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Predictable clinical benefits without synergy in trials of combination therapies with immune checkpoint inhibitors

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ABSTRACT

Hundreds of clinical trials are currently underway testing combinations of Immune Checkpoint Inhibitors (ICIs) with other cancer therapies in the hope that combination therapy will be more effective than monotherapy. Enhanced efficacy is often equated with drug additivity or synergy arising from mechanisms such as immune priming. In this paper we re-analyze progression free survival data from thirteen recent Phase III trials of ICI combinations and conclude that observed benefits are accurately accounted for by an increased chance that each patient will respond to a single agent. This is consistent with the predictions of drug independence not additivity or synergy. Using independence calculations, the efficacy of new ICI combinations can be predicted from monotherapy data (Pearson $r=0.98$, $P < 5 \times 10^{-9}$, $n = 4173$ patients and 8 types of cancer), although predicting adverse effects is not yet possible. The benefits from true pharmacological additivity or synergy exceed those of drug independence, but achieving them is likely to require methods that identify patients in whom multiple constituents of a drug combination are active.

INTRODUCTION

The introduction of immunotherapy is one of the most important recent developments in oncology. Immune checkpoint inhibitors (ICIs), particularly those directed against PD-1, PD-L1 and CTLA4, have improved survival for many but not all types of cancer¹. To increase rates and durability of responses to ICIs, hundreds of combination clinical trials are currently underway involving a wide range of drug classes². A key hypothesis motivating these trials is that targeted drugs, cytotoxic chemotherapies and immunotherapies themselves can enhance responsiveness to ICIs by increasing tumor immunogenicity³ or by other less well understood mechanisms⁴. An anticipated outcome is that individual patients will experience a superior response to a combination than to either drug alone as a

consequence of pharmacological additivity or synergy. However, as Emil Frei described in 1961⁵, drug combinations can also confer clinically meaningful benefit through independent action^{6,7}, in which patient *populations* benefit (as measured by population-averaged outcomes, such as response rates or median Progression-Free Survival - PFS) even without additive or synergistic benefit to *individual* patients.

In a drug combination that improves on monotherapy via independent action, individual patients benefit primarily or entirely from whichever single drug is most active for them^{6,7}. A combination provides a statistically significant benefit at the population level because each patient has more than one opportunity for a meaningful response to a single drug in the combination. This contrasts with additive or synergistic interaction in which drugs work together at the level of individual patients. Previous work has shown that independent action is broadly relevant to anti-cancer therapy in part because - in practically all types of cancer - patients vary widely in their sensitivities to individual drugs, and because responses are weakly correlated within and across drug classes⁶. Improvements conferred by combination therapies exhibiting independent action can therefore be understood as a form of ‘bet-hedging’. Using current disease classifications and biomarker-based stratification, predicting which drug is best for an individual patient remains uncertain. A combination hedges this uncertainty by administering multiple drugs and thereby increases the chance of a single strong anti-tumor response. This concept is less familiar today than drug synergy but the earliest human trials of combination chemotherapy calculated the expected benefit from independent action and found that it accurately accounted for improvements in response rates^{5,8,9}.

Clinical evidence for additivity or synergy is provided when the activity of a combination therapy surpasses the null hypothesis of independent action, as calculated from single-agent data (independent action is also an appropriate null hypothesis based on the Akaike Information Criterion,

AIC⁶). We have previously analyzed responses to single and combined cancer therapies in multiple Phase III clinical trials, and in hundreds of patient-derived tumor xenografts, and found that many approved combination therapies provide a magnitude of patient benefit (as measured by the hazard ratio estimated from the Kaplan-Meier estimator of PFS) that is fully accounted for by drug independence⁶. A minority of approved combinations exhibited additivity or synergy by this definition; such cases have involved one or more drugs being relatively inactive on their own; this was true, for example, of bevacizumab in combination with chemotherapy for metastatic ovarian or colorectal cancers. It is not possible to distinguish additivity from synergy in clinical data using the methods described here (or any other methods currently available). We therefore tested whether a trial exceeded the expectations of drug independence, based on an inference of best ‘single-agent’ activity from trials of the constituent drugs; if it did, the null hypothesis was rejected in favor of drug interaction (i.e. either additivity or synergy). In the case of combinations of three or more drugs, ‘single-agent’ is used as shorthand for a constituent treatment that is itself a combination of multiple drugs (e.g. etoposide plus platinum as the ‘chemotherapy’ arm of the IMpower133 trial in Small-Cell Lung Cancer¹⁰).

Our previous analysis of independent action chiefly involved combinations of targeted therapies and chemotherapies⁶ as phase III data were available at the time for only one ICI combination: Ipilimumab (a CTLA-4 mAb) plus Nivolumab (a PD-1 mAb) in metastatic melanoma. We found that the duration of response (as measured by PFS) as well as changes in tumor volume were precisely consistent with independent action. Additional evidence for independent action in PD-1 inhibitor combinations was recently reported by Schmidt *et al*¹¹ based on analysis of objective response rates. In this paper we analyze PFS data from all clinical trials of ICI combination therapies as of April 2020 for which data on single agent and combination arms are available and look for evidence of additive or synergistic drug interaction.

RESULTS

We analyzed thirteen recently reported Phase III trials of combinations involving ICIs in melanoma, squamous and nonsquamous non-small-cell lung cancers (NSCLC), small-cell lung cancer, renal cell cancer, triple-negative breast cancer, gastric and gastroesophageal junction cancer, and head and neck squamous cell carcinoma as well as a Phase II trial in BRAF-mutant melanoma^{10,12-24} (Supplementary Tables 1-3). Eleven of these trials led to approval by the Food and Drug Administration (FDA) of new combination therapies, several of which are practice-changing. As described previously⁶, we digitized plots of the Kaplan-Meier estimator for PFS observed in combination therapy trials and their constituents, and computed an expected curve under the null hypothesis of independence by randomly sampling single-agent PFS durations (with correlation $\rho=0.3\pm 0.2$; see Methods). Each simulated patient was assigned the longer of the two sampled PFS values, thereby assuming that the other therapies had no detectable effect on survival (**Figure 1**). Two trials in small-cell lung cancer of etoposide plus platinum with or without PD-L1 inhibition were merged for analysis^{10,19}. We also updated our analysis of ipilimumab plus nivolumab⁶ in melanoma because longer follow-up data (42 months) are now available¹².

We found that eleven trials exhibited PFS distributions very close to the prediction of the independence model (**Figure 2a-j**). In the case of the IMpower150 trial in nonsquamous NSCLC²⁴, observed PFS exceeded the prediction of independence and in the KEYNOTE-022 trial in BRAF-mutant melanoma²¹ it was worse, as discussed in detail below. For the KEYNOTE-048 trial in head and neck squamous cell carcinoma²² and KEYNOTE-062 trial in gastric and gastroesophageal junction cancers¹⁸, published data made it possible to analyze cohorts with or without enrichment for PD-L1 expression. We found that PFS data for both PD-L1-enriched and non-enriched populations conformed to the expectations of drug independence (**Figure 2i, j**). Thus, even though biomarker-based stratification increases average response, it does not select for patients in which drugs interact pharmacologically.

To quantify concordance or deviation from independence, we computed hazard ratios by digitally reconstructing individual participant data^{25,26} and compared these to the predictions of drug independence. Once again, all combination therapy trials but IMpower150 were consistent with, or inferior to, the null hypothesis of independent action, as demonstrated by hazard ratios near 1.0 (**Figure 3a**). Moreover, observed PFS and expected PFS under the assumption of independence exhibited a very strong linear correlation, as illustrated in **Figure 3b** for a ‘landmark’ assessment after 12 months on treatment (Pearson correlation $r = 0.98$, $P < 10^{-8}$, $n = 13$ trials). When the same question was asked of PFS at all observed times (excluding BRAF-mutant melanoma which was an inferior outlier), Pearson correlation was 0.99 and the mean absolute error of the independence model was less than 3%, which is within the margins of error of trial data (**Figure 3c**; in this case, our analysis of time-series data - which are not independent - precluded calculation of a P value). These findings constitute strong evidence that the dominant mode of benefit provided by ICI combinations is explainable by the null model of independent drug action.

Analyzing a possible case of additive or synergistic drug interaction in nonsquamous NSCLC

In the IMpower150 trial PFS in the ICI-containing arm exceeded the expectation of independence with a hazard ratio of 0.84 ($P = 0.01$, $n = 356$; the benefit attributable to drug interaction had a median PFS effect of +9 days; **Figures 2k, 3a**). IMpower150 evaluated first-line treatment of nonsquamous NSCLC with a combination of bevacizumab plus carboplatin plus paclitaxel with or without the PD-L1 inhibitor atezolizumab²⁴. Analysis of this trial was more complex than any other in our dataset and we describe it in detail to highlight challenges associated with the analysis of clinical trials in rapidly developing therapeutic areas for which single-agent data are not always available. IMpower150 did not evaluate atezolizumab alone and the only available data on atezolizumab monotherapy in nonsquamous NSCLC without PD-L1 pre-selection comes from the OAK trial²⁷, which enrolled patients receiving their second or third line of treatment. However, a different trial of

atezolizumab in NSCLC of all histologies (the BIRCH trial; 72% nonsquamous, all tumors $\geq 5\%$ PD-L1-positive)²⁸ demonstrates that atezolizumab is more active as first-line than as second- or third-line therapy, which is consistent with clinical experience that previously-treated tumors are less responsive to therapy. Thus, our initial test of independence likely underestimated atezolizumab's single-agent activity. To address this we used clinically observed differences in atezolizumab activity by line of therapy²⁸ to construct a synthetic arm - as recently discussed for NSCLC³⁰ - of atezolizumab for first-line treatment of nonsquamous NSCLC (**Figure 2k; Supplementary Figure 1**) and found that IMpower150 now closely matched the expectation of independence (Hazard Ratio 1.04, $P = 0.46$, $n = 356$; **Figure 3a**, dotted line denotes adjusted hazard ratio).

We are therefore left with two competing hypotheses about the four-drug combination tested in IMpower150: (a) atezolizumab is slightly less active at second-line than first-line, and independent action explains the benefit of adding atezolizumab to bevacizumab plus carboplatin plus paclitaxel, (b) atezolizumab is equally active at first and later lines of therapy and drug additivity or synergy is observed. Because atezolizumab is known to be more effective at the first-line of therapy in other NSCLC cohorts²⁸ we conclude that hypothesis (a) is more likely. A more exact test of independence in cases such as this is likely to be impossible because combination therapy is so much better than monotherapy that the latter can no longer be ethically tested as a first-line option. In **Figure 3** we summarize whether evaluating independence necessitated the use of external control arms or the types of adjustments described above for IMpower150. Of note, for more than half of the drug combinations investigated in this paper, matched monotherapy data were available and the analysis was straightforward.

Inferiority to independent action in a combination therapy for melanoma

The KEYNOTE-022 trial of BRAF plus MEK inhibitors (dabrafenib plus trametinib) with or without pembrolizumab in BRAF-mutant melanoma²¹ stood out as a case in which observed PFS was

substantially worse than predicted by independence (Hazard Ratio=1.75, $P=0.0025$, $n=60$). The inferiority of the triple therapy may arise from the fact that nearly all patients required dose reduction, interruption, or discontinuation due to treatment-related adverse events. Dose reductions or interruptions can compromise the efficacy of each constituent of a treatment regimen and negate the benefit of bet-hedging. This is likely of greatest concern when toxicity from an agent providing little benefit to an individual patient compels dose-reduction of an agent that is effective for that patient. This interpretation finds support in the analysis of volume change data from KEYNOTE-022, where initial responses in terms of volume change are approximately as good as independence predicts (**Supplementary Figure 3**; method from ⁶), so inferiority is observed only in durability of response. The benefit potentially achievable in BRAF-mutant melanoma from using three agents (as predicted by independent action) could in principle be achieved by optimally stratifying patients to PD1 or BRAF plus MEK inhibition, making development of a predictive biomarker(s) for responses from PD1 or kinase inhibition a priority in this disease.

Limitations in the analysis

Retrospective analysis and trial reconstruction as performed here has inherent methodological limitations. First, the benefit conferred by a combinations exhibiting independence varies with the correlation in response to individual agents; we have used a range that accounts for partial cross-resistance⁶ based on data obtained on many drugs in PDX models (albeit not ICIs). Given the limitations of mice in reproducing human immunotherapy responses, we note that some clinical evidence is available arguing for low cross-resistance between ICIs and other therapies: for example, among patients who have progressed on non-ICI first-line therapy, second-line ICI therapy achieves response rates that are only modestly lower than first-line ICI^{28,31–33}. Strong cross-resistance would imply that after the failure of a first-line therapy, tumors would also be resistant to the second therapy, which is evidentially not the case for second-line ICIs. To account for uncertainty in the degree of cross-resistance, we

compute independence for a range of correlation values ρ , which gives rise to a range of predicted PFS outcomes (**Figure 2**; gray range; mean width 4%, inter-quartile range 2% to 6%).

Second, the impact of differences in patient demographics on our analysis is largely unknown because demographically-linked response data are generally not published. Aggregate demographics are available and we checked that they were similar across matched monotherapy and combination therapy trial arms (**Supplementary Table 2**). However we cannot perform the sophisticated confounder studies being applied to real world data and to synthetic control arms^{34,35} for which demographics and response must be linked; we encourage sponsors to perform this analysis themselves.

A third limitation is that some of the trials we studied did not include a monotherapy arm for the ICI under study, requiring the use of response data from another - typically earlier - trial testing the same ICI in a comparable patient cohort (**Supplementary Tables 1 and 2**). In these cases we matched the line of therapy and dosing to the greatest extent possible. Crucially, we permitted no substitutions or imperfections in the data that could bias against the discovery of additivity or synergy (such as monotherapy data at higher doses or in healthier cohorts than combination therapies), but we tolerated some biases in an opposite direction that would be expected to produce false evidence of synergy. These cases are described in detail below.

In two cases (labelled orange in **Figure 3**) monotherapy data are not available for one constituent of a combination but instead for a similar drug known to be clinically ‘non-inferior’. The first case is the KEYNOTE-407 trial in squamous NSCLC¹⁴ (**Figure 2c**), where single agent data is not available for anti-PD1 antibody pembrolizumab. The anti-PD1 antibody nivolumab is suggested as a non-inferior comparator by a meta-analysis of 1887 patients having NSCLC: no significant difference in PFS or overall survival between pembrolizumab and nivolumab was observed³⁶. Thus, in the analysis of KEYNOTE-407, it is justifiable to use data on nivolumab in squamous NSCLC from CheckMate-017³⁷

(note that CheckMate-017 studied second-line treatment which may bias in favor of synergy). The second case occurs in the renal cell carcinoma trials KEYNOTE-426¹⁶ and JAVELIN Renal 101¹⁵, in which the PDGFR/VEGFR/c-Kit receptor tyrosine kinase inhibitor axitinib was used in the combination arm and the PDGFR/VEGFR/c-Kit receptor tyrosine kinase inhibitor sunitinib was used in the monotherapy arm. The assumption that axitinib is not inferior to sunitinib is supported by real-world clinical data³⁸.

In five cases ICI monotherapy data were obtained from previously-treated (rather than untreated) patients (arms labelled '2L' and data colored red; this includes IMpower150 described above). This biases us to overestimate - not underestimate - the likelihood of additivity or synergy, since cancer treatments are generally less, not more, active in second-line than first-line (because treatment promotes drug resistance). Thus, drug independence is almost always the more conservative model, not only from the perspective of information theory (e.g. AIC), but also when real limitations in available data are considered. If we consider only trials in which no compromises were necessary when comparing combination and monotherapy data the correlation between data and the model of independence remains $r = 0.97$ and $P = 3 \times 10^{-4}$ for PFS at 12 months. Thus, we conclude that our findings remain statistically significant under multiple scenarios of data inclusion and exclusion.

DISCUSSION

Based on retrospective analysis of 13 combination immunotherapy Phase III trials in eight types of cancer (all of the combination ICI trials published up to April 2020 for which an analysis of independence is possible) we conclude that there is no clinical evidence of synergistic or additive interaction among ICIs or ICIs and other drugs. Instead, combinations examined are as beneficial as expected under the null hypothesis of independent drug action; this includes many combinations that

have become first-line standards of care and are considered practice-changing. Thus, independent action can confer significant and highly meaningful clinical benefit through a process analogous to bet hedging. This conclusion is robust to the imperfections that are inevitably associated with retrospective analysis of clinical trial data, including the need to adjust for differences in first and second line-responses, the shortage of data on some monotherapies, and the absence of detailed on patient demographics. Sponsors in possession of the original clinical data are in a position to study the implications of independent action more thoroughly, with the resulting benefit that they will be better able to predict the likely outcome of future trials.

It is possible that longer follow-up of ICI trials may uncover drug additivity or synergy that is not yet evident. However, when sufficient time has passed on therapy for PFS to reach a low value (e.g. $\approx 20\%$ of patients not progressing) and independent drug action is a sufficient explanation for benefit, we can conclude that additivity or synergy is absent in at least $\approx 80\%$ of patients; this is true of seven of the trials examined. In three trials one-third or more of patients were not progressing at the longest times reported (15 to 42 months), raising the formal possibility of as-yet unobserved drug interaction in future survival data. In our estimation the case is strongest for pembrolizumab plus chemotherapy in PD-L1-high metastatic nonsquamous NSCLC¹³, and pembrolizumab or avelumab plus axitinib for advanced renal cell carcinoma^{15,16}; longer follow-up will settle this issue. In the case of ipilimumab plus nivolumab for metastatic melanoma, 37% PFS was observed at three years, but tumor volume changes were consistent with independence across the entire patient population^{6,42} and sustained monotherapy responses continue to explain sustained combination therapy responses.

There is great interest in the potential of immunotherapies to confer highly durable benefits analogous to the curative chemotherapy combinations developed for several blood cancers³⁹. Because single chemotherapies are almost never curative, cures in principle require combinations exhibiting

additive or synergistic activity (for example, the RCHOP regimen used for lymphoma is additive)⁴⁰. Used individually, ICIs have been remarkable in achieving long-lasting ‘treatment free survival’ as single agents^{12,41}. As such, synergistic interaction is unnecessary for ICIs to elevate long-term survival when added to established therapies, provided that an ICI exhibits single-agent activity in the disease of interest. It is important to note that the absence of drug interaction in existing ICI combinations in no way detracts from the clinical importance of these therapies. In fact, the opposite is true. Since the activity resulting from drug additivity or synergy exceeds that of independent action (by definition), working out how to achieve synergy in patients has the potential to unlock substantial additional therapeutic benefit using existing ICIs.

Widespread evidence of drug independence in ICI trials appears to conflict with pre-clinical data on immunotherapy combinations, including the concept of immune priming. Why might this be true? One possibility is that drug interactions that are measurable at a molecular level⁴³ do not prolong patient survival, which is the only response evaluated in this work. Thus, drug interaction at a molecular level is not incompatible with drugs conferring independent survival benefits. Another possibility is that tumor volume changes measured in animal models, the common pre-clinical setting, do not correlate well with durability of response (PFS) in humans. However, we previously found that both volume changes and PFS exhibit independence in most xenografts. Moreover, in BRAF-mutant melanoma, near-term response (measured by volume change) is consistent with independence but durability of response (PFS) is inferior, likely because adverse events hinder the sustained administration of combination therapy. Thus, we do not believe that different ways of measuring response explain the difference between animal models and human trial data.

The most obvious difference between pre-clinical analysis of ICIs and clinical trials is that the former are performed primarily in syngeneic and genetically engineered mouse models, each of which is homogenous genetically (or nearly so). In contrast, patient populations are genetically heterogeneous

and exhibit high variability in drug response (variability in pharmacokinetics is also a source of variability in response). As a result, even if drug interactions identified in pre-clinical studies do occur in humans, too few patients are likely to receive sufficient benefit from both drugs for additivity or synergy to be manifest. A corollary of this hypothesis is that pre-clinical testing of ICI combinations would benefit from analysis in heterogeneous panels of tumor models. This has become routine in the case of patient-derived xenograft (PDX) mouse models and targeted anti-cancer therapies.⁴⁴ However, animals used for traditional PDX modeling are immunocompromised and cannot be used to evaluate ICIs; generating panels of genetically heterogeneous mouse models with functional immune systems remains a daunting challenge.

What are the current and future implications of our findings? First, calculating the benefits from drug independence provides a sound strategy for any research team designing a new ICI combination to predict activity; effective prediction is desirable as the number of possible combinations grows. If the predicted benefits of independence are insufficient for a new combination to exceed standard-of-care, the based on available data a combination is likely to fail. Proceeding in this case would require exceptionally strong pre-clinical data, for example in panels of mouse models. These observations are of immediate use in helping drug developers with portfolio prioritization. As monotherapy data become available for stratified subgroups (e.g. PD-L1 status, prior treatment, and patient demographics) it may also be possible to predict the activity of combination therapies in specific patient subsets. Adverse effects remain the primary unknown, and better methods for predicting, preventing or mitigating toxicity are therefore a priority. Second, concurrent administration of independent drugs is not strictly necessary for benefit under the assumption of independence, and evaluation of sequential treatment or biomarker-guided choice of treatments is potentially warranted. However, in patients with rapidly progressing disease for whom second-line therapy may not be an option (due to declining functional status), using drugs in combination provides more chances for effective treatment upfront.

How can we move beyond independent drug action and realize the benefits of drug synergy? We hypothesize that the key is better patient stratification. If we can identify patients who respond to all or the majority of drugs in a combination⁴⁵, we are likely enriched for drug additivity or synergy. It may be possible to develop predictive biomarkers for each therapy based on pre-treatment state, similar to those for ICI monotherapies^{46,47}. An alternate approach that requires less knowledge about mechanism is to start patients on a multi-drug combination and then use pharmacodynamic biomarkers and on-treatment biopsies (or even pharmacokinetic data) to guide withdrawal of one or more inactive drugs and continuation or dose escalation of active ones. In either case, the discovery that existing ICI combinations operate via independent action serves to emphasize the importance of achieving greater precision in cancer therapy based on new or improved response biomarkers.

METHODS

Data sources.

We sought data for all combination therapies with ICIs that were Food and Drug Administration (FDA)-approved as of April 2020. To assess whether a combination of therapies produces ‘additive or synergistic’ efficacy, we required Kaplan-Meier plots of PFS for the combination therapy, and for the different therapies comprising the combination, in matching patient cohorts. Several trials tested combinations of three or more drugs, where a standard-of-care combination (therapies ‘A+B’) was compared with a combination of more therapies (‘A+B+C’). In such cases the control arm combination (A+B) is regarded as one treatment; our analysis therefore assessed interactions between that standard treatment and the new therapy (‘C’), and is agnostic to drug interactions within control arms. Thus ‘single-agent response’ in some cases refers to a response to a previously established combination (this distinction is made clear in **Figure 2**).

Some trials randomized patients to three treatment arms, spanning two monotherapy treatments and their combination, and therefore contain all data needed for analysis. Other trials were lacking at least one monotherapy arm. In such cases we searched publications and conference proceedings for a clinical trial of that therapy meeting the following criteria: (i) patients had the same type and stage of disease (ii) patients were treated at the same or near-identical dose, and (iii) treatments involve the same line of therapy (for all combinations analyzed in this paper this was first-line). In 5 of 26 monotherapy arms, data was only available in previously-treated patients (second or third line). The impact of this discrepancy is addressed in the discussion. Complete treatment details and patient characteristics from the trials analyzed are presented in **Supplementary Table 1** and **Supplementary Table 2**.

Ultimately we found suitable combination and control monotherapy data for all but 3 of the 14 ICI combinations approved by the FDA (**Supplementary Table 3**). Two of the omitted combinations are nivolumab plus ipilimumab for renal cell cancer⁴⁸, and nivolumab plus ipilimumab for microsatellite unstable or mismatch repair deficient metastatic colorectal cancer⁴⁹; in both cases monotherapy data is unavailable making conclusions about drug interaction impossible. The third exception is lenvatinib plus pembrolizumab for advanced endometrial cancer⁵⁰; we did not include this trial in the main text due to a shortage of pembrolizumab monotherapy data, and mismatching monotherapy cohorts, but a limited analysis is provided in **Supplementary Figure 2**.

We also included three ICI combination therapies lacking FDA approval where complete combination and monotherapy data was available for analysis: (i) pembrolizumab plus chemotherapy for advanced gastric and gastroesophageal junction cancers¹⁸ (ii) ipilimumab plus dacarbazine for metastatic melanoma²⁰, and (iii) pembrolizumab plus dabrafenib and trametinib for metastatic BRAF-mutant melanoma²¹. The latter case was a notable exception from our requirement for near-identical dosing between arms, as most patients receiving ‘triple combination therapy’ for BRAF-mutant melanoma

required dose reductions or interruptions to ameliorate treatment-related adverse events, the effect of which is discussed in the article.

Data extraction

Published Kaplan-Meier curves of Progression Free Survival were opened in Adobe Illustrator to remove extraneous labels, and to produce separate figures for each treatment arm. Figures that were only available in rasterized form were digitally traced in Adobe Photoshop. Kaplan-Meier curves were digitized in Wolfram Mathematica 12 using published algorithms⁶. For Hazard Ratio calculations, individual patient data were reconstructed from Kaplan-Meier functions and ‘At Risk’ tables using published methods²⁶.

Simulation of independent action

As previously described⁶, Progression Free Survival (PFS) expected for the null hypothesis of independence was computed by randomly sampling data pairs of $(PFS_{\text{therapyA}}, PFS_{\text{therapyB}})$ from a joint distribution constructed from the clinically observed single-agent distributions, and assigning each simulated patient the better of their two PFS values (maximum of $PFS_{\text{therapyA}}, PFS_{\text{therapyB}}$). These joint PFS distributions were constructed with correlations of $\rho=0.3\pm 0.2$, which accounts for partial cross-resistance between therapies. As reported⁶, this degree of cross-resistance was informed by drug responses in a large cohort of tumor xenografts, and is broadly consistent with clinical observations from sequential monotherapy trials and from comparing response rates at first and second line^{5,28,31–33,51}. Partial correlations in drug response could in principle arise both from tumor-intrinsic properties and from patient status (e.g. age and co-morbidities). Simulations are performed with $\geq 10^4$ simulated patients in order to overcome sampling noise and produce consistent distributions, whereas stochastic variation is evident when simulating smaller cohorts. Identical predictions, which are fully deterministic, can be calculated from the equation

$$PFS_{\text{therapyA+B}}(t) = PFS_{\text{higher of A or B}}(t) + (1 - PFS_{\text{higher of A or B}}(t)) \times PFS_{\text{lower of A or B}}(t) \times (1 - \rho)$$

where t is time, and the calculation must be performed at each time point (e.g. in 0.05 month increments) to compute the full Kaplan-Meier curve. This is effectively Frei's 1961 calculation⁵ with an adjustment for cross-resistance (ρ) and applied to time-series survival data. Additivity or synergy is supported when the efficacy of a combination therapy violates (by surpassing) the null hypothesis of independent action. Supplementary Code provides software and source data to execute these simulations for all trials analyzed here.

Applicability of independent action model to PFS in advanced cancers, not adjuvant therapy, indolent tumors, or Overall Survival data.

The calculation of independent action applies to situations for which an observed rate of tumor control (Progression Free Survival) can be attributed to the effect of treatment. This calculation would not be valid in scenarios where the 'survival' percentage does not reflect the percentage of patients in which treatment has prevented tumor growth up to the time point in question. Thus, valid modeling scenarios include PFS for advanced cancers that will grow (progress) if they are not treated, for time points after a patients' first or second scan (before that, there is likely to have been little opportunity to observe progression). This is demonstrated by analysis of clinical trials in advanced cancers that included a 'placebo-only' arm, in which large majorities of patients exhibit progression before 4 months (**Supplementary Figure 4**). Logically, combining two placebos should provide no benefit. To apply our modeling approach to this scenario recall that any treatment is 'cross-resistant' with itself, resulting in $\rho=1$, in which case independent action expects no benefit from combining a treatment with itself. Because 'placebo + placebo' combination is the same 'treatment' given twice, it provides no benefit in the independent action model implemented in this paper. Alternatively, it is possible to take an empirical approach and treat placebos like any other therapy described in this paper and being subject to independent modeling (with $\rho=0.3\pm 0.2$). Under this assumption, the benefit predicted for placebo plus

placebo arms at 12 months ranges between 0% and 1.5% for five trials involving different types of cancer (average 0.6%; **Supplementary Figure 4**). This is negligible when compared to the degree of benefit observed in successful ICI trials.

Several clinical scenarios cannot or should not be analyzed using the independent action model described here. These include ‘Disease Free Survival’ for adjuvant therapy following surgery with curative intent, because when some patients are cured by surgery prior to therapy, the DFS rate cannot be attributed to the efficacy of adjuvant therapy (e.g. if surgery cures 50% of patients, and surgery plus adjuvant therapy cures 60%, one cannot conclude that adjuvant therapy is effective in 60% of patients). Indolent or benign tumors, often subject to a ‘watch and wait’ approach, are also invalid scenarios because PFS may be high and long-lasting with no therapy. Finally, the independent action calculation should not be applied to Overall Survival (OS) data, because OS can remain high even after ineffective therapy, and post-progression survival has many influences aside from the therapy assigned in a trial, including second-line or salvage therapies that may be used following progression. Empirically, in trials that include a ‘placebo only’ arm, OS distributions can show a substantial tail (**Supplementary Figure 4**). Because OS percentages are systematically higher the percentage of patients in which therapy was effective (up to any given query time), the independent activity of a drug cannot be inferred from OS data, so the independent action simulation should not be applied to OS data.

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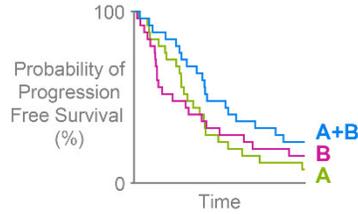
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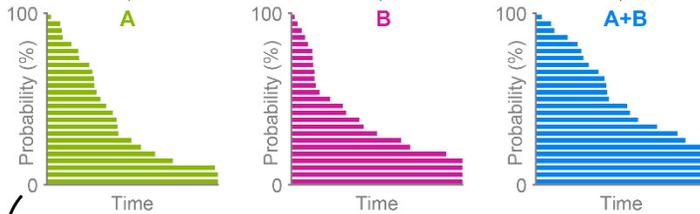
DISCLOSURE

PKS is a member of the SAB or Board of Directors of Glencoe Software, Applied Biomath and RareCyte Inc and has equity in these companies. In the last five years the Sorger lab has received research funding from Novartis and Merck. Sorger declares that none of these relationships are directly or indirectly related to the content of this manuscript. BI is a consultant for Merck and Volastra.

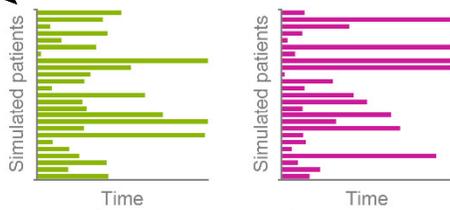
1. Identify and assemble monotherapy and combination therapy patient cohorts.



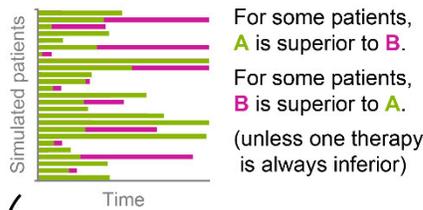
2. Digitize probability distribution of PFS



3. Simulation: Randomly assign patients' responses to each monotherapy (partial correlation between therapies accounts for cross-resistance)



4. Compare individual patients' responses to each monotherapy



5. Assign each patient their best monotherapy response

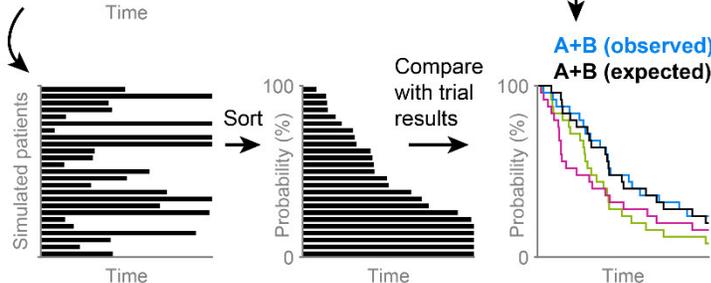


Figure 1. Calculating the expected activity of a combination therapy under the null hypothesis of independent drug action. Solely for clarity of illustration, quanta of probability are drawn as large (4%), and simulated patients are few (25); in practice PFS is resolved to $<0.1\%$, and $>10^4$ patients are simulated. Step 4 illustrates how patient-to-patient variability in best single-agent responses causes combination therapy to improve average response, but this does not occur if one therapy is so inferior to the other that it is never a better option for any individual patient.

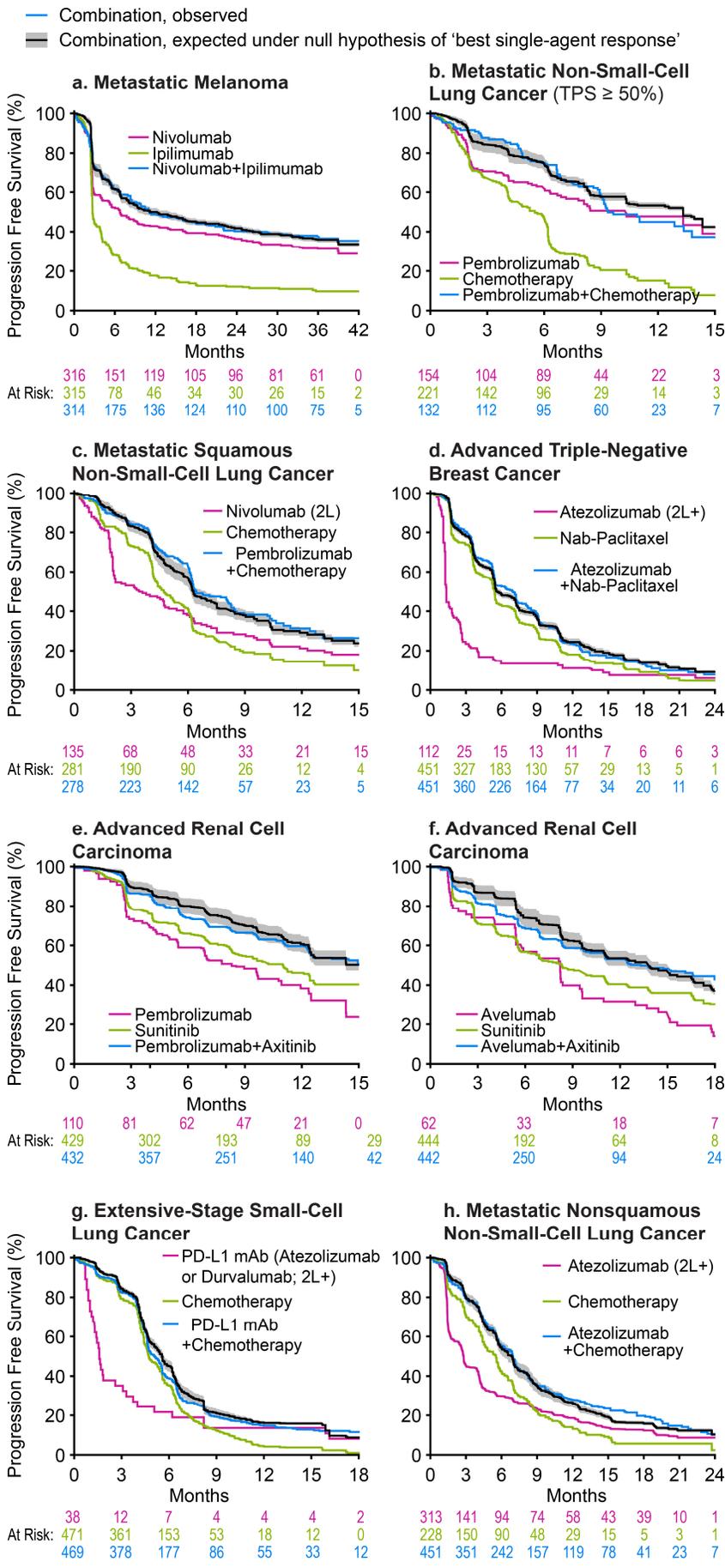


Figure 2,
left Page

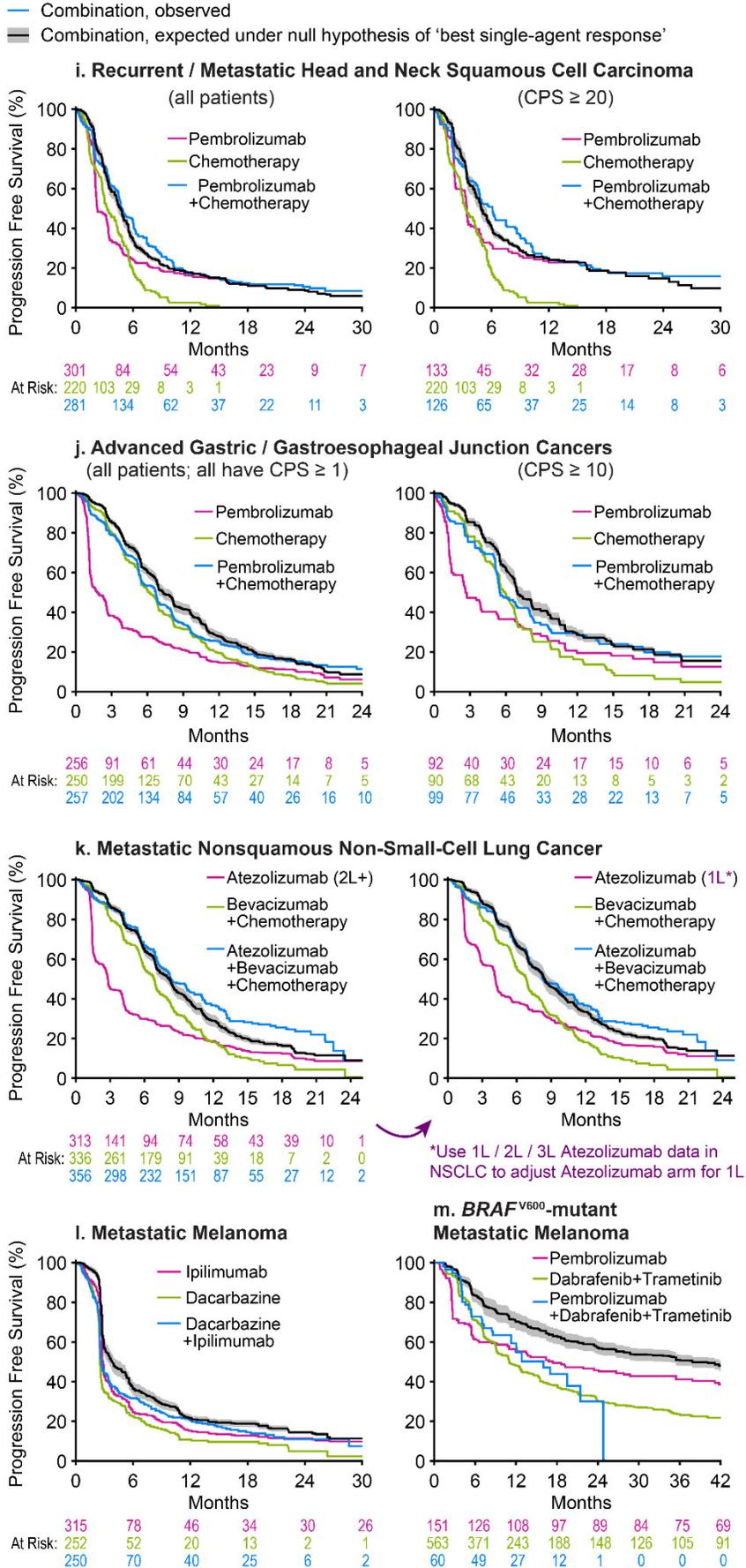
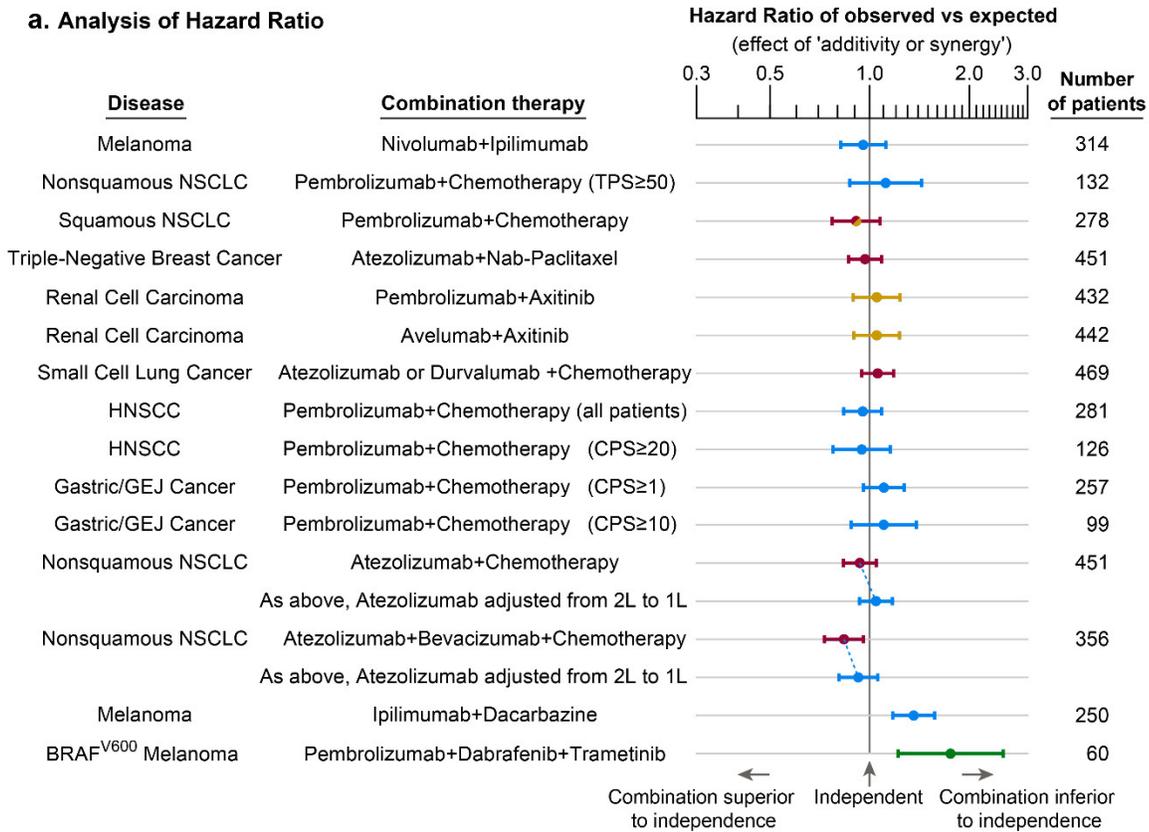


Figure 2, right page

Figure 2. Progression Free Survival for combination therapies as observed in clinical trials and as predicted from independent activity of the therapies comprising the combination. Progression Free Survival (PFS) observed for each combination therapy (blue) was compared to that expected from the PFS distributions of the constituents of the combination (green and magenta) under the null hypothesis that each patient's PFS is the best of their two possible responses to constituent therapies (black line and grey range, which reflects uncertainty in response correlation ($\rho = 0.3 \pm 0.2$) or cross-resistance). 2L and 2L+ indicate data from patients treated at second-line or later; all other data are from patients previously untreated for metastatic or advanced cancer. TPS: PD-L1 Tumor Proportion Score. CPS: PD-L1 Combined Proportion Score. Combination therapy data from: **a** CheckMate 067¹², **b** KEYNOTE-189¹³, **c** KEYNOTE-407¹⁴, **d** IMpassion130¹⁷, **e** KEYNOTE-426¹⁶, **f** JAVELIN Renal 101¹⁵, **g** IMpower133¹⁰ and CASPIAN¹⁹, **h** IMpower130²³, **i** KEYNOTE-048²², **j** KEYNOTE-062¹⁸, **k** IMpower150²⁴ (note that the difference between the prediction of independence – black line – and observed PFS – blue line - is significant for left panel and not for right panel; see Figure 3), **l** NCT00324155²⁰. **m** KEYNOTE-022²¹. Data sources, patient characteristics, and limitations are described in Supplementary Tables 1 and 2.

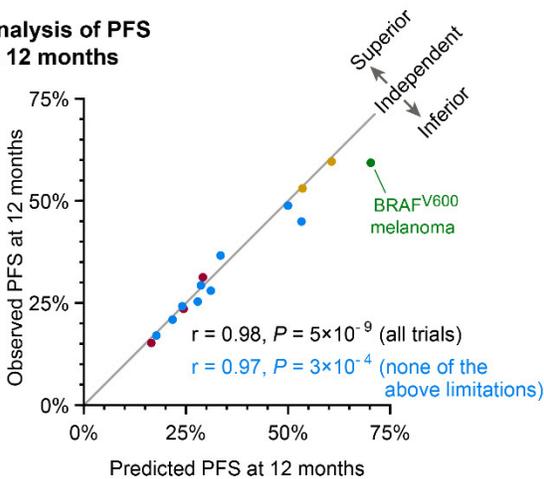
a. Analysis of Hazard Ratio



Limitations in the data:

- Monotherapy data from second line (2L)
- Monotherapy data from different drug with same target(s)
- Combination involved substantial dose reductions/interruptions
- None of the above limitations

b. Analysis of PFS at 12 months



c. Analysis of PFS at all measured times

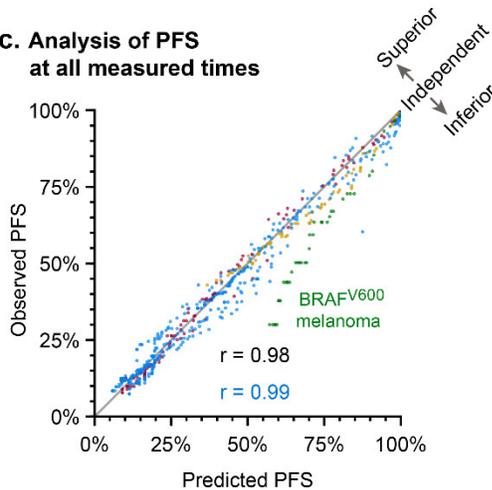


Figure 3. Trials combining Immune Checkpoint Inhibitors with other cancer therapies are consistent with, or inferior to, independent drug action. a. Patient events (progression or censoring)

from clinical trials were compared to the prediction of independent drug action by computing the Hazard Ratio (Cox Proportional Hazards model). Error bars are 95% confidence intervals. Superiority to independence would indicate ‘drug additivity or synergy’, while inferiority could occur for multiple reasons including antagonistic interaction, toxicity necessitating dose reduction/interruption, or strong cross-resistance. HNSCC: Head and Neck Squamous Cell Carcinoma; NSCLC: Non-Small-Cell Lung Cancer; TPS: PD-L1 Tumor Proportion Score; CPS: PD-L1 Combined Proportion Score. Data in this and subsequent panels are color coded to denote deviation from the ideal case of a combination in which directly comparable monotherapies are available. See text for details. **b, c.** Observed PFS has a strong linear correlation with PFS expected under the null hypothesis of independent drug action, both at a landmark of 12 months (Pearson’s $r = 0.98$, $P < 10^{-8}$, all trials) and over all measured times; $r = 0.99$ for trials excluding KEYNOTE-022²¹ of pembrolizumab + dabrafenib+trametinib for BRAF^{V600} melanoma, which was inferior to independence and for which dosing violated model assumptions (green points).

Figures

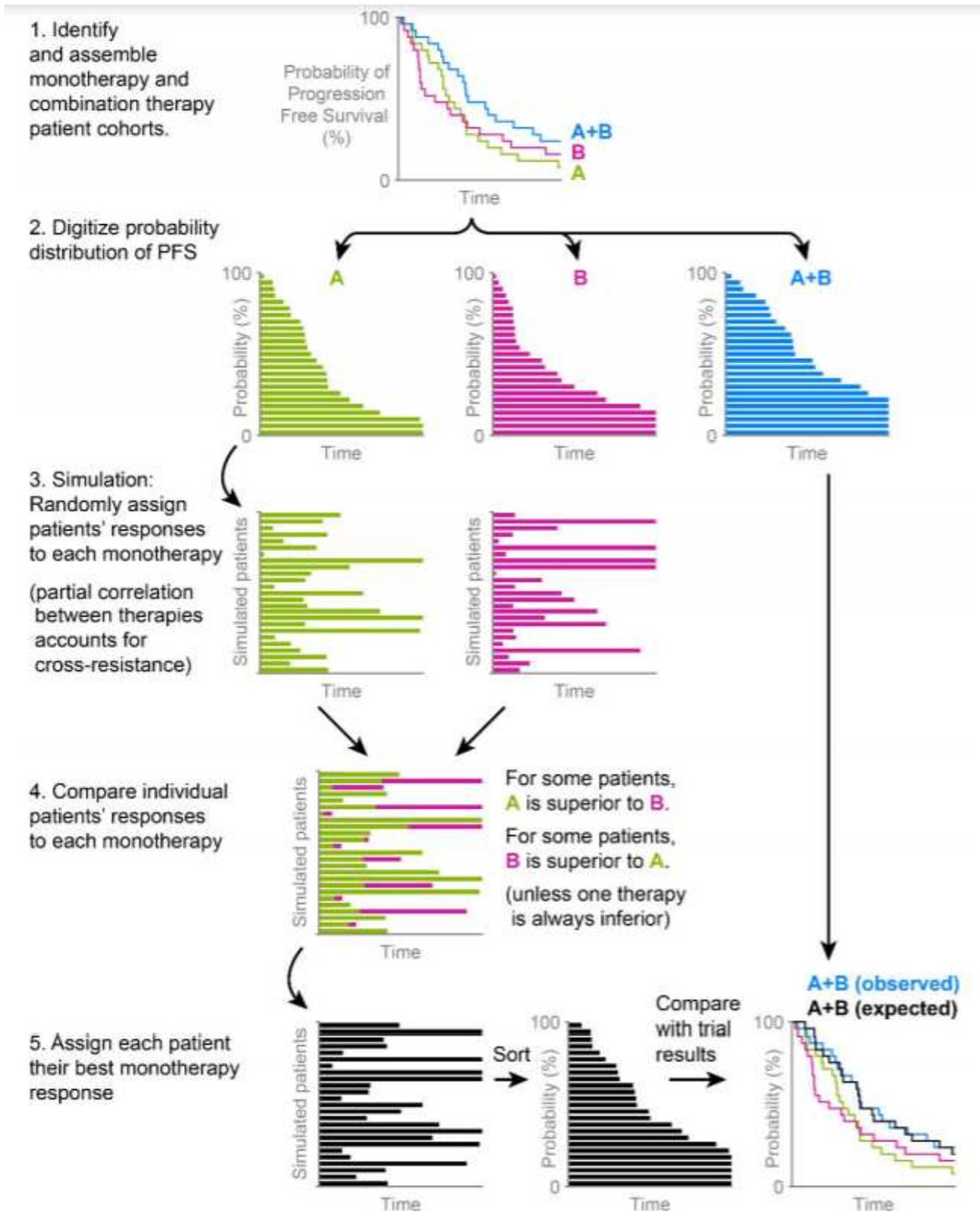


Figure 1

Calculating the expected activity of a combination therapy under the null hypothesis of independent drug action. Solely for clarity of illustration, quanta of probability are drawn as large (4%), and simulated patients are few (25); in practice PFS is resolved to <0.1%, and >104 patients are simulated. Step 4

illustrates how patient-to-patient variability in best single-agent responses causes combination therapy to improve average response, but this does not occur if one therapy is so inferior to the other that it is never a better option for any individual patient.

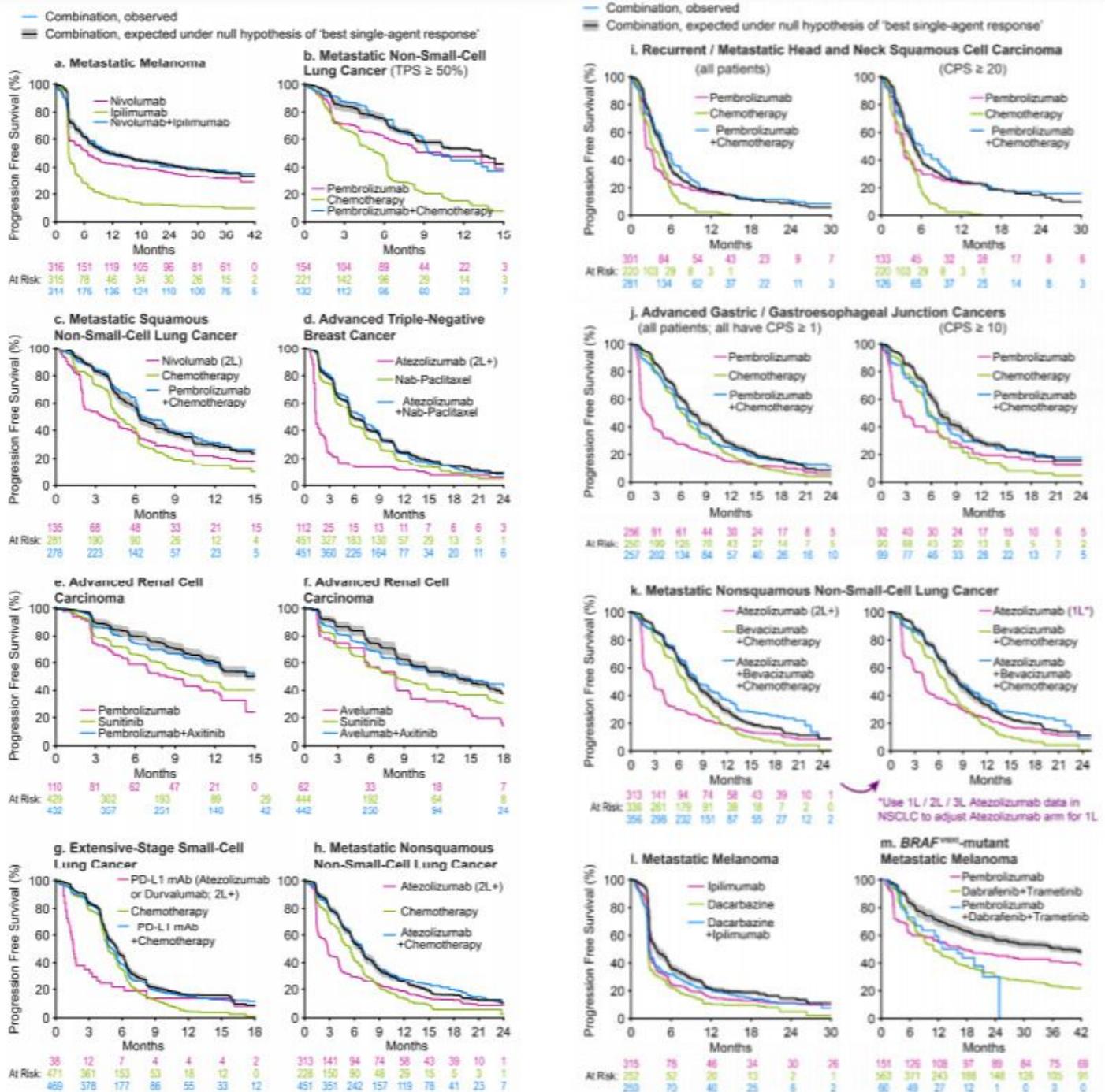
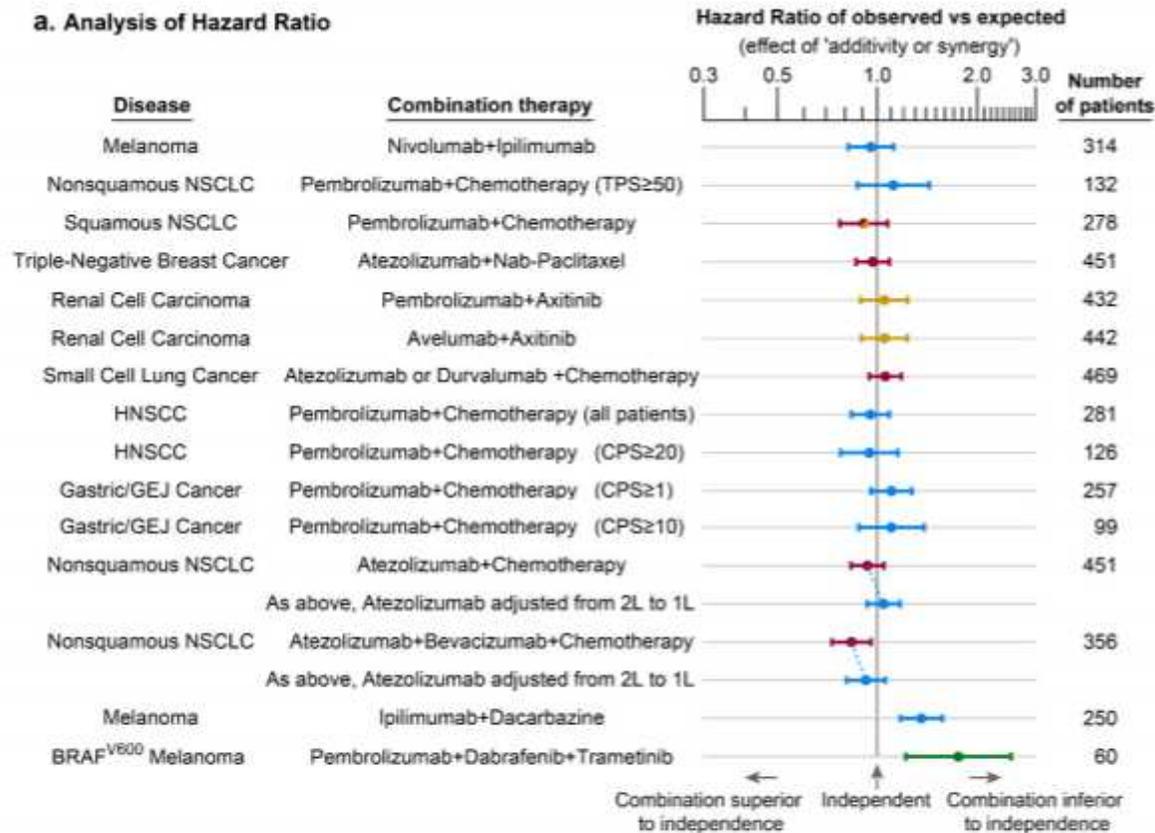


Figure 2

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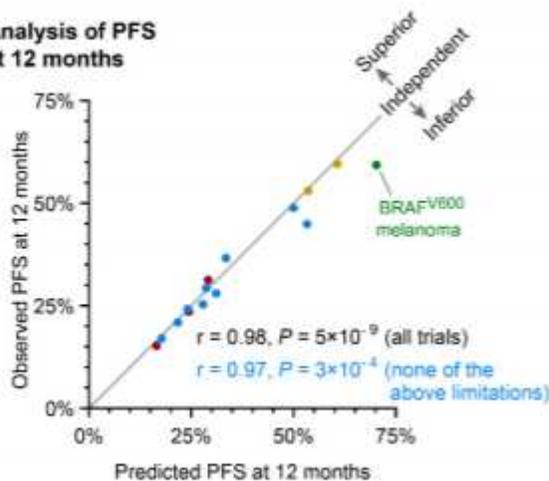
PFS is the best of their two possible responses to constituent therapies (black line and grey range, which reflects uncertainty in response correlation ($\rho = 0.3 \pm 0.2$) or cross-resistance). 2L and 2L+ indicate data from patients treated at second-line or later; all other data are from patients previously untreated for metastatic or advanced cancer. TPS: PD-L1 Tumor Proportion Score. CPS: PD-L1 Combined Proportion Score. Combination therapy data from: a CheckMate 06712, b KEYNOTE-18913, c KEYNOTE-40714, d IMpassion13017, e KEYNOTE-42616, f JAVELIN Renal 10115, g IMpower13310 and CASPIAN19, h IMpower13023, i KEYNOTE-04822, j KEYNOTE-06218, k IMpower15024 (note that the difference between the prediction of independence – black line – and observed PFS – blue line - is significant for left panel and not for right panel; see Figure 3), l NCT0032415520. m KEYNOTE-02221. Data sources, patient characteristics, and limitations are described in Supplementary Tables 1 and 2.

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b. Analysis of PFS at 12 months



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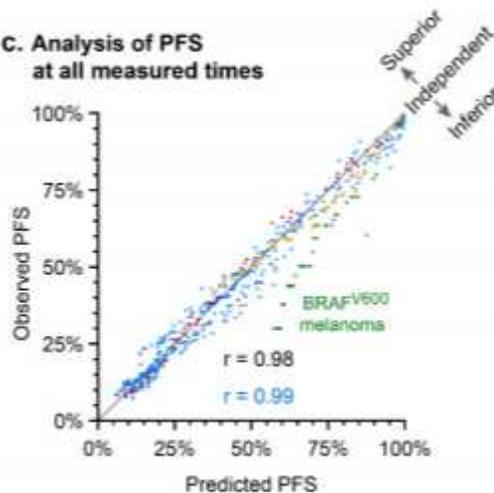


Figure 3

Trials combining Immune Checkpoint Inhibitors with other cancer therapies are consistent with, or inferior to, independent drug action. a. Patient events (progression or censoring) from clinical trials were compared to the prediction of independent drug action by computing the Hazard Ratio (Cox Proportional Hazards model). Error bars are 95% confidence intervals. Superiority to independence would indicate 'drug additivity or synergy', while inferiority could occur for multiple reasons including antagonistic

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Supplementary Files

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