional promising approach to immune therapy combinations. Given the relatively poor mechanistic understanding of PD-1 combination therapies, using small cohorts of patients in clinical studies looking for large effect sizes may be the best approach to identify optimal combinations. Overall, the success of combinations based on independent contributions of components will likely encourage the continued development of combinations of orthogonal agents with PD-1 pathway inhibitors.

ARTICLE INFORMATION
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REFERENCES


**SUPPLEMENT.**

eTable 1. Master Table of All Combination Data

eTable 2. Monotherapy Objective Response Rates Used in Calculations of Increased Activity

eTable 3. Details, References, and Calculated Fold Change for Randomized Clinical Trials Shown in Figure 2

eTable 4. Details, References, Bliss Independent Additivity, and Clinical Synergy (Z) Calculations for Randomized Clinical Trials Shown in Figure 4

eTable 5. Figure 5 X-Axis Labels With References

eTable 6. Approved Combination Regimens Using PD-1 Pathway Inhibitors

eReferences.