SUPPLEMENTARY TEXTS

SI Text S1. Reversibility of cellular alterations

Reverse transitions do not imply that resistance mechanisms are necessarily reversible. A cell can undergo a pro-sensitivity transition (e.g., transition from *RS* to *SS*) if a new alteration (e.g., a genetic lesion independent of the first, or a micro-environmental change) cause some new weakness in the cell that makes it more vulnerable to drug treatment. The mechanism of the new weakness might be quite different from the original mechanism of drug sensitivity. Furthermore, while mutational events that destroy DNA (1–3) are not reversible, some resistance mechanisms may be reversible, for example if they involve micro-environmental changes (4) and some transcriptionally or epigenetically regulated processes (5–7).

Reversibility is included in the full stochastic simulation for the completeness of the state-transition model, but it is not important to the results, and it is neglected in the analytical approximation model. Although all phenotype transitions in the model are bi-directional, reverse transitions are very infrequent due to the relative population sizes. In the initial stage of the evolution, the population contains a large population of *SS* cells, a small number of singly-resistant cells, and no *RR* cells. This population make-up causes predominantly forward transitions, as the small size of resistant subpopulations creates fewer chances for reverse transitions. At later stages when resistant cells make the majority of the cell population, the number of reverse-transitioning cells becomes trivial compared to the growth of the resistant cells, due to the small rate of alterations.

SI Text S2. Derivation of the equation for quantifying the effect of combination therapy

According to the response surface model developed by Greco *et al*. (8), the interaction of a two-drug combination can be described by the following equation:

$$1 = \frac{d_1}{\mathrm{ED}_{50,1}\left(\frac{E-B}{Emax-E+B}\right)^{1/m_1}} + \frac{d_2}{\mathrm{ED}_{50,2}\left(\frac{E-B}{Emax-E+B}\right)^{1/m_2}} + \alpha\left(\frac{d_1 d_2}{\mathrm{ED}_{50,1}\mathrm{ED}_{50,2}\left(\frac{E-B}{Emax-E+B}\right)^{1/2m_1}\left(\frac{E-B}{Emax-E+B}\right)^{1/2m_2}}\right), \quad [S1]$$

and the dose-response relationship can be defined as follows:

$$E = \frac{Emax\left(d_y/ED_{50,y}\right)^{m_y}}{1+\left(d_y/ED_{50,y}\right)^{m_y}} + B. \quad [S2]$$

Here, we employed the interpretation of Greco (8)'s equations to describe the relationship between drug concentration and the measured pharmacological effect (instead of the measured outcome). Therefore, in the above equations, m_y, the slope of the concentration-effect curve, is positive; meanwhile, d_y is the dose of drug y, $\mathrm{ED}_{50,y}$ is the 50% effective dose of drug y, E is the observed treatment effect, E_{max} is the maximum effect at infinite treatment, and B is the background effect at zero treatment. The interaction parameter α indicates additivity if $\alpha = 0$, synergism if $\alpha > 0$, and antagonism if $\alpha < 0$. In setting up our model, we

assumed a dose-response curve with m_y = 1 for all drugs, and a constant potency ratio between the 2 drugs ($R = d_1/d_2$).

Our model allows the flexibility of defining the extent of manifestation of drug effect in proliferation and/or apoptosis, by defining E as the normalized treatment effect (hence, $E_{max} = 1$), and using two scaling factors to modulate absolute drug effects in proliferation and apoptosis. Defining $E_{max} = 1$ and B = 0, the normalized effect of treatment on subpopulation i, E_i, can be calculated by firstly reducing equation [S1] to

$$1 = \frac{d_1}{\mathrm{ED}_{50,1}\left(\frac{E_i}{1-E_i}\right)} + \frac{d_2}{\mathrm{ED}_{50,2}\left(\frac{E_i}{1-E_i}\right)} + \alpha\left(\frac{d_1 d_2}{\mathrm{ED}_{50,1}\mathrm{ED}_{50,2}\left(\frac{E_i}{1-E_2}\right)}\right), \qquad [S3]$$

and from manipulating equation [S2], the concentration of a particular drug y that would engender a normalized effect of E_i can be obtained from

$$d_y = \mathrm{ED}_{50,y}\frac{E_i}{(1-E_i)}. \qquad [S4]$$

From equations [S3] and [S4], we can apply the concept of dose equivalence (9) to calculate the "equivalent dose" of drug 1, denoted by D_1, which has the same magnitude of effect as the combined effect of the (d_1, d_2) dose pair, by manipulating equation [S3] to give

$$D_1 = d_1 + d_2 R + \alpha\frac{d_1 d_2}{ED_{50,2}}. \qquad [S5]$$

The normalized combined effect of the drug pair (d_1, d_2) could finally be calculated from D_1 by substituting it into equation [S2]. As different sensitive and resistant subpopulations are exposed to different dose combinations, the equivalent dose of drug 1 that is effectively sensed by a subpopulation will differ from one subpopulation to the next. By accounting for the dose sensitivities of each subpopulation to the drugs, we can calculate $D_{1,i}$, the effective equivalent dose of drug 1 that is sensed by subpopulation i, by transforming equation [S5] into

$$D_{1,i} = S_{1,i}d_1 + S_{2,i}d_2 R + \alpha S_{1,i}S_{2,i}\frac{d_1 d_2}{ED_{50,2}}, \qquad [S6]$$

where $S_{1,i}$ and $S_{2,i}$ are the dose sensitivities of subpopulation i to drug 1 and drug 2, respectively. The normalized effect on subpopulation i can then be calculated from

$$E_i = \frac{E_{max}\left(D_{1,i}/\mathrm{ED}_{50,1}\right)}{1+\left(D_{1,i}/\mathrm{ED}_{50,1}\right)} = \frac{D_{1,i}}{\mathrm{ED}_{50,1}+D_{1,i}}. \qquad [S7]$$

From E_i, we can calculate the cellular phenotype as a result of the treatment, by using 2 modulating parameters to define the extent of drug effect on proliferation and apoptosis. Our model defined 2 drug-effect parameters, namely the reduction in proliferation probability PP_i, and drug-induced apoptosis rate a_i. The parameter PP_c modulates how much drug effect manifests in proliferation (PP_c = 1 if drug effect manifests 100% in proliferation, and PP_c = 0 if drug effect does not affect proliferation), while the parameter a_c modulates how much drug effect manifests in apoptosis (a_c = 1 if drug effect manifests 100% in apoptosis, and a_c = 0 if drug effect does not affect apoptosis).

The proliferation probability of subpopulation i as a result of the treatment, PP_i, can be calculated from

$$PP_i = 1 - PP_c E_i, \qquad \text{where} \quad 0 \le PP_c \le 1. \qquad [S8]$$

Meanwhile, the drug-induced apoptosis rate, a_i, can be calculated from

$$a_i = a_c E_i, \qquad \text{where} \quad 0 \leq a_c \leq 1. \qquad \text{[S9]}$$

SI Text S3. Alternative definitions of drug-effect parameters

Many strategies have been employed in designing anti-cancer drugs, and the different mechanisms of action manifest differently in the cellular phenotype of the cancer cells. Some agents target the proliferation pathway (10), while others target the apoptosis pathway (11). However, other strategies display the ability to affect both proliferation and death, such as therapies that involve the DNA damage mechanism (12), radiation (13), or some cell signalling targets (14). To describe a generalized case, our main simulations assumed that drug effect is exhibited in both proliferation and apoptosis, but as described in **SI Text S1**, our method of quantifying combination therapy effect allows for a flexibility of defining how much anti-proliferative and/or pro-apoptotic effect the treatment has.

To test the robustness of our conclusions across drug combinations with different manifestation of effects, we ran simulations of cases where drug effect was exclusively anti-proliferative (by setting $PP_c = 1$, $a_c = 0$ in equations [3] and [4]), or exclusively pro-apoptotic (by setting $PP_c = 0$, $a_c = 1$). **SI Fig. S1** displayed that in both these scenarios (**A**, exclusively anti-proliferative; **B**, exclusively pro-apoptotic), the trends we found in the main simulations were also observed: in a Constant-Dose comparison, T_{RR} and T_{lethal} were prolonged with more synergistic combinations, whereas in a Constant-Efficacy comparison, T_{RR} and T_{lethal} were prolonged with more antagonistic combinations.

SI Text S4. Approximation of T_{RR}, the time until double resistance arises

S4.1. Derivation of the equation for the approximation of T_{RR}

In this derivation, we assumed a model of cancer cells with 4 subpopulations (*SS*, *RS*, *SR*, and *RR*). Without phenotype alterations, the subpopulations would increase or decrease geometrically with growth factors k_{SS}, k_{RS}, k_{SR}, and k_{RR}, where

$$N_{SS}(t+1) = k_{SS} N_{SS}(t), \qquad \text{where } k_{SS} = (1 + {}^{\text{prolif}}k_{SS})(1 - {}^{\text{death}}k_{SS})$$

$$N_{RS}(t+1) = k_{RS} N_{RS}(t), \qquad \text{where } k_{RS} = (1 + {}^{\text{prolif}}k_{RS})(1 - {}^{\text{death}}k_{RS})$$

$$N_{SR}(t+1) = k_{SR} N_{SR}(t), \qquad \text{where } k_{SR} = (1 + {}^{\text{prolif}}k_{SR})(1 - {}^{\text{death}}k_{SR})$$

$$N_{RR}(t+1) = k_{RR} N_{RR}(t), \qquad \text{where } k_{RR} = (1 + {}^{\text{prolif}}k_{RR})(1 - {}^{\text{death}}k_{RR}).$$

We considered cases where the combination therapy would destroy a tumour of *SS* cells (if they did not alter into another resistance state), but a tumour of *RR* cells would grow, meaning that $k_{SS} < 1$ and $k_{SS} > 1$. It was also assumed that k_{SS} would be less than k_{RS} and k_{SR}, and that k_{RS} and k_{SR} would be less than k_{RR}.

Average alteration rates out of a subpopulation were proportional to the subpopulation's size with coefficients μ_1 and μ_2, conferring resistance to drug 1 and drug 2 respectively. In the stochastic simulations, proliferation, death, and cellular alterations were each estimated by a Poisson random number. Use the symbol $M_{i \to j}$ to denote the number of i cells that transform into j cells. Let $M_{SS \to RS}(t)$ be a Poisson random number with mean

$\mu_1 N_{SS}(t)$, let $M_{SS\to SR}(t)$ be Poisson with mean $\mu_2 N_{SS}(t)$, let $M_{RS\to RR}(t)$ be Poisson with mean $\mu_2 N_{RS}(t)$, and let $M_{SR\to RR}(t)$ be Poisson with mean $\mu_1 N_{SR}(t)$. We neglected reverse transitions that restored sensitivity, such as *SR* → *SS*.

The growth dynamics thus occurred in discrete generations following the process of

$$N_{SS}(t+1) = \mathrm{Po}\big(k_{SS}N_{SS}(t)\big) - M_{SS\to RS}(t) - M_{SS\to SR}(t)$$
$$N_{RS}(t+1) = \mathrm{Po}\big(k_{RS}N_{RS}(t)\big) + M_{SS\to RS}(t) - M_{RS\to RR}(t)$$
$$N_{SR}(t+1) = \mathrm{Po}\big(k_{SR}N_{SR}(t)\big) + M_{SS\to SR}(t) - M_{SR\to RR}(t)$$
$$N_{RR}(t+1) = \mathrm{Po}\big(k_{RR}N_{RR}(t)\big) + M_{RS\to RR}(t) + M_{SR\to RR}(t). \qquad \text{[S10]}$$

Because model [S10] disregarded reverse phenotype alterations, and because we assumed $k_{RR} > 1$, $N_{RR}(t)$ would grow exponentially as soon as *RR* cells emerge. Thus, the primary performance measure of how successfully we suppress the evolution of cancer resistance is the time until *RR* cells first arise from singly-resistant cells. In other words, if we assume that $N_{RR}(0) = 0$, we look to find how many generations there would be before $N_{RR}(t) > 0$.

The number of *RR* cells can only be changed from zero by an alteration event from the *RS* or *SR* cells. During generation t, the total number of *RS* and *SR* cells is $N_{RS}(t) + N_{SR}(t)$. Because the sum of independent Poisson random numbers is also a Poisson number, the total number of cells that transform into *RR* cells is then Poisson with mean $\mu_1 N_{SR}(t) + \mu_2 N_{RS}(t)$. According to the Poisson distribution formula, the probability that 0 cells become *RR* in generation t+1 is

$$e^{-\mu_1 N_{SR}(t) - \mu_2 N_{RS}(t)},$$

where $N_{SR}(t)$ and $N_{RS}(t)$ are random. In terms of conditional probability, this is expressed as

$$\mathrm{P}[N_{RR}(t+1) = 0 \mid N_{RR}(t) = 0,\ N_{SR}(t) = n_{SR},\ N_{RS}(t) = n_{RS}] = e^{-\mu_1 n_{SR} - \mu_2 n_{RS}}. \qquad \text{[S11]}$$

Therefore, we aimed to find a deterministic approximation to the dynamics of $N_{SR}(t)$ and $N_{RS}(t)$, to get information about T_{RR} from formula [S11]. To this end, we made two simplifications to model [S10]. First, we replaced all terms in equation [S10], which are Poisson random numbers, by their respective mean values (e.g., replace $M_{RS\to RR}(t)$ by $\mu_2 n_{RS}(t)$, $\mathrm{Po}\big(k_{SS}N_{SS}(t)\big)$ by $k_{SS}n_{SS}(t)$, etc.). Second, we neglected negative alteration terms (e.g., $-M_{SR\to RR}(t)$, $-M_{SS\to RS}(t)$, etc.), meaning that the reduction of subpopulation size caused by cells transforming into another state – which was small compared to the subpopulation size – was assumed to be zero. The deterministic approximation of [S10] then becomes

$$n_{SS}(t+1) = k_{SS}n_{SS}(t)$$
$$n_{RS}(t+1) = k_{RS}n_{RS}(t) + \mu_1 n_{SS}(t)$$
$$n_{SR}(t+1) = k_{SR}n_{SR}(t) + \mu_2 n_{SS}(t), \qquad \text{[S12]}$$

Equations [S12] can be solved

$$n_{SS}(t) = (k_{SS})^t\, n_{SS}(0)$$
$$n_{RS}(t) = \frac{\mu_1}{k_{RS}-k_{SS}}\big((k_{RS})^t - (k_{SS})^t\big)\, n_{SS}(0) + (k_{RS})^t\, n_{RS}(0)$$

$$n_{SR}(t) = \frac{\mu_2}{k_{SR}-k_{SS}}((k_{SR})^t - (k_{SS})^t)\, n_{SS}(0) \; + \; (k_{SR})^t\, n_{SR}(0). \qquad \text{[S13]}$$

We can use formula [S13] with formula [S11] to obtain information about T_{RR}. The probability that *RR* cells have not emerged at time t (or, the probability that alteration events have yet produced an *RR* cell) is given by

$$\begin{aligned} \mathrm{P}(T_{RR} > t) \; &= \; \mathrm{P}(N_{RR}(t) = 0) \\ &= \; \mathrm{P}(N_{RR}(t-1) = 0) \bullet \mathrm{P}[N_{RR}(t) = 0 \mid N_{RR}(t-1) = 0] \\ &= \; \mathrm{P}(T_{RR} > t-1) \bullet \mathrm{P}[N_{RR}(t) = 0 \mid N_{RR}(t-1) = 0]. \qquad \text{[S14]} \end{aligned}$$

Given that $T_{RR} > t-1$, and assuming that the deterministic approximation is valid at least until $t = T_{RR}$, formula [S11] gives

$$\mathrm{P}[N_{RR}(t) = 0 \mid N_{RR}(t-1) = 0] \approx e^{-\mu_1 n_{SR}(t-1) - \mu_2 n_{RS}(t-1)}.$$

Substituting this into formula [S14] and repeating the same argument again and again results in the approximation:

$$\begin{aligned} \mathrm{P}(T_{RR} > t) &\approx e^{-\mu_1 n_{SR}(0) - \mu_2 n_{RS}(0)} \bullet e^{-\mu_1 n_{SR}(1) - \mu_2 n_{RS}(1)} \bullet \ldots \bullet e^{-\mu_1 n_{SR}(t-1) - \mu_2 n_{RS}(t-1)} \\ &= \; \exp[-\mu_1 (n_{SR}(0) + n_{SR}(1) + \ldots + n_{SR}(t-1))] \\ &\quad \bullet \exp[-\mu_2 (n_{RS}(0) + n_{RS}(1) + \ldots + n_{RS}(t-1))]. \qquad \text{[S15]} \end{aligned}$$

Substituting formula [S13] into [S15] and simplifying it using the geometric series formula, we finally obtain

$$\begin{aligned} &\mathrm{P}(T_{RR} > t) \approx \exp\left[\frac{-\mu_1\mu_2}{k_{RS}-k_{SS}}\left(\frac{1-(k_{RS})^t}{1-k_{RS}} - \frac{1-(k_{SS})^t}{1-k_{SS}}\right) n_{SS}(0) - \mu_2 \frac{1-(k_{RS})^{t+1}}{1-k_{RS}} n_{RS}(0)\right] \\ &\bullet \exp\left[\frac{-\mu_1\mu_2}{k_{SR}-k_{SS}}\left(\frac{1-(k_{SR})^t}{1-k_{SR}} - \frac{1-(k_{SS})^t}{1-k_{SS}}\right) n_{SS}(0) - \mu_1 \frac{1-(k_{SR})^{t+1}}{1-k_{SR}} n_{SR}(0)\right]. \qquad \text{[S16]} \end{aligned}$$

This formula shows how the success of combination therapies depends on the rates k_{SS}, k_{RS}, and k_{SR}, and the initial conditions $n_{SS}(0)$, $n_{SR}(0)$, and $n_{RS}(0)$.

The above probability is simply the product of the independent probabilities for the *RS* → *RR* and *SR* → *RR* alterations. With $\mathrm{P}(T_{RR} > t)$ one can compute $\mathrm{P}(T_{RR} = t)$ and mean(T_{RR}) using the following formulas:

$$\begin{aligned} \mathrm{P}(T_{RR} = t) \; &= \; \mathrm{P}(T_{RR} > t-1) - \mathrm{P}(T_{RR} > t) \\ \mathrm{mean}(T_{RR}) \; &= \; \sum_{t=0}^{\infty} t\, \mathrm{P}(T_{RR} = t) = \; \sum_{t=0}^{\infty} \mathrm{P}(T_{RR} > t). \end{aligned}$$

If the combination drugs are delivered at the same effective dose, if the *RS* and *SR* cells were assumed to exist at the same amount, the alteration processes for the *RS* and *SR* subpopulations can be lumped together into one subpopulation *RS* + *SR*, where $k_{RS} = k_{SR} = k_{RS+SR}$. Substituting this and $\mu_1 = \mu_2 = \mu$, formula [S16] can then be simplified to

$$\mathrm{P}(T_{RR} > t) \approx \exp\left[-r\left(\frac{1-(k_{RS+SR})^t}{1-k_{RS+SR}} - \frac{1-(k_{SS})^t}{1-k_{SS}}\right)\right] \bullet \exp\left[-\mu \frac{1-(k_{RS+SR})^{t+1}}{1-k_{RS+SR}} n_{RS+SR}(0)\right]$$

$$\text{where} \qquad r = \frac{2\mu^2}{k_{RS+SR} - k_{SS}}\, n_{SS}(0). \qquad \text{[S17]}$$

It is convenient to investigate cases where $n_{RS+SR}(0) = 0$, because one obtains less complicated formulas. In case $n_{RS+SR}(0) = 0$,

$$\mathrm{P}(T_{RR} = t) \;=\; \mathrm{P}(T_{RR} > t-1) - \mathrm{P}(T_{RR} > t)$$

$$= \left[-r\left(\frac{1-(k_{RS+SR})^{t-1}}{1-k_{RS+SR}} - \frac{1-(k_{SS})^{t-1}}{1-k_{SS}}\right)\right]\left(1 - e^{-r\,((k_{RS+SR})^{t-1}-(k_{SS})^{t-1})}\right). \qquad \text{[S18]}$$

In case $k_{RS} = k_{SR} = k_{RS+SR} < 1$, there is a positive probability that the tumor population is eradicated, that is, $\mathrm{P}(T_{RR} = \infty)$. For example, in case $n_{RS+SR}(0) = 0$,

$$\mathrm{P}(T_{RR} = \infty) \;\approx\; \exp[-n_{SS}(0)\ \mathrm{C}\ \mu_1\mu_2]$$

$$\text{where C} = \frac{1}{1-k_{SS}}\left(\frac{1}{1-k_{RS}} + \frac{1}{1-k_{SR}}\right). \qquad \text{[S19]}$$

S4.2. Agreement between analytical approximation and stochastic simulation

The approximation model in the preceding section treats the large subpopulations deterministically, along the lines of Tomasetti and Levy (15). To verify that the approximations and assumptions in the analytical model of T_{RR} in equation [S18] can mirror the full stochastic simulation, we tested the agreement between the analytical approximation and the stochastic simulation. **Fig. 3** shows the histograms of T_{RR} generated by the stochastic simulation model using the parameters used in **Fig. 2** (Monte Carlo, n = 10,000), compared to the probability distribution curves of T_{RR} generated by the approximation model. For each scenario, the probability distribution curve from the approximation model closely resembles the histogram generated from the stochastic model, and for all the cases tested, the mean T_{RR} estimated by the approximation deviates 0.25% on average from the mean T_{RR} of the stochastic model.

S4.3. Comparisons to other models

As illustrated in section **S4.1**, the formula for calculating T_{RR} can be used to calculate the probability of eradication, because $T_{RR} = \infty$ implies treatment success where fully resistant cells never arise and escape therapy. Methods for calculating the probability of tumor eradication have been developed for example by Michor *et al*. (16) and Bozic *et al*. (17). Michor *et al*. (16) used a continuous time multi-type branching process to calculate the probability of tumour escaping therapy where resistance is acquired in two steps, meaning that two mutations are required to develop full resistance towards a treatment. Michor (16)'s formula for the probability of treatment success for a cancer population with size N is given by

$$\mathrm{P} = \exp(-NCu_1u_2z),$$

where u_1 and u_2 are the rates of acquiring the first and second alterations, respectively; the parameter z signifies the probability that fully resistant cells are formed and escape therapy; and C is the risk coefficient, which is a function of the basic reproductive ratios and the fitnesses of each sub-clone. The formalisms of Michor (16)'s formula is rather comparable to formula [S19] from our model, although Michor (16)'s formula was derived from a much more sophisticated model. The differences lie in the fact that our model assumed no fitness cost from developing partial or full resistance, no direct transformation from fully sensitive (or wild-type) to fully resistant, and no possibility that fully resistant cells could die. Formula [S19] is also similar to the corresponding formula derived by Bozic *et al*. (17), which was obtained from a solution of a multi-type branching process to simulate the evolution of resistance in a solid tumor treated with dual combination therapy. Bozic (17)'s model took into account the possibility of obtaining resistance towards a drug through multiple pathways. Additionally,

formulas very similar to formula [S16] have also been derived in the literature in a similar way to what we have done, for instance by Bozic *et al*. (17) and Tomasetti and Levy (15). Nonetheless, the utility of formulas like formula [S16] in these papers was not for finding the probability distribution of when fully resistant cells first appear, but rather for calculating the number of resistant cells at the time of detection. In summary, several studies of cancer evolution have chosen similar ways to simplify the biological complexity, resulting in similar mathematical formalisms. We use these previously-studied formalisms, and apply them to address the unique questions of our study.

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