Supplemental Text for "Computationally predicting clinical drug combination efficacy with cancer cell line screens and independent drug action"

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SUPPLEMENTAL TEXT DESCRIPTION

This file contains supplemental figures, tables, results, discussion, and references that relate to the findings of the main text but could not be included there due to a lack of space. In general, the text in this document simply expands on findings and discussions from the main text without introducing entirely new findings or discussion topics.

SUPPLEMENTAL FIGURES

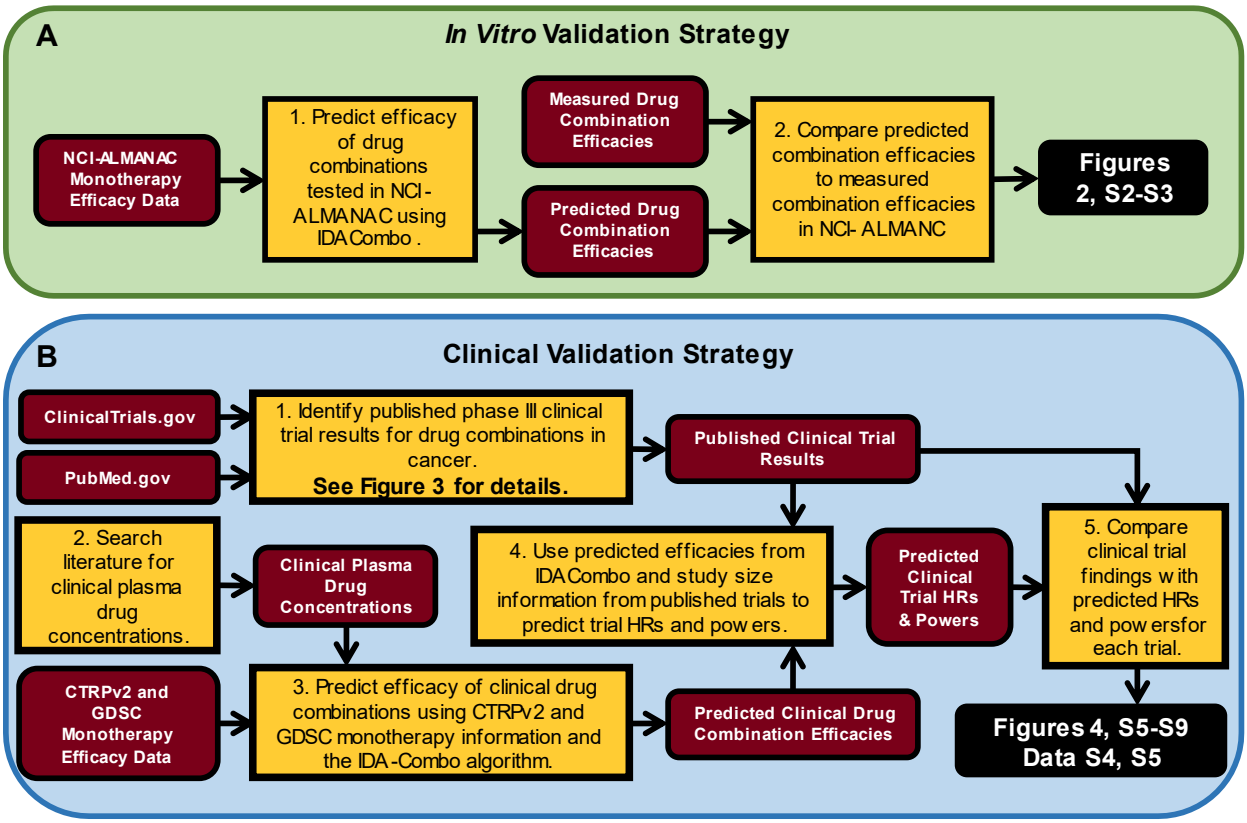

Figure S1. Pipelines to validate IDACombo predictions both in vitro and in clinical trial data. A) In vitro validation strategy. Monotherapy data from NCI-ALMANAC is used to predict drug combination efficacies, and these efficacies are compared to the measured combination efficacies that are also in NCI-ALMANAC. **B)** Clinical trials are systematically identified using ClinicalTrials.gov and PubMed.gov, and efficacy predictions are made for each treatment in each trial using clinical drug concentrations and monotherapy cell line data from CTRPv2 and/or GDSC. These predictions are used to estimate hazard ratios (HRs) and powers for each trial, and these HRs and powers are compared to reported clinical trial outcomes.

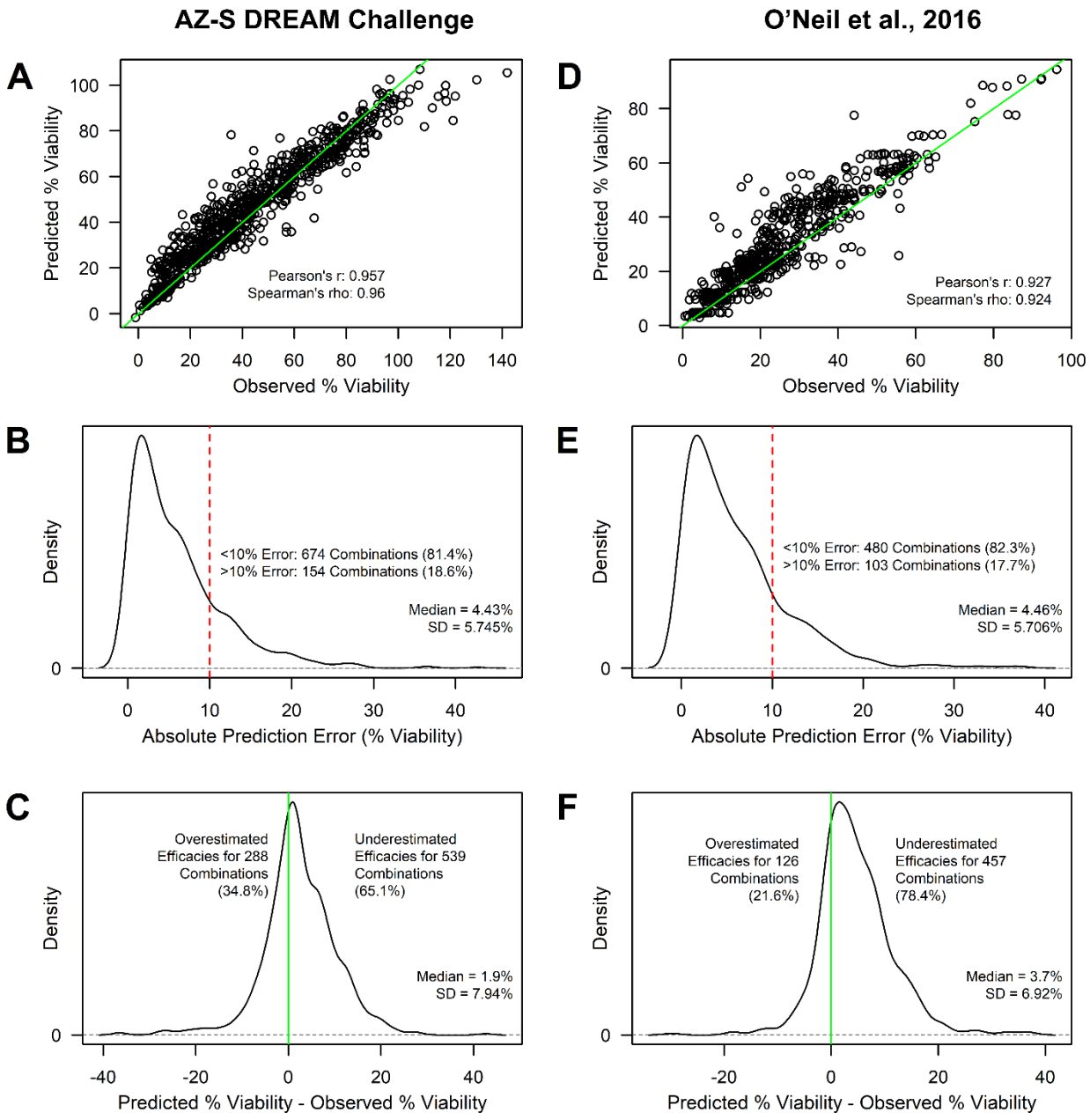

Figure S2. Agreement between predicted and observed combination viabilities in the AstraZeneca-Sanger DREAM Challenge and O'Neil et al., 2016 drug combination datasets. A-C) Results using the AstraZeneca-Sanger DREAM challenge (AZ-S DREAM) drug combination dataset. **D-F)** Results using the O'Neil et al., 2016 drug combination dataset. **A&D)** Scatterplot showing high correlation between predicted average percent viability and experimentally observed average percent viability for each drug combination in the dataset. Predictions were made using monotherapy data from the dataset. The green line is a reference diagonal with slope = 1 and intercept = 0. Note that predictions were only made for the maximum concentration tested for each drug. **B&E)** Density plot showing that the absolute values of the differences between the predicted percent viabilities and the observed percent viabilities for each drug combination are generally below 10%, with >50% of drug combinations having an absolute prediction error below 5%. The red line marks a difference of ±10% viability between predicted and observed values. **C&F)** Density plot showing that the differences between the predicted percent viabilities and the observed percent viabilities for each drug combination have a slight tendency towards being positive—indicating that IDA-Combo underestimates efficacy more often than it overestimates efficacies. Source data are provided with this paper.

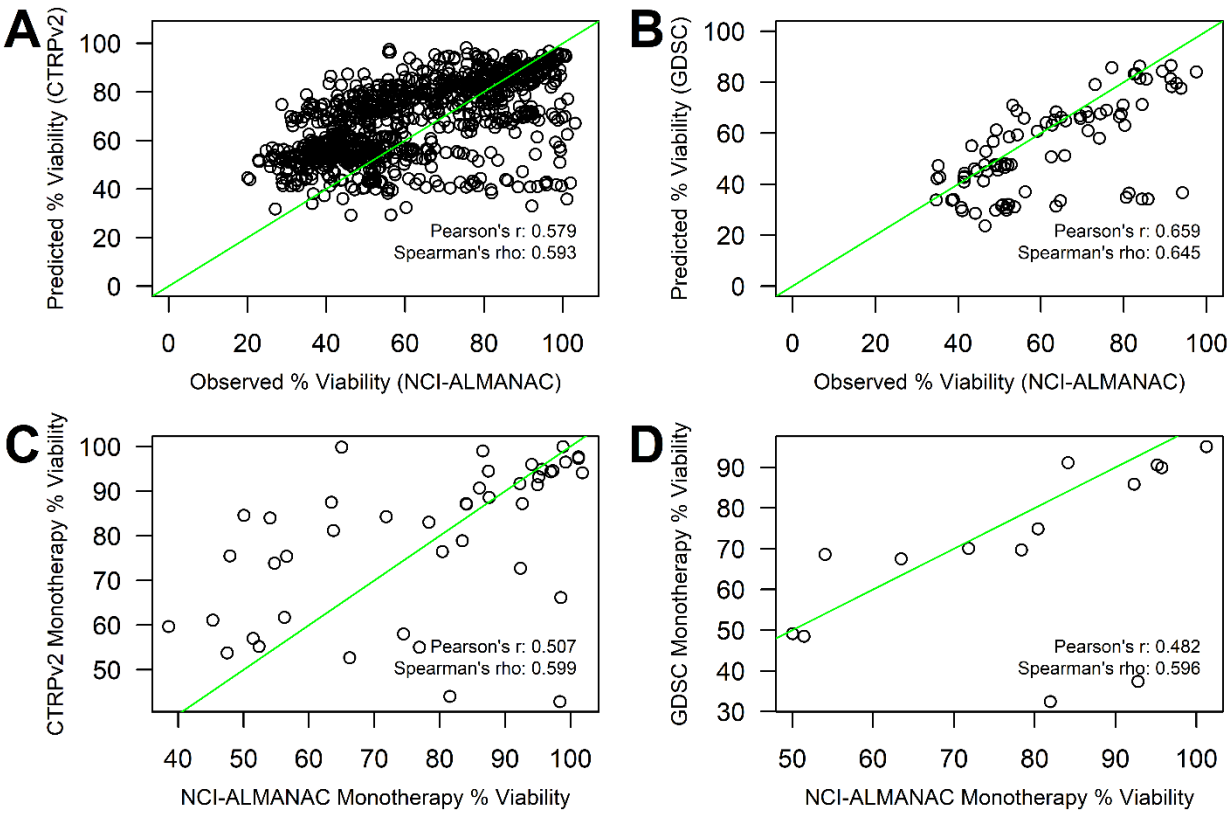

Figure S3. Agreement between drug combination efficacy predictions made with CTRPv2 or GDSC and measured efficacies in NCI-ALMANAC A-B) Scatterplots showing the correlation between drug combination mean % viabilities predicted with IDACombo and **(A)** CTRPv2 or **(B)** GDSC monotherapy data vs measured mean % viabilities for those combinations in NCI-ALMANAC. The green line is a reference diagonal with slope = 1 and intercept = 0. Note that CTRPv2 and GDSC predictions were made using all available cell lines for each combination in the dataset, so the predicted and measured mean % viabilities were produced with different cell line sets. Also note that predictions were only made for the maximum tested NCI-ALMANAC concentrations for each drug and that overlapping combinations were excluded if the concentration tested in NCI-ALMANAC exceeded the maximum tested concentration in CTRPv2 (for **A)** or GDSC (for **B**) for any drug in the combination. **C-D)** Mean monotherapy % viabilities for each drug included in at least one of the drug combinations plotted in **A** or **B** for **C** and **D** respectively. Monotherapy viabilities are plotted for **C)** CTRPv2 vs. NCI-ALMANAC and **D)** GDSC vs NCI-ALMANAC with average viabilities being calculated for all available cell lines in each dataset for each drug. The green line is a reference diagonal with slope = 1 and intercept = 0. Note that measured viability averages are at the maximum tested NCI-ALMANAC concentrations used for that drug in each combination the drug was included in. If the maximum concentration for a drug differed between different combinations involving that drug in NCI-ALMANAC, the most commonly used maximum concentration was selected for plotting in panels **C** and **D**. Source data are provided with this paper.

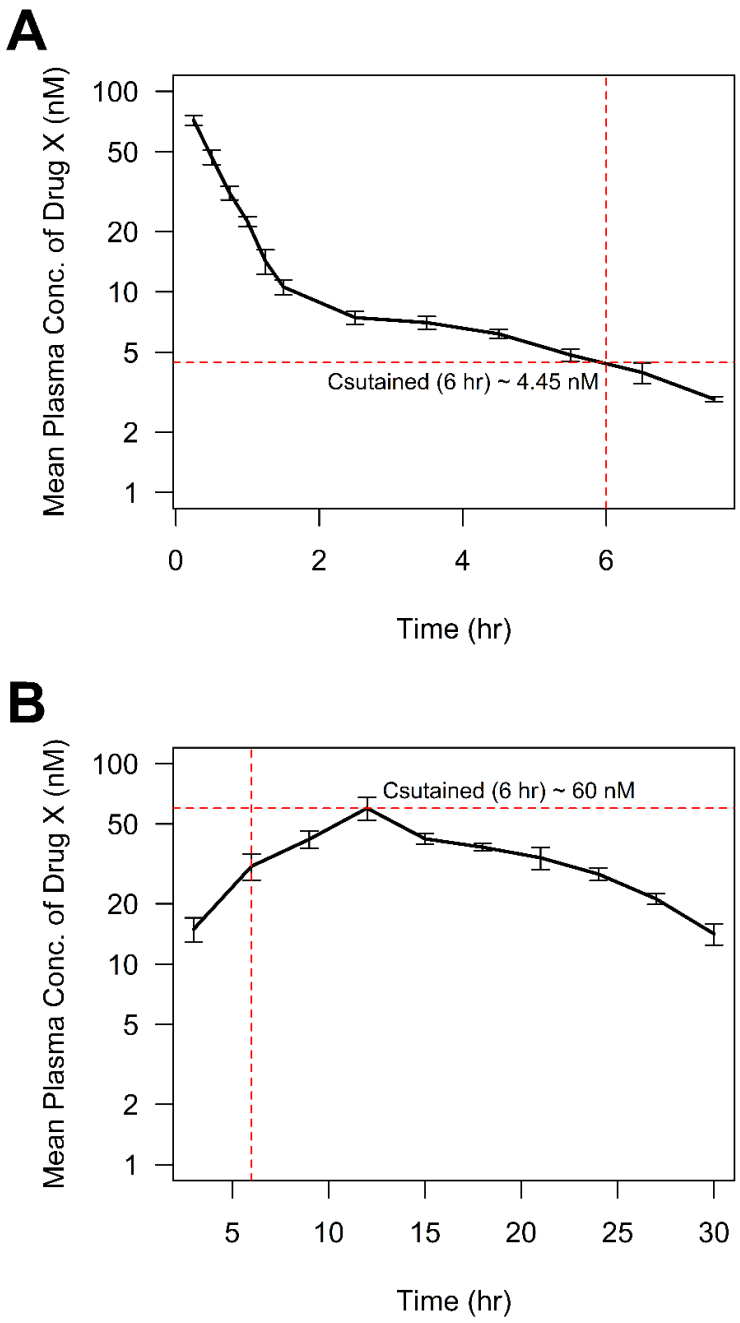

Figure S4. Calculating Csustained,6hr from clinical plasma concentration curves. This figure gives two hypothetical examples to illustrate how Csustained is calculated from plasma concentration curves identified in phase I or II clinical trials. **A)** When mean plasma drug concentrations constantly decrease following administration of a drug, Csustained,6hr is simply the mean plasma concentration at 6 hours after drug administration. **B)** When mean plasma drug concentrations continue rising for more than 6 hours following administration of a drug, Csustained,6hr is the maximum plasma concentration achieved at least 6 hours after drug administration. Error bars represent mean ± standard error.

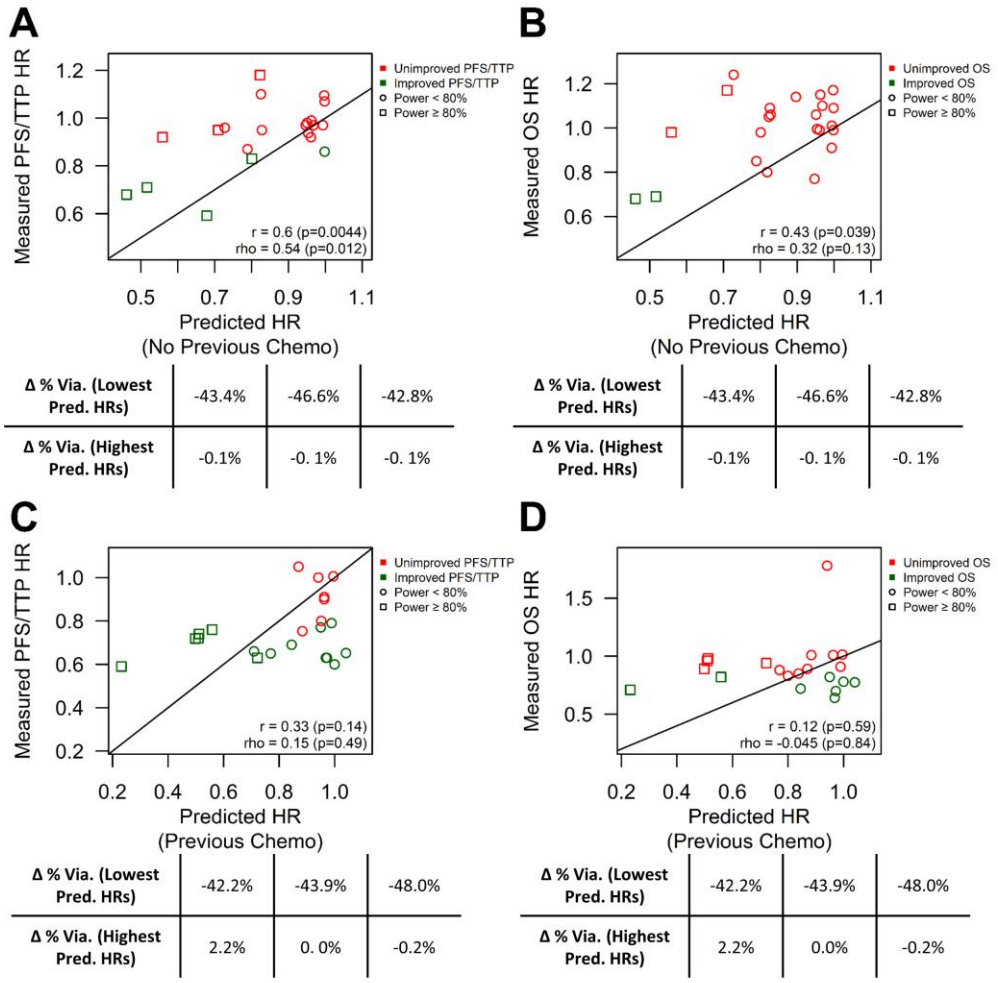

Figure S5. Predicted vs measured hazard ratios for clinical validation analysis. This figure shows how hazard ratios (HRs) predicted with IDACombo (x-axes) compare to HRs reported by the clinical trials selected for the clinical trial validation analysis (y-axes). Note that, while this figure includes largely the same set of trials used in Figure 4 in the main text, some of those trials are not included in this figure because they did not report HRs. Red points represent trials which did not report a HR that was statistically less than 1, while green points represent trials that did report a HR that was statistically less than 1. Circles represent trials where the power predicted by IDACombo for that trial was <80%, while squares represent trials where the predicted power was ≥80%. Pearson's r and Spearman's rho are reported alongside two-sided p-values for whether or not the measured correlation is significantly different from 0. **A)** Measured PFS/TTP HRs vs predicted HR in clinical trials where patients had not received chemotherapy prior to trial entry. **B)** Measured OS HRs vs predicted HR in clinical trials where patients had not received chemotherapy prior to trial entry. **C)** Measured PFS/TTP HRs vs predicted HR in clinical trials where patients had received chemotherapy prior to trial entry. **D)** Measured OS HRs vs predicted HR in clinical trials where patients had received chemotherapy prior to trial entry. Note that further information for these trials and IDACombo's predictions for them is included in Supplementary Data 3. The tables below each plot indicate the change in predicted mean viability for the experimental therapy vs. the control therapy for the three highest predicted HRs and the three lowest predicted HRs from each panel (negative values indicate experimental therapy has lower predicted viability than control therapy). Source data are provided with this paper.

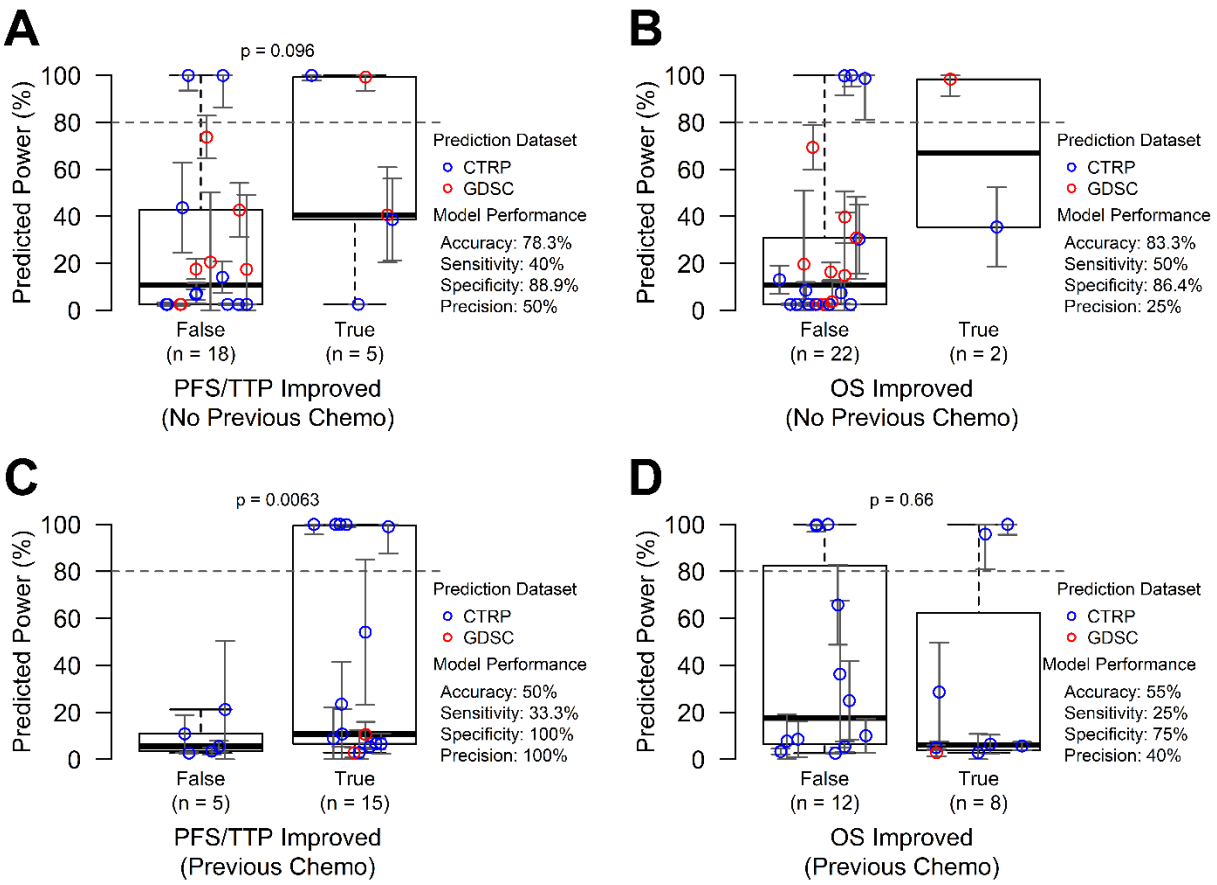

Figure S6. Using only cancer-specific cell lines does not improve model performance for clinical trial power predictions. Identical to Figure 4, except that predictions were made for each trial using sets of cell lines specific to the cancer type being studied in each trial. **A)** Predicted power of each trial in previously untreated patients to detect a significant improvement in PFS/TTP at an alpha of 0.05 versus whether or not the study actually detected a significant improvement in PFS/TTP. **B)** Predicted power of each study in previously untreated patients to detect a significant improvement in OS at an alpha of 0.05 versus whether or not the study actually detected a significant improvement in OS. **C)** Predicted power of each trial in previously treated patients to detect a significant improvement in PFS/TTP at an alpha of 0.05 versus whether or not the study actually detected a significant improvement in PFS/TTP. **D)** Predicted power of each study in previously treated patients to detect a significant improvement in OS at an alpha of 0.05 versus whether or not the study actually detected a significant improvement in OS. Error bars for each plotted clinical trial power represent mean estimated power ± standard error (bounded between 0 and 100% power). P values were calculated using one-tailed t-tests. Blue circles indicate predictions made using the CTRP dataset, and red circles indicate predictions made using the GDSC dataset. Boxplots are plotted so that the lower and upper whiskers indicate the extreme lower and upper values respectively, the box boundaries indicate the first and third quartiles, and the center line indicates the median. Source data are provided with this paper.

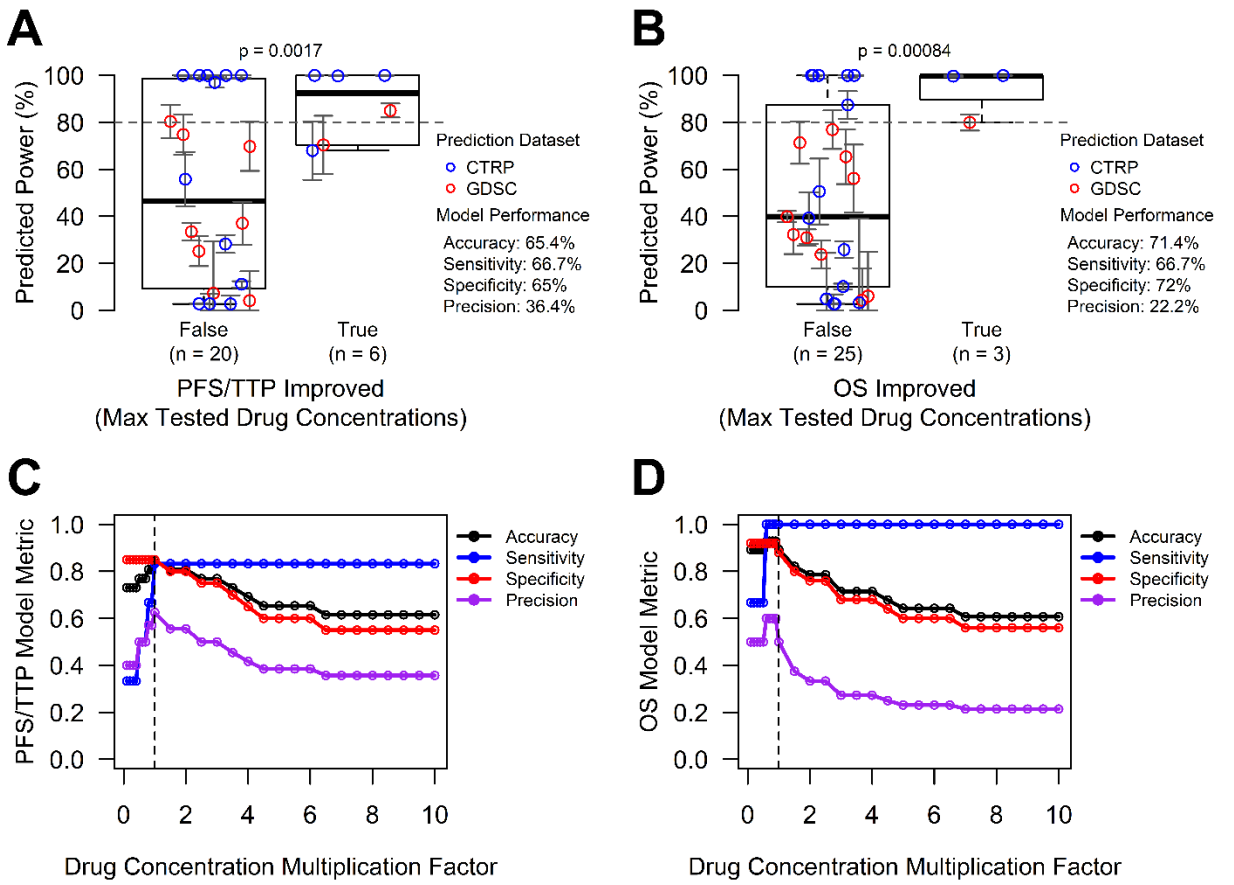

Figure S7. Clinical power predictions are dose-dependent. A&B) Similar to Figure 4A and 4B, all available cell lines were used to create predictions of study power for trials in chemo-naïve patients and compared to whether or not the trials saw a statistically significant improvement in PFS/TTP **(A)** or OS **(B)**. In this figure, however, maximum tested concentrations were used for each drug instead of Csustained concentrations. Notably, these predictions with the maximum tested concentration of each drug results in much poorer model performance than the Csustained predictions in Figure 4. **C&D)** In an effort to determine how sensitive our method is to dose perturbation, power predictions were made for each trial in chemo-naïve patients using Csustained drug concentrations which have been multiplied by a multiplication factor between 0.1 and 10. Model performance metrics for PFS/TTP **(C)** or OS **(D)** were then calculated using predictions from each dose multiplication factor, and those metrics are plotted here. Error bars for each plotted clinical trial power represent mean estimated power ± standard error (bounded between 0 and 100% power). P values in **A** and **B** were calculated using one-tailed t-tests. Blue circles indicate predictions made using the CTRP dataset, and red circles indicate predictions made using the GDSC dataset. Boxplots are plotted so that the lower and upper whiskers indicate the extreme lower and upper values respectively, the box boundaries indicate the first and third quartiles, and the center line indicates the median. Source data are provided with this paper.

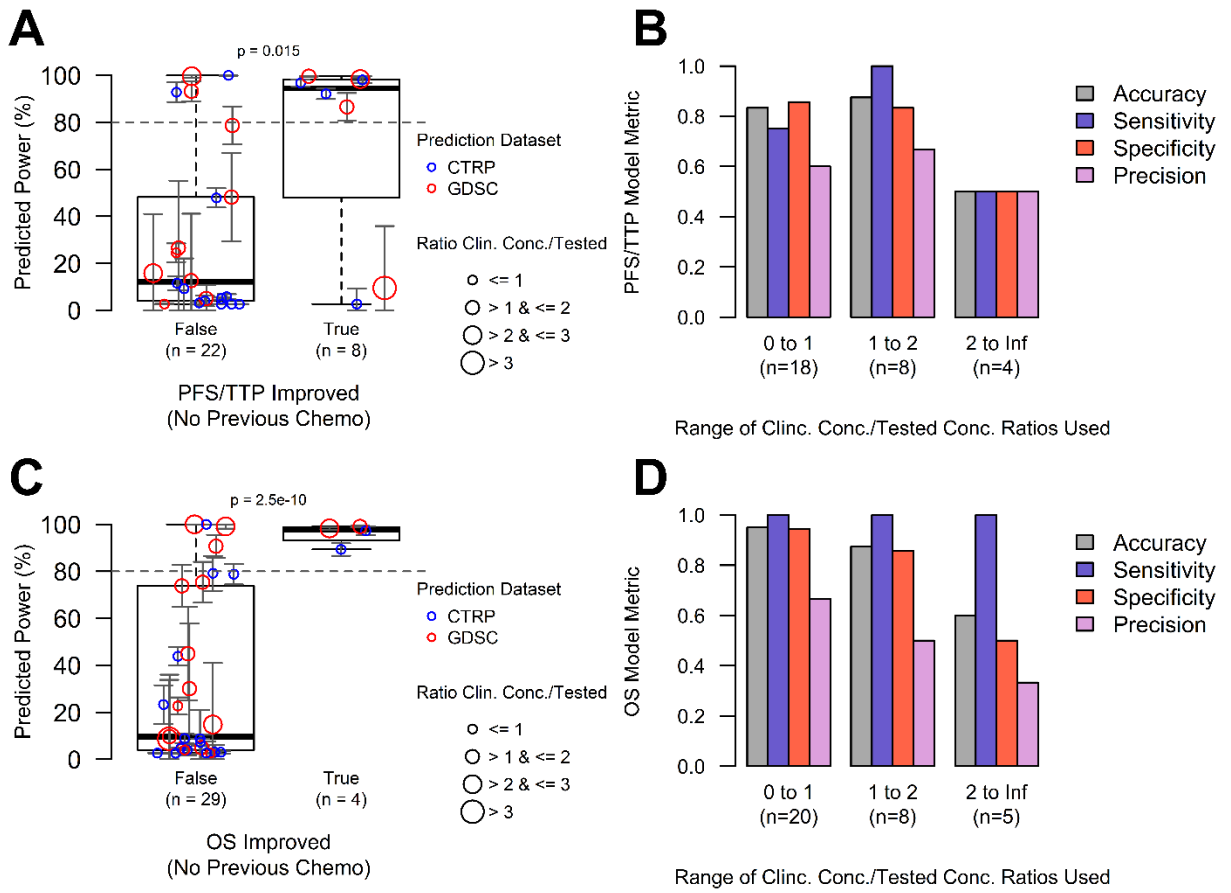

Figure S8. IDACombo predictions become less accurate when made using drug concentrations beyond the tested monotherapy concentration range. A) Similar to Figure 4A, this plot shows predicted clinical trial powers for PFS/TTP in trials with chemo-naïve patients, separated based on whether or not the trial actually observed a statistical improvement in PFS/TTP with the test treatment. Trial points are sized according to the maximum ratio of the Csustained concentrations used for the drugs in the trial to the maximum tested concentrations of those drugs in CTRPv2 or GDSC. Ratios above 1 indicate that the Csustained concentration is higher than the maximum available concentration in CTRPv2 or GDSC. Notably, most of the incorrectly classified trails have ratios > 1 and most of the correctly classified trials have ratios < 1. **B)** Barplot showing PFS/TTP model performance for trials with chemo-naïve patients that fall within three different ranges of ratios of drug Csustained concentration to tested concentration in CTRPv2 or GDSC. Notably, trials with a Csustained/tested concentration ratio > 2 are predicted much more poorly than trials with a ratio between 0 and 1 or with a ratio between 1 and 2. **C)** Same as **A**, except for OS in trials with chemo-naïve patients. **D)** Same as **B**, except for OS in trials with chemo-naïve patients. Error bars for each plotted clinical trial power represent mean estimated power ± standard error (bounded between 0 and 100% power). P values in **A** and **C** were calculated using one-tailed t-tests. Blue circles indicate predictions made using the CTRP dataset, and red circles indicate predictions made using the GDSC dataset. Boxplots are plotted so that the lower and upper whiskers indicate the extreme lower and upper values respectively, the box boundaries indicate the first and third quartiles, and the center line indicates the median. Source data are provided with this paper.

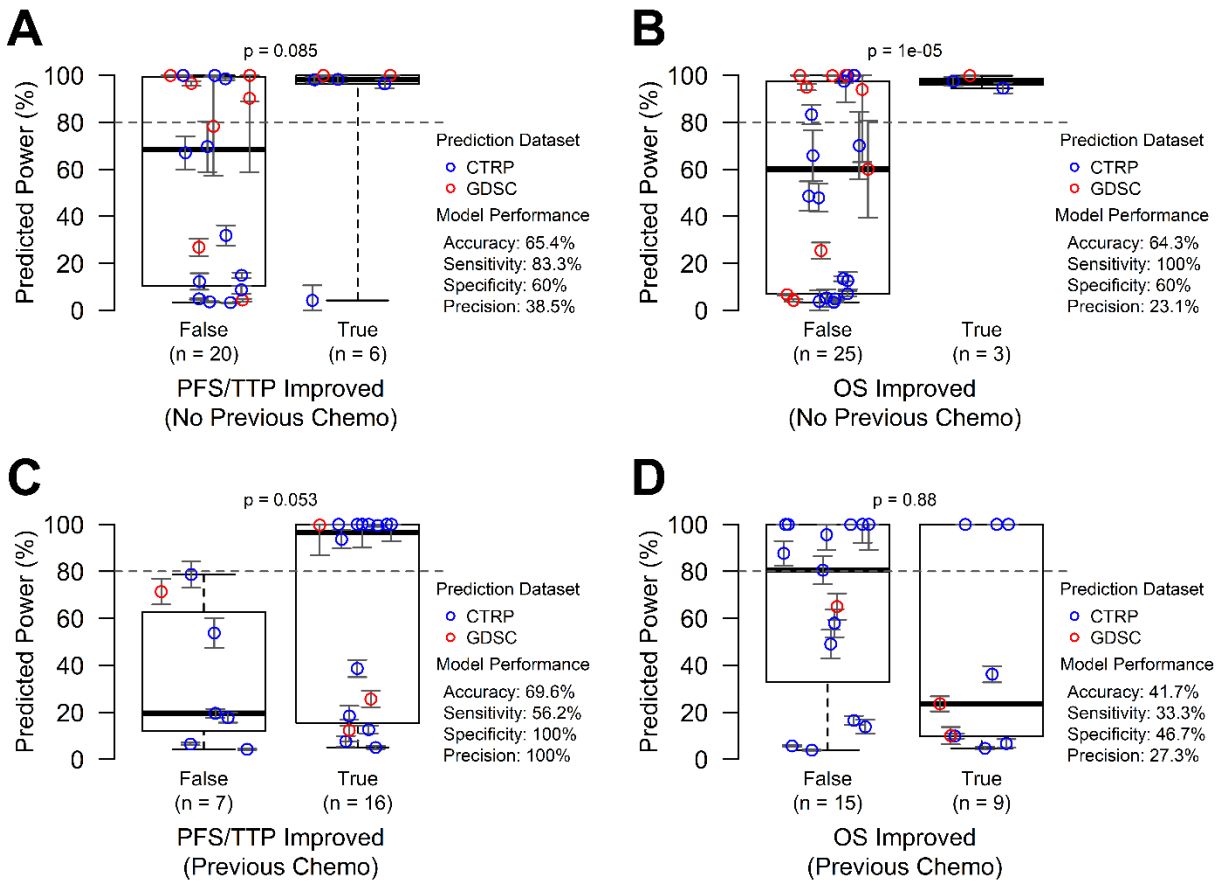

Figure S9. Predictions made using Bliss independence are less accurate than those made with independent drug action. Power predictions were made for the clinical trials shown in Figure 4, but using the Bliss independence model rather than the IDA model. In general, when compared to the IDA predictions in Figure 4, Bliss Independence inflates estimated powers, leading to decreased precision, specificity, and accuracy while providing marginal improvements in sensitivity. Error bars for each plotted clinical trial power represent mean estimated power ± standard error (bounded between 0 and 100% power). P values were calculated using one-tailed t-tests. Blue circles indicate predictions made using the CTRP dataset, and red circles indicate predictions made using the GDSC dataset. Boxplots are plotted so that the lower and upper whiskers indicate the extreme lower and upper values respectively, the box boundaries indicate the first and third quartiles, and the center line indicates the median. Source data are provided with this paper.

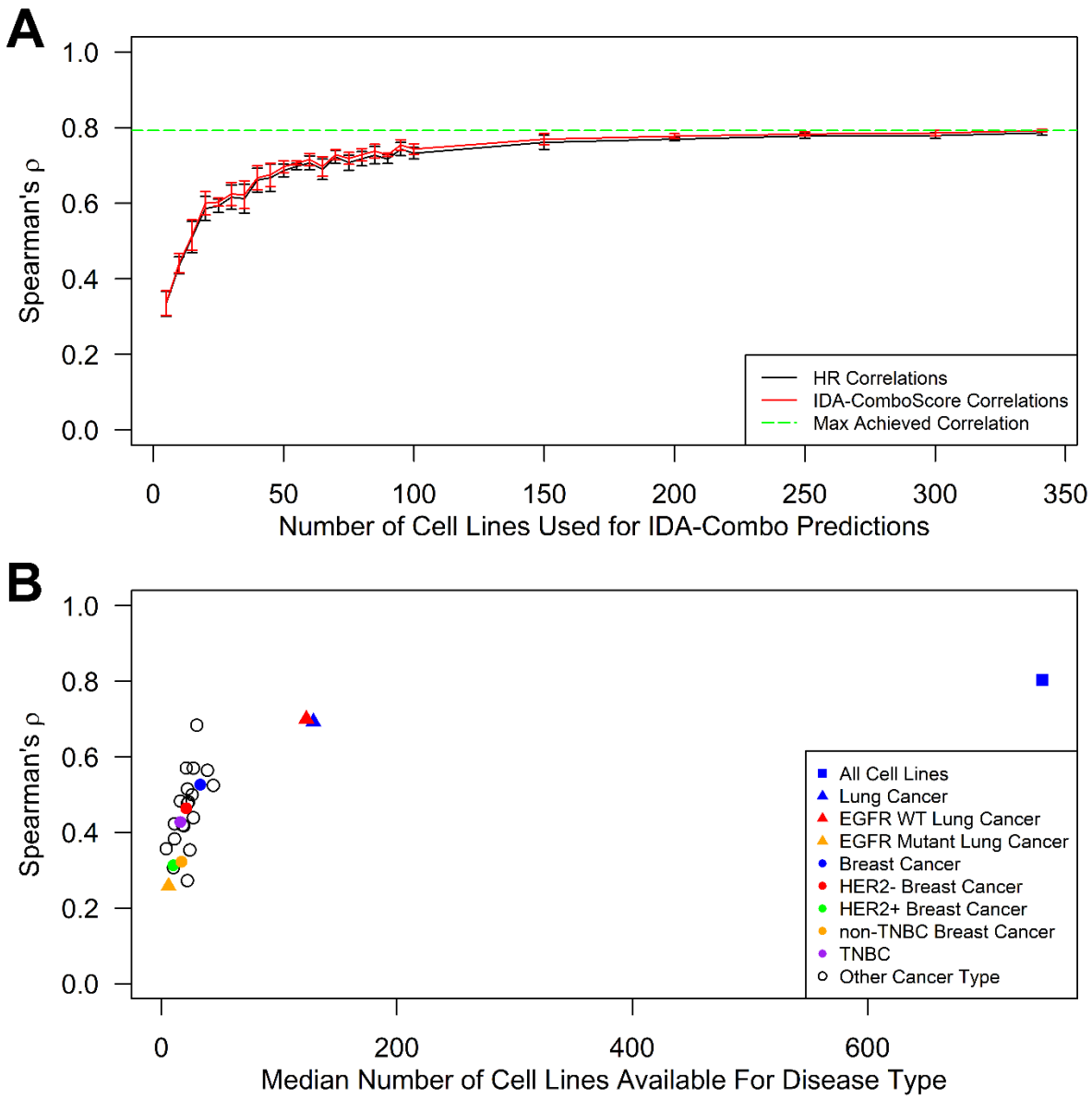

Figure S10. IDAcomboscore agreement between CTRPv2 and GDSC is affected by the number of cell lines available to make predictions with. In an effort to determine how many cell lines are required to estimate drug combination efficacy, IDAcomboscore correlations between CTRPv2 and GDSC are plotted versus the number of cell lines used to make those predictions. **A)** IDA-comboscore predictions were made using randomly sampled sets of cell lines of varying sizes. Sampling was performed three times for each number of cell lines and the mean of each triplicate is plotted with error bars representing the standard deviation of the triplicate correlation measurements. Notably, agreement between CTRPv2 and GDSC decreases rapidly as the number of cell lines is reduced below 50. **B)** Correlations are plotted for predictions made using cancer-specific cell lines. Note that the x-axis denotes the median number of cell lines available for that cancer type for each drug combination, as the number of cell lines available for each cancer type varies from drug to drug. Subsets of breast cancer and lung cancer are highlighted in the plot. Note that for both panels **A** and **B**, correlations were only calculated for drug combinations that used drugs for which their clinical doses were available in both CTRP and GDSC so as to avoid calculating correlations between predictions made with different drug concentrations between the two datasets. Source data are provided with this paper.

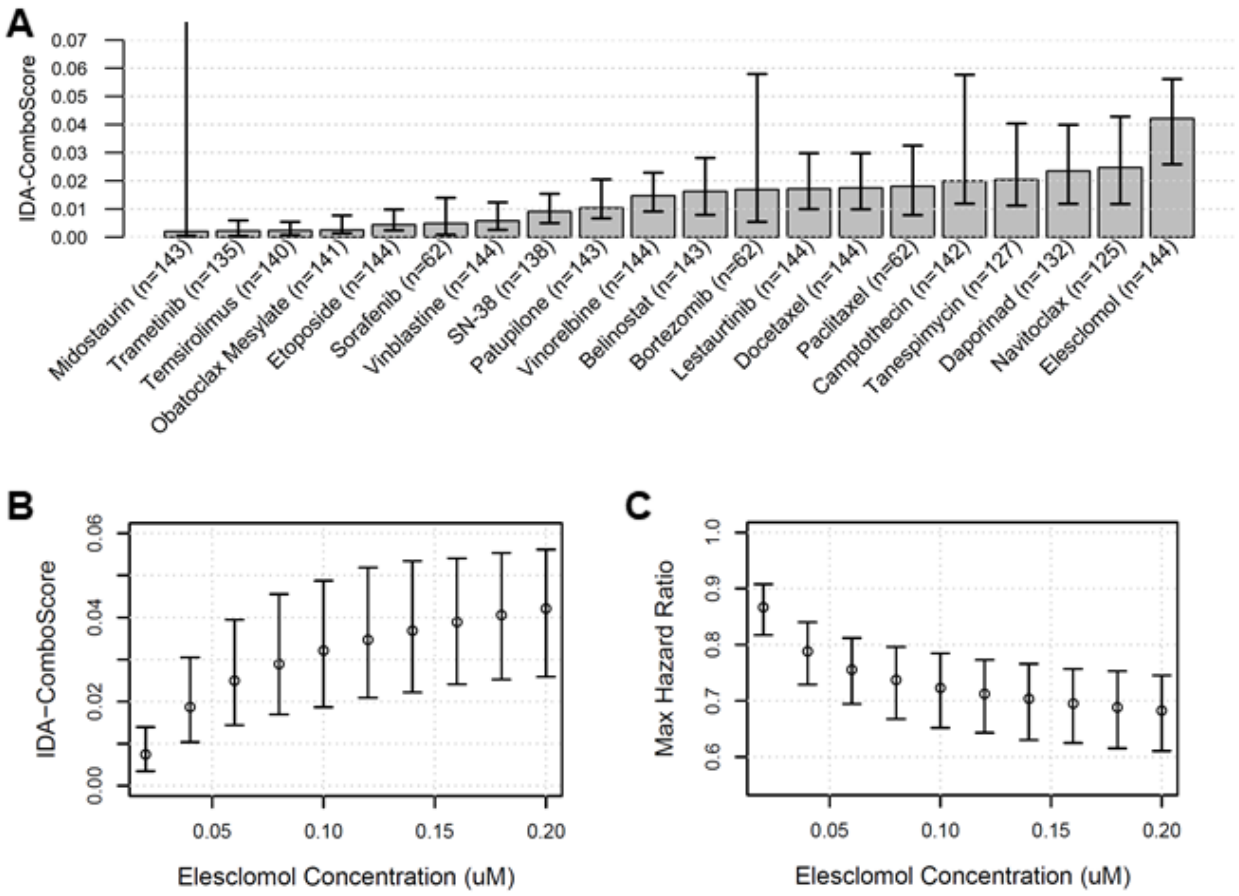

Figure S11. IDACombo predicts that elesclomol will efficaciously combine with cisplatin+gemcitabine in EGFR WT lung cancer. A) IDAcomboscores were calculated for the addition of late-stage clinical drugs in GDSC at their Csustained concentrations to the control treatment combination of Cisplatin (6.44μM) + Gemcitabine (1.14μM) in EGFR WT lung cancer. The number of cell lines available to generate predictions for combinations with each additional drug are provided in parentheses in the x-axis labels. Only the top 20 IDAcomboscores are plotted here. **B)** Predicted IDAcomboscores for the addition of elesclomol to the combination of Cisplatin (6.44μM) + Gemcitabine (1.14μM) across a range of concentrations of elesclomol in EGFR WT lung cancer. **C)** Maximum predicted hazard ratios for the addition of elesclomol to combination of Cisplatin (6.44μM) + Gemcitabine (1.14μM) in EGFR WT lung cancer across a range of concentrations of elesclomol. Maximum hazard ratio is defined as the higher hazard ratio (i.e. the hazard ratio that indicates less efficacy improvement from the test treatment vs the control treatment) of either: 1. elsclomol+cisplatin+gemcitabine vs cisplatin+gemcitabine or 2. elesclomol+cisplatin+gemcitabine vs elesclomol monotherapy. **A-C)** Error bars represent mean ± 95% confidence interval as estimated using Monte Carlo Simulations (see Online Methods). Source data are provided with this paper.

SUPPLEMENTAL TABLES

Table S1. R packages used in the analyses performed in this paper.

Package Name	Package Version	Package Citation	Package WebLink
car	2.1.5	Fox and Weisberg, 2011	https://CRAN.R-project.org/package=car
ComplexHeatmap	1.14.0	Gu et al., 2016	https://bioconductor.org/packages/release/bioc/html/ComplexHeatmap.html
drc	3.0.1	Ritz et al., 2015	https://CRAN.R-project.org/package=drc
IDACombo	1.0.2	This paper.	https://github.com/Alexander-Ling/IDACombo
openxlsx	4.1.4	Schauberger and Walker, 2019	https://CRAN.R-project.org/package=openxlsx
parallel	3.4.2	R Core Team, 2017	Created by the R Core team and included in R since R version 2.14.0.
pbapply	1.3.3	Solymos and Zawadzki, 2017	https://CRAN.R-project.org/package=pbapply
powerSurvEpi	0.0.9	Qiu et al., 2015	https://CRAN.R-project.org/package=powerSurvEpi
precrec	0.9.1	Saito and Rehmsmeier, 2017	https://CRAN.R-project.org/package=precrec
progress	1.1.2	Csárdi and FitzJohn, 2016	https://CRAN.R-project.org/package=progress
RColorBrewer	1.1.2	Neuwirth, 2014	https://CRAN.R-project.org/package=RColorBrewer
readr	1.1.1	Wickham et al., 2017	https://CRAN.R-project.org/package=readr
readxl	1.0.0	Wickham and Bryan, 2017	https://CRAN.R-project.org/package=readxl
rgl	0.98.1	Adler et al., 2017	https://CRAN.R-project.org/package=rgl
rvest	0.3.2	Wickham, 2016	https://CRAN.R-project.org/package=rvest
sandwich	2.4.0	Zeileis, 2004, 2006	https://CRAN.R-project.org/package=sandwich
xlsx	0.5.7	Dragulescu, 2014	https://CRAN.R-project.org/package=xlsx

SUPPLEMENTAL RESULTS

Clinical Trial Validation

Identifying clinical drug concentrations for clinical validation of IDACombo

As mentioned in the main text, we searched published phase I and II clinical trials to identify clinical plasma concentrations for each drug at the administered doses used in each trial in our clinical trial validation analysis. Since maximum plasma concentrations (Cmax) are extremely transient for some drugs, especially those administered via IV bolus, we decided to use the maximum plasma concentrations achieved at least 6 hours after drug administration (a metric we termed Csustained,6hr) as our concentrations for IDACombo predictions. Figure S4A illustrates how Csustained is calculated for drugs with constantly decreasing plasma concentrations over time, and Figure S4B illustrates how Csustained is calculated for drugs with increasing plasma concentrations beyond 6 hours. A more detailed description of this metric and why it was chosen is included in the Online Methods. Csustained values for each drug in the clinical trial analysis, along with the citations used to determine them, are included in Supplementary Data 4.

Misclassified trials in Figure 4A: PFS/TTP powers in first-line therapy trials

The first false positive in Figure 4A tested the addition of vinorelbine to gemcitabine in non-small cell lung cancer (NSC lung cancer)[1]. Notably, the National Comprehensive Cancer Network (NCCN) currently classifies vinorelbine + gemcitabine as a category 1 therapy useful in certain circumstances for the first-line treatment of advanced NSC lung cancer[2], indicating that the predicted utility of this combination may not be entirely inappropriate. Furthermore, this trial was unusual in our clinical validation dataset in that it only enrolled elderly patients (≥70 years old), most of whom had multiple comorbidities and non-zero ECOG scores, and death from unknown causes or losing patients to follow up was considered as progression in this study.

The other two false positives in Figure 4A were ovarian cancer trials that tested: 1) the addition of paclitaxel to carboplatin[3] and 2) the addition of gemcitabine to paclitaxel + carboplatin[4]. While NCCN guidelines do not recommend paclitaxel + carboplatin + gemcitabine for ovarian cancer[5], paclitaxel + carboplatin is considered the backbone of first-line therapy for ovarian cancer[6]. That said, there is reason to doubt IDACombo's predictions for these treatments, because dimethyl sulfoxide (DMSO) was used as the solvent for drug testing in CTRPv2, and DMSO is known to inactivate platinum complexes[7]. Indeed, carboplatin monotherapy produces an average viability of 97% in CTRPv2 (Supplementary Data 3), suggesting that the drug may be inactivated in the dataset and, therefore, is not being properly accounted for in the control therapies for these trials.

The false negative in Figure 4A was also an ovarian cancer trial, this time testing the addition of nintedanib to paclitaxel + carboplatin[8]. Since carboplatin inactivation in this case would have increased the predicted benefit of nintedanib, it cannot be the cause of this misclassification. While it is possible that this case represents a case of drug additivity/synergy, we believe the fact that three out of four misclassified trials are ovarian cancer trials suggests that the pan-cancer set of cell lines used to generate these predictions may perform poorly when making predictions for ovarian cancer trials. It is also worth noting that, while this study did detect a statistically significant improvement in PFS, the study's authors note that the

improvement is “of limited clinical relevance” and that the study’s results “do not support a role for nintedanib in ovarian cancer”[8].

Clinical IDACombo predictions with cancer type/subtype specific sets of cell lines

As mentioned in the main text, we performed analyses to evaluate the suitability of IDACombo to predict the efficacy of targeted therapies, which are often only effective in specific molecular subsets of cancer. Two of the clinical trials in our dataset tested targeted therapies and reported full study results for patients with and without the molecular features targeted by those therapies. We made power predictions for these two trials using sets of cell lines with or without the relevant molecular features for each reported patient subgroup. The resulting predictions for these trials are shown in Supplementary Data 5. Notably, IDACombo’s predictions agreed with clinical findings that there is a higher expected benefit for patients with the molecular features targeted by the targeted therapies than for patients without those molecular features. However, the subtype-specific predictions did not reach the 80% power cuttoff necessary to correctly classify the trials. This may be due to the fact that very few cell lines were available for these subtype-specific predictions, leading to relatively high prediction uncertainties and a relatively small population in which to detect phenotypic heterogeneity.

To further assess the utility of making predictions with sets of cell lines matched to patient phenotypes, we predicted clinical trial powers using cancer-specific sets of cell lines for each clinical trial (Figure S6). Note that clinical trials were excluded if fewer than 5 cancer-specific cell lines were available with which to make predictions. The cancer-specific predictions resulted in accuracies > 80% for trials in chemo-naïve patients, but model performance was generally reduced and prediction uncertainties increased for cancer-specific predictions versus pan-cancer predictions. This result, along with the analysis of the two targeted therapy trials, suggests that predictions made using cancer and subtype-specific sets of cell lines could be preferable to pan-cancer predictions if sufficient numbers of cell lines were available for each cancer type, but there are currently too few cell lines available for each cancer type in these datasets for this approach to be viable. In the meantime, pan-cancer predictions appear to be adequate for most of the drug combinations used in our clinical trial dataset.

Clinical IDACombo predictions are affected by selected drug concentrations, but remain accurate, sensitive, and specific across a range of concentrations

Beyond the selection of cell lines, we also wanted to investigate the importance of drug concentration selection for IDACombo predictions. We examined the importance of drug concentration selection by assessing whether or not prediction performance was harmed by using drug concentrations that deviated from clinical plasma concentrations. When predictions were made using the maximum concentrations tested for each drug in either CTRPv2 or GDSC rather than Csustained concentrations, prediction accuracies in treatment-naïve trials fell dramatically (65.4% accuracy for PFS/TTP and 71.4% accuracy for OS) (Figures S7A and S7B). Alternatively, when the Csustained concentrations for each drug in a trial were multiplied by factors between 0.1 and 10, we found that uniformly increasing drug concentrations kept the method’s sensitivity high but decreased accuracy, specificity, and precision for both PFS/TTP and OS. Uniformly decreasing concentrations quickly reduced sensitivity and precision (Figures S7C and S7D). These results suggest that correctly identifying clinical drug concentrations is important for *in vitro* predictions using IDA, with underestimated concentrations decreasing

model performance more than overestimated concentrations when clinical dose ratios between drugs are preserved.

Clinical IDACombo prediction accuracy drops when predicting efficacy for trials with drugs which have plasma concentrations beyond the tested in vitro concentrations

To further assess the importance of drug concentration for model performance, we looked at trials that used treatments which resulted in Csustained concentrations greater than the concentrations tested for those drugs *in vitro*. Several of the trials identified from ClinicalTrials.gov tested drugs with Csustained concentrations above the tested concentrations for those drugs in CTRPv2 or GDSC, with several trials including drugs with Csustained concentrations > 2x the tested *in vitro* concentrations in GDSC (Figures S8A and S8C). To determine whether or not this would affect IDACombo based power predictions for these trials, we calculated model performance for both PFS/TTP and OS for these trials (specifically trials in chemo-naïve patients) and compared model performance to whether or not trials included drugs with Csustained concentrations higher than tested *in vitro* concentrations. Trials with at least one drug with a Csustained concentration > 2x the maximum tested *in vitro* concentration for that drug showed largely reduced accuracy, specificity, and precision in both PFS/TTP and OS predictions relative to trials with drugs that have Csustained concentrations ≤2x the maximum tested *in vitro* concentrations (Figures S8B and S8D). As a result of this finding, only trials with drugs that have Csustained concentrations ≤2x the maximum tested *in vitro* concentrations were included in the clinical analyses in this paper.

Prospective Analysis

IDAcomboscore Clusters

As mentioned in the main text, the clusters in Figure 5 can partially be explained by drug mechanisms of action, as drugs with the same mechanism of action often end up in the same hierarchical clusters (at least, this is the case for the few mechanisms of action for which we have more than one drug). This does not fully explain the clustering, however, as we can see with topoisomerase inhibitors and EGFR inhibitors, which are divided between several small clusters. A more detailed analysis of the drugs' mechanisms of action may partially explain this, as, for the topoisomerase inhibitors, drugs are separated by whether or not they inhibit topoisomerase I or II and whether or not they act by binding DNA or intercalating DNA. This is highly speculative, however, given the small number of drugs available for each mechanism of action. It is also notable that drugs which have similar average viabilities across all cell lines when used as a monotherapy tend to be more closely clustered. This suggests that the clustering observed in Figure 5 may be explained partially by similarity in drug mechanisms and partially by similarity in the average monotherapy efficacies of drugs at their clinical concentrations. Unfortunately, a more detailed analysis of which mechanisms and monotherapy efficacies provide the most effective combinations is prevented by the limited number of drugs available for each drug mechanism.

The accuracy of cancer-specific IDACombo predictions is currently limited by the number of available cell lines for each cancer type

As discussed in the main text, we sought to determine how many cell lines are necessary to create accurate predictions using IDACombo. Since the true efficacy of most drug combinations is not known, we decided to use agreement between predictions made using

CTRPv2 and GDSC as a metric of prediction accuracy. Notably, we only compared CTRPv2 and GDSC predictions for combinations in which Csustained was available for both drugs in both datasets and which had at least 400 cell lines available to make predictions with—this resulted in comparisons for 351 drug combinations involving 27 compounds.

For the comparison, we calculated Spearman's ρ between CTRPv2 and GDSC predictions made with varying number of cell lines and plotted them in Figure S10A. This revealed that a ρ as high as 0.8 could be achieved using 250 or more cell lines, and that this correlation slowly decreased to ~0.7 as the number of cell lines was reduced to 50. With less than 50 cell lines, ρ decreased more rapidly, to ~0.6 with 25 cell lines and ~0.3 with 5 cell lines. This suggests that most cancer-specific predictions will be suboptimal, owing to their having less than 50 cell lines available to make predictions with, but it also suggests that there is some level of reproducibility using those numbers of cell lines. To quantify this reproducibility specifically for the cancer types available in CTRPv2 and GDSC, we plotted Spearman ρ's between cancer-specific IDAcomboscores versus the median number of cell lines available for each of 27 cancer types/subtypes (Figure S10B). The results largely agreed with the downsampling approach in Figure S10A, showing that Spearman ρ's for cancer-specific predictions ranged from ~0.7 to ~0.3 depending roughly on how many cell lines were available for each cancer type. A full list of correlation coefficients for each cancer type can be found in Data S6. These findings suggest that highly reproducible cancer-specific predictions are currently possible for some cancer types, but IDACombo predictions for most cancer types would likely be significantly improved by increasing the number of cell lines available for those cancer types.

SUPPLEMENTAL DISCUSSION

As briefly mentioned in the main text, there are several limitations of our method that must be considered when using it in the future.

First, while IDACombo's predicted efficacies strongly correlate with measured efficacies in NCI-ALMANAC and deviations of predicted efficacies from measured efficacies are generally small, it is still obvious that examples can be found where the measured effect of a drug combination is significantly different from the predicted effect. These may represent true cases of drug synergy, additivity, or antagonism, and the drug interactions present in these combinations could have a significant impact on the clinical behavior of these treatments. Given this result and the fact that synergistic drug combinations are likely to outperform combinations that work via IDA[9], it is likely that predictions based on IDA will fail to identify a subset of highly effective drug combinations. Synergy and additivity based prediction methods will need to be developed to identify such combinations. Fortunately, however, the results of our clinical trial validation analysis suggest that this is not a problem for most clinical drug combinations, as the large majority of them were predicted well using IDACombo, at least for trials in previously untreated patients.

This brings us to a second, and perhaps more serious, limitation of the method, which is an apparent unsuitability of cell-line based IDA predictions for patients who have undergone previous cancer drug treatment. We do not have sufficient data from our analyses to definitively explain this finding, but we can propose several hypotheses for future testing. First, there is the possibility that the difference in model performance between previously treated and previously untreated patients is coincidental—merely due to the model working better for some drugs than

for others and to different drugs being tested in trials of previously treated or untreated patients. Upon a closer inspection of the drugs involved in misclassified trials, however, we believe this is unlikely to be the case. Of the 12 drugs involved in trials that were misclassified for PFS/TTP improvement, all except vandetanib and nintedanib (which were both used in only a single trial) were also used in trials that were correctly classified, and 8 of the 12 drugs were used in correctly classified trials at least as often as they were used in misclassified trials. A more likely explanation for this finding could be that the cell line models in CTRPv2 and GDSC may more accurately represent chemo-naïve tumors than previously treated tumors. It is well known that drug treatment can induce clonal selection in tumors in ways that alter the tumors' drug sensitivities[10]. While these altered sensitivities may be reflected in cell lines that were generated from the tumors of previously treated patients[11], it is likely that the cell lines in CTRPv2 and GDSC were derived under a diverse set of circumstances. As such, we would not expect our population of available cell lines to be a good representation of a population of tumors which had all recently received similar drug treatments. In the future, it may be possible to test this hypothesis by creating panels of cell lines that are derived from patients who had received the same prior therapies as the patients in the trials which were poorly predicted in this study and then test whether predictions made with these cell line panels agree with the clinical findings of those trials.

A third limitation of this study is that our method is currently unable to make predictions for combinations which include immunotherapies or drugs which function by acting systemically on non-tumor cells, such as drugs that act systemically to block hormone synthesis. This is because our predictions rely on *in vitro* drug screening data, and the *in vitro* systems that have been used for high-throughput cancer cell line drug screens lack the ability to mimic immune responses or non-tumor processes such as systemic hormone production. This does not mean, however, that IDA based predictions of drug combination efficacy are unsuitable for immunotherapies or drugs which act outside of the tumor. Efforts are underway to generate *in vitro* models which may be suitable for screening immunotherapies in the future[12] and which could allow for IDA based predictions to be made for immunotherapy combinations. While those models mature, however, IDA based predictions of efficacy for combinations with immunotherapies/systemically acting therapies may be made using the results of monotherapy based clinical trials and the method developed by Palmer and Sorger[9], providing that cross-resistance can be estimated between combined treatments.

Despite these limitations, our results are notable for several reasons which are briefly discussed in the main text. A more detailed discussion of these reasons is as follows.

First, these results demonstrate that *in vitro* drug screening data can be used to generate clinically meaningful predictions for drug combination efficacies in patients, and, furthermore, they suggest that many of these predictions can be made using pan-cancer sets of cell lines. This is somewhat unexpected given the wide range of genetic and phenotypic diversities observed between different cancer types. On the other hand, our results suggest that it will be necessary to make predictions using cell lines of the appropriate cancer type/subtype for targeted therapies, and we believe it is likely that cancer-specific IDACombo predictions could be comparable to or better than pan-cancer predictions if not for the fact that many cancer types currently have relatively few available cell lines in CTRPv2 and GDSC. The solution to this problem, however, may be more complicated than simply increasing the number of cell lines for each cancer type. That is because it must also be noted that, beyond the limited numbers of cell

lines available for many cancer types, the ethnic diversity of available cancer cell lines is also very limited—particularly for ethnicities other than Caucasian or Asian [13]. This means that caution will be necessary when applying the predictions made in this paper to ethnicities that are poorly represented in the cell lines currently available in CTRPv2 and GDSC. Fortunately, others in the field have already recognized the need to increase the number and genetic diversity of available cancer cell lines [14], and the Broad Institute has received an NCI contract to create new cancer cell lines (https://portals.broadinstitute.org/cellfactory). This has already lead to the creation of over 100 validated cancer models. The use of these models in future monotherapy drug screens may improve predictions made with IDACombo even further.

A second reason that the success of IDACombo is notable is that, despite our extensive efforts to identify clinical relevant drug concentrations for each drug in our analysis, these concentrations remain only rough estimates of true clinically relevant concentrations. Beyond the fact that measured plasma concentrations are simply unavailable for some drugs and doses for patients of each cancer type, there is little available information about how plasma drug concentrations relate to intratumoral drug concentrations *in vivo.* Similarly, there is little available information about how media drug concentrations relate to intracellular drug concentrations *in vitro*. In the single study we were able to find that did examine these relationships, researchers found that the clinically relevant *in vitro* drug concentration for paclitaxel may be an order of magnitude below clinically measured plasma concentrations [15]. Even with this information, the appropriate paclitaxel concentration to use for different cancer types is unclear, because the concentrations identified in the study were based on only two cell lines and six patients in a single cancer type. Given that our results suggest that varying drug concentrations can significantly affect prediction performance, it is possible that IDACombo predictions could be improved by future research aimed at identifying the *in vitro* drug concentrations that most closely mimic the drug exposure of tumor cells in the clinic. It is notable, however, that IDACombo works as well as it does—especially given the high uncertainties in the drug concentrations we used to estimate clinical trial powers. It is our hope that this method will help researchers identify promising combinations for future clinical development and that they will ultimately lead to improved therapies for cancer patients.

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