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Supplementary information

A theoretical analysis of tumour containment

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A THEORETICAL ANALYSIS OF TUMOUR CONTAINMENT: SUPPLEMENTARY INFORMATION

Contents

This supplementary material is organized as follows. Section 1 recalls a number of previous models related to our work. Section 2 studies Model 1 from the main text. For this general model, we qualitatively compare reference treatments and an arbitrary treatment, in terms of sensitive and resistant population sizes and the time until tumour size exceeds an arbitrary threshold. This time is shown to be maximized by an idealized version of containment at this threshold. Different choices of threshold lead to results on time to progression, time to treatment failure, or survival time. The proofs are based on variants of Gronwall's inequalities.

Section 3 considers various density- and frequency-dependent models. Explicit formulas are derived for the time at which tumour size exceeds an arbitrary threshold under various treatments. This result is then applied to Gompertzian growth (Model 3 in the main text). Building on these findings, Section 4 compares reference treatments qualitatively and quantitatively. Section 5 studies the impact of resistant

costs on the best possible outcome, and on the clinical benefits of containment. This section provides an approximate formula for time to treatment failure under containment or ideal containment in the presence of resistance costs.

Section 6 discusses some potential issues with the containment treatment if some of our assumptions are not satisfied. Finally, Section 7 discusses possible protocols to implement containment at a target size.

1. Partial survey of related works

We recall here some of the models most related to our work.

1.1. Lotka-Volterra and density-dependent models.

Zhang *et al.* (2017) [1] consider a Lotka-Volterra model with three types of tumour cells (two sensitive and one resistant to treatment), and carrying capacities that depend on whether treatment is on or off. Through simulations, they compare an intermittent containment treatment (maintaining the tumour between its initial size N_0 and $N_0/2$) to no treatment, maximal tolerated dose (MTD) and a form of metronomic therapy with an induction period. Cunningham *et al.* (2018) [2] extend this model to allow for intermediate dose treatments. This extended model could be simplified by grouping the two types of sensitive cells, leading to a two-type Lotka-Volterra model of the form:

$$\dot{s} = \rho_s s \left(1 - \frac{(\alpha_1 s + \alpha_2 r)}{K_s}\right) \tag{1}$$

$$\dot{r} = \rho_r r \left(1 - \frac{(r + \beta s)}{K_r}\right) \tag{2}$$

with K_r independent of treatment, and K_s linearly varying as a function of the dose between $K_{max} = K_r$ and a much lower value $K_{min} = K_r/100$. The competition coefficient β is assumed less than 1, so the tumour cannot be stabilized at a size smaller than K_r.

Carrère (2017) [3] studies a similar two-type Lotka-Volterra model but with a higher impact of sensitive cells on resistant cells, and a different treatment-induced death term. She discusses how to optimally control the tumour for various objective functions. Carrère and Zidani (2019) [4] consider an extension of Carrère's model, in particular adding uncertainties on some parameters, and use optimal control to study how to bring and maintain tumour size below a certain threshold. Pouchol *et al.* (2018) [5] uses optimal control techniques to study a model with infinitely many types and two types of drug: cytostatic and cytotoxic.

A precursor of such optimal control approaches for models with intratumour competition is Martin *et al.* (1992) [6]. They consider, with some approximations, a general density-dependent two-type model with mutations, and study how to optimally tune tumour size in order to maximize survival time. Applications are made to exponential, logistic, and Gompertzian growth. The analysis is extended to combination chemotherapies in [7]. Building on this seminal work, Hansen *et al.* (2017) [8] focus on the logistic and Gompertzian case, and compare two treatments: a form of ideal containment, and elimination of sensitive cells, in a context broader than cancer. We borrowed the term containment from them.[1] In a follow-up paper, Hansen *et al.* (2020) [9] compare experimentally and theoretically the growth of a partially resistant strain of *E. coli*, with or without adding competing sensitive bacteria. Hansen and Read (2020) [10] consider a stochastic birth-death model allowing for a positive probability of cure even when resistant cells are initially present. They discuss the trade-off between a higher probability of cure and a shorter time to progression in case of failed cure (see also [11]).

Monro and Gaffney (2009) [11], in a paper published a few months before the first article on adaptive therapy (Gatenby *et al.* 2009 [12]), study constant dose treatments in a two-type model with Gompertzian growth and no resistance cost. This is the model we use for simulations (except that we neglect mutations). They show that reducing the dose or delaying treatment may increase survival time.[2]

[1] Containment in Hansen *et al.* (2017) [8] is as our ideal containment treatment except that they also allow tumour size to *increase* instantly from its initial size to a possibly higher size, at which the tumour is then maintained. We only allow for an instantaneous *decrease* of tumour size.

[2] Gatenby *et al.* (2009) [12] also contains a model, but substantially different and more involved that the models we use, and we will not discuss it here.

1.2. **Frequency-dependent models.** Another line of models assumes frequency-dependent competition. For instance, Silva *et al.* (2012) [13] considers a discrete-time, difference equation model, which in a continuous-time, differential equation framework would take the form

$$\begin{aligned} \dot{s}/s &= \rho_s \frac{s}{s+r} - \lambda_s C \\ \dot{r}/r &= \rho_r \frac{r}{s+r} - \lambda_r C \end{aligned}$$

where C is a measure of treatment intensity, λ_s and λ_r represent sensitivity to treatment of sensitive and resistant cells, and the growth-rate parameters ρ_r and ρ_s vary as a function of some auxiliary treatment. In this model, as the frequency of resistant cells $x_r = \frac{r}{s+r}$ approaches zero, the relative fitness of resistant cells approaches zero, allowing for a huge, unbounded advantage of containment over MTD. Bacevic *et al.* (2017) [14] considers a similar frequency-dependent model, but where the resistant population growth rate is proportional to a function $f(x_r)$ with f bounded away from zero. The relative gain of containment compared to MTD (that is, the ratio of the time it takes under these treatments for the tumour to reach a given size) is then bounded by $1/f(0)$. Bacevic *et al.* also studies models mixing frequency dependence and Gompertzian, density-dependent growth, and models where the carrying capacity is dynamic and reduced by treatment, in the spirit of Hahnfeldt *et al.* (1999) [15]. In the latter case, resistant cells are, indirectly, still partially sensitive to treatment, and our analysis does not apply.

Some features of these models are summed up in Supplementary Table 1. A number of other interesting approaches are less connected to our work. For instance, Gallaher *et al.* (2018) [16] studies a spatial dose modulation model through simulations. West *et al.* (2018) [17] considers game theoretical models with sensitive and resistant cells, but also normal cells as a third type. Ledzewicz and Schättler (2019) [18] review optimal control models for heterogeneous tumours with more or less resistant cells, but the objective functions are different and the models studied do not take into account competition between cell types. This mini-review is far from exhaustive and we apologize for all the fine works that are not mentioned above.

The main differences between our work and the bulk of the adaptive therapy literature are the generality of our results, and in particular the fact that we provide analytical results that apply to many different models instead of relying on simulations of a particular model. The main differences with the bulk of the optimal control literature (with some exceptions, e.g., Martin *et al.* (1992) [6, 7], Carrère and Zidani (2019) [4]) are the focus on intra-tumour competition, our objective function (maximizing the time at which tumour exceeds a given size), and the fact that our proofs rely on basic variants of Gronwall's lemma rather than the heavier optimal control machinery.

1.3. **Comparison of our work and preceding studies.** We provide here a detailed discussion of three particular papers upon which our work builds.

Carrère and Zidani (2020) [4]. This article considers an extension of Carrère's Lotka-Voltera model [3] that accounts for uncertainties surrounding drug effectiveness and the effect of competition (parameter β in Eq. (2)). The authors use optimal control techniques to study how to maintain tumour size below a certain threshold indefinitely, or, when this is not possible, how to minimize the time after which tumour size is permanently under this threshold, for any realization of the uncertainties. There is no limit on the instantaneous drug dose but a global health indicator that evolves as a function of the drug dose must remain above a given level. Although the idea of maintaining tumour size below a certain threshold is reminiscent of our maximal tolerable size, our tools and goals are substantially different. Carrère and Zidani perform a mathematically-involved analysis of a specific, complicated model (Lotka-Volterra with a log-kill rate and uncertainties), whereas we aim at deriving simple, accessible conclusions from more general models. Carrère and Zidani use a Hamilton-Jacobi approach to characterize the value function of the optimal control problem and then numerical methods to reconstruct optimal strategies from the value function. We instead rely on comparison principles, which are elementary differential equations tools. Moreover, Carrère and Zidani have in mind to study in-vitro tumour growth and emphasize cases where tumour size may be permanently maintained below some threshold. They also allow tumour size to first grow to a large size if this is the quickest way to eventually bring it back under the desired threshold for ever. Together with large competition coefficients, this permits a strategy that consists in first letting the tumour grow until the fitter sensitive cells eliminate most resistant cells and then applying large drug doses, as in [5], to quickly go back under the desired threshold. In contrast, we have in mind treatment of incurable

SUPPLEMENTARY TABLE 1. **Features of adaptive therapy and containment models.** In the treatment column, "containment" refers to various implementations of the general containment idea.

Study	**Types**	**Treatment**	**Competition type**	**Methods**	**Other features**
Martin *et al.* (1992) [6]	2	any	density-dependent; Gompertzian; Lotka-Volterra	optimal control	no resistance cost; mutations
Monro & Gaffney (2009) [11]	2	constant dose; delaying treatment	Gompertzian	simulations	no resistance cost; mutations
Gatenby *et al.* (2009) [12]	various	containment; metronomic; MTD	unconventional	analytical results; simulations	resistance cost; microenvironmental feedback
Silva *et al.* (2012) [13]	2	containment; MTD	specific frequency-dependent	simulations	bolus doses; manipulation of resistance cost
Hansen *et al.* (2017) [8]	2	containment; ideal MTD	Lotka-Volterra; Gompertzian	analytical results	resistance cost or not; mutations
Carrère (2017) [3]	2	any	Lotka-Volterra	optimal control	resistance cost
Bacevic *et al.* (2017) [14]	2	containment; MTD	specific frequency & density-dependent	simulations; analytical results	bolus doses; resistance cost; partial resistance
Zhang *et al.* (2017) [1]	3	containment; metronomic; MTD	Lotka-Volterra	simulations	clinical data
Pouchol *et al.* (2018) [5]	any	any	Lotka-Volterra	optimal control	cytostatic and cytotoxic drugs
Cunningham *et al.* (2018) [2]	3	any	Lotka-Volterra	numerical optimal control	fixed total dose
Hansen *et al.* (2020) [9]	2	containment; ideal MTD	Lotka-Volterra	simulations	corresponding *in vitro* experiments
Hansen and Read (2020) [10]	2	containment; ideal MTD	Lotka-Volterra	simulations; analytical results	possibility of cure
Carrère and Zidani (2019) [4]	2	any	Lotka-Volterra	optimal control	tolerable tumour size
Current study	2	any	general frequency- & density-dependent	simulations; analytical results; comparison principle	resistance cost or not; tolerable tumour size

human tumours. Hence we emphasize cases where tumour size cannot be permanently maintained at a tolerable size, and we assume that treatment fails the first time the tumour burden becomes intolerable.

Martin et al. *(1992) [6].* This pioneering work considers a variant of the general model referred to as Model 2 in our main text. Our aims and tools are however importantly different. Whereas we aim to derive general conclusions from simple models, neglecting mutations after treatment initiation, Martin *et al.* appear to assume that containment is optimal in such models and then focus on analyzing the trade-off that arises in the presence of mutations from sensitive to resistant cells (see the corresponding section in our main text) using optimal control techniques (more precisely, necessary optimality conditions derived from Pontryagin's maximum principle). In spite of simplifying assumptions, mutation terms complicate their analysis, and the optimality conditions obtained are difficult to analyse in general. The authors thus eventually focus on three specific models: exponential growth, logistic growth (Lotka-Volterra), and Gompertzian growth. They conclude that a version of ideal containment is slightly worse than ideal MTD for exponential growth of the resistant population; similar for logistic growth; and much better for Gompertzian growth.

Hansen et al. *(2017) [8].* Following Martin *et al.* [6], this study examines a trade-off that arises if mutations from sensitive cells to resistant cells are taken into account. The trade-off is between maximizing competition (to decrease the growth-rate of existing resistant cells) and minimizing the number of sensitive cells (to minimize mutations from sensitive to resistant cells). The authors focus on specific models: logistic growth (a Lotka-Volterra model) and, to a lesser extent, Gompertzian growth. They also study only specific treatments: ideal containment and ideal MTD. Their question is whether ideal containment is better than ideal MTD, whereas we go further by showing that, in simple situations (without mutations), ideal containment is better than *any* other treatment. Moreover, in spite of focusing on specific models, Hansen *et al.* do not study the magnitude of clinical gains. Although they consider conditions under which containment improves over elimination of sensitive cells, it is unclear whether these conditions are likely to be met. As we point out (see this Supplementary material, Section 4.1.1), in the absence of mutations, and at least when the maximal tolerable size is far from the carrying capacity, logistic growth models lead

to very small gains of containment – much smaller than under Gompertzian growth models. Thus, taking into account mutations after treatment initiation (or other factors we neglect) is much more likely to make MTD preferable to containment in a logistic growth model than in a Gompertzian growth model. This can be seen in the conditions derived in Hansen *et al.* but is not discussed. The focus on logistic growth and the qualitative approach of this study may thus suggests that mutations from sensitive to resistant cells are a much more serious problem than we believe them to be (at least for the kind of mutations envisioned by Hansen *et al.*).

2. Qualitative comparison of treatments under a general model

2.1. **Model, treatments, notation.** We study here Model 1 from the main text. We first recall it, and clarify assumptions that are only informally described in the main text. The model reads

$$\left\{ \begin{array}{rcll} \dot{S}(t) & = & S(t)g_s(S(t),R(t),C(t)) & ; \quad S(0)=S_0\geq 0 \\ \dot{R}(t) & = & R(t)g_r(S(t),R(t)) & ; \quad R(0)=R_0>0 \end{array} \right. \tag{3}$$

where $S(t)$, $R(t)$ are the number of sensitive and fully resistant cells, respectively, and $C(t)$ is the drug dose or more generally the treatment level at time t.[3] The total tumour population size is $N(t)=S(t)+R(t)$, with initial value $N_0=S_0+R_0$.

Model assumptions. The key assumptions are that resistant cells are fully resistant and that g_r is non-increasing in S. We also assume that g_s is non-increasing in R and in C, and that as long as the patient is alive ($N<N_{crit}$), the size of an untreated or fully resistant tumour strictly increases.[4].

Finally, we make technical assumptions: functions g_r and g_s are continuously differentiable on the relevant domain ($N>0$, $C\geq 0$); solutions are defined for all $t\geq 0$; and function C is piecewise continuous on $[0,+\infty)$ (this simplifies proofs but our main results also hold under weaker assumptions, e.g., allowing for discontinuities in the sensitive population size).

Objective. Treatment is said to fail when tumour size exceeds a *maximum tolerable size* N_{tol}.[5] This size need not be known in advance but could instead be identified during treatment. Our treatment objective is then to maximize *time to treatment failure*: the largest time τ such that $N(t)\leq N_{tol}$ on $[0,\tau]$. To simplify the exposition, we assume by default that the maximum tolerable size is no smaller than the initial size: $N_{tol}\geq N_0$ (the case $N_{tol}<N_0$ is discussed in Section 2.5). We make no other assumption about N_{tol}. In particular, taking $N_{tol}=N_0$ leads to results on *time to progression*, and setting N_{tol} to be the lethal tumour burden gives results on *survival time*.

Treatments. We consider the following treatments (with corresponding subscript in parenthesis):

- No treatment (noTreat): $C(t)=0$ throughout.
- MTD (MTD): $C(t)=C_{max}$ throughout.
- delayed MTD (del-MTD): does not treat until $N=N_{tol}$, then $C(t)=C_{max}$ for ever.
- containment at N_{tol} (Cont): does not treat until $N=N_{tol}$, then stabilizes tumour size at N_{tol} as long as possible with a dose $C(t)\leq C_{max}$, then treats at C_{max} once $N>N_{tol}$ (unless tumour size goes back to N_{tol}, in which case tumour is again stabilized at size N_{tol} as long as possible, and so on). See Figs. 1d, 1e.[6]
- intermittent containment between N_{tol} and $N_{min}<N_{tol}$ (Int): does not treat until $N=N_{tol}$, then treats at C_{max} until $N=N_{min}$, and iterates as long as possible, as in [1] (Fig. 1g).[7]

We also consider idealized versions, which may be thought of as relaxing the constraint $C(t)\leq C_{max}$:

[3]The difference between drug dose and treatment level is two-fold: first, the model applies to treatments such as radiotherapy that are not naturally described as drugs; second, we neglect pharmacodynamics and pharmacokinetics. As already pointed out by Norton and Simon (1977) [19], "depending on the type of therapy used and such factors as route of administration or concurrent medication, [treatment level] may be related to the dose administered in a complicated fashion".

[4]The assumption that g_s is non-increasing in R is typically not satisfied in models with a Norton-Simon kill-rate, and in particular in the Gompertzian model that we use for simulations (Model 3 in the main text). Nevertheless, our key results hold for this model due to alternative arguments. This is further discussed in Section 2.4

[5]If tumour size exceeds N_{tol} at some point but later becomes lower than N_{tol} again, treatment is said to fail *the first time* that tumour exceeds N_{tol}.

[6]Though this is not what we expect in practice, our assumptions do not exclude the possibility that the resistant population increases initially very quickly in absolute terms, but then much more slowly, due to some peculiar form of density dependence. It could then be that tumour grows above N_{tol} at some point, but then goes back to N_{tol} as the growth of the resistant population slows down.

[7]Our results actually hold for any other way of maintaining tumour size between N_{min} and N_{max}. Note also that it could be that after progressing beyond N_{max}, tumour size goes back to N_{max}. In this case, we assume that intermittent containment again tries to contain the tumour between N_{min} and N_{max}.

- ideal MTD (idMTD): instantly eliminates sensitive cells ($S(t) = 0$ for all $t > 0$.)[8]
- delayed ideal MTD (del-idMTD): does not treat until $N = N_{tol}$, then instantly eliminates sensitive cells.
- ideal containment at N_{tol} (idCont): does not treat until $N = N_{tol}$, then stabilizes tumour size at N_{tol} as long as some sensitive cells remain.
- ideal intermittent containment (idInt): as intermittent containment, except that upon reaching N_{tol}, tumour size is instantly reduced to N_{min} (or to R, if $R > N_{min}$).

We compare these treatments between themselves and to an arbitrary alternative treatment, that we only assume regular enough to avoid technical issues. To simplify some statements, all treatments are assumed to treat at C_{max} after treatment failure.

Notation. Times to treatment failure are denoted by $t_{noTreat}$, t_{MTD}, $t_{del-MTD}$, t_{Cont} and t_{Int}, respectively, for non-idealized treatments; t_{idMTD}, $t_{del-idMTD}$, t_{idCont} and t_{idInt}, for idealized treatments; and t_{alt} for the alternative treatment. Similar subscripts are used to refer to treatment level, and to the sensitive, resistant, and total tumour sizes under these treatments (e.g., $C_{alt}(t)$, $S_{alt}(t)$, $R_{alt}(t)$, and $N_{alt}(t)$ for the alternative treatment).

2.2. **Informal description of results.** Intuitively, if resistant cells are fully resistant, then the only way to fight them is via competition with sensitive cells. Our aim is to turn this intuition into rigorous mathematical results allowing to compare the effect of various treatments in Model 1. The key result (Proposition 1) is that, in our model, more sensitive cells lead to fewer resistant cells, and this implication can be formally proven. Similarly, a larger tumour burden – or a lower dose – leads to fewer resistant cells (and more sensitive cells). It follows that eliminating sensitive cells maximizes the resistant population, and minimizes time to treatment failure among treatments that fully eliminate sensitive cells before failing (Proposition 2). Conversely, by maintaining tumour size as high as possible before failing, ideal containment maximises time to treatment failure (Proposition 3).

Under the constraint $C(t) \leq C_{max}$, containment does not exactly maximize time to treatment failure, because switching to MTD shortly before treatment failure would result in a small delay. However, any treatment that switches to MTD after failing would lead to a larger resistant population at all times, hence typically a larger long-term tumour burden (Proposition 4). In particular, though containment fails before its idealized version, the constraint $C(t) \leq C_{max}$ leads to a lower resistant population than in ideal containment.

A yet more realistic protocol is intermittent containment, which aims at maintaining tumour burden between two thresholds [1]. Consistent with intuition, intermittent containment is intermediate between containment at the lower threshold and containment at the higher threshold in terms of sizes of resistant and sensitive populations, and in terms of time to treatment failure in the idealized case (Propositions 5 and 6). Similarly, delaying treatment before treating at MTD is intermediate between MTD and intermittent containment (Proposition 7, which also sums up the comparison between all reference treatments).

Finally, Section 2.5 considers the case in which the initial tumour burden is above the tolerable threshold ($N_0 > N_{tol}$). The ideal containment strategy then first reduces tumour size to the maximum tolerable size (if $R_0 < N_{tol}$), and then stabilizes the size of the tumour as long as it is not fully resistant. This strategy is shown to maximize the time for which tumour size is no larger than the maximal tolerable size (Proposition 8).

2.3. **Formal results.** We begin with a key result, proved in Section 2.6. It shows that keeping more sensitive cells, a larger tumour burden, or treating less, leads to fewer resistant cells.

Proposition 1. *(key result) Let $0 \leq t_0 \leq t_1$. Consider two piecewise continuous treatment level functions C_1, C_2, with associated tumour subpopulation sizes (S_1, R_1) and (S_2, R_2), satisfying (3). Let $N_i = S_i + R_i$, $i = 1, 2$, denote total tumour size. Assume that at time t_0, the resistant population is no-larger, and the sensitive population no-smaller under the first treatment than under the second: i) $R_1(t_0) \leq R_2(t_0)$; and ii) $S_1(t_0) \geq S_2(t_0)$. Assume moreover that between t_0 and t_1, at least one of the following conditions holds: under treatment 1,*

iiia) the sensitive population is larger: $\forall t \in [t_0, t_1], S_1(t) \geq S_2(t)$;
or iiib) total tumour size is larger: $\forall t \in [t_0, t_1], N_1(t) \geq N_2(t)$;

[8]This treatment is called "aggressive treatment" or "elimination of sensitive cells" by Hansen *et al.* (2017, 2020) [8, 9]. We may think of this as a hypothetical infinite-dose treatment, or more precisely a treatment with an infinite kill-rate. Alternatively, in an experimental setting, ideal MTD may correspond to the initial condition of a fully resistant population of cells (cf. Hansen *et al.*, 2020 [9]).

or iiic) treatment level is lower: $\forall t \in [t_0, t_1], C_1(t) \leq C_2(t)$.
Then, for all t *in* $[t_0, t_1]$, $R_1(t) \leq R_2(t)$ *and* $S_1(t) \geq S_2(t)$.

It follows that ideal MTD (or MTD, under the constraint $C(t) \leq C_{max}$) maximizes the resistant population size (see also [7], [8]). Ideal MTD also minimizes time to treatment failure among all treatments that eliminate sensitive cells before failing.[9]

Proposition 2. *(comparison with no treatment, MTD and ideal MTD)*

a) *For all times* $t \geq 0$, $R_{noTreat}(t) \leq R_{alt}(t) \leq R_{MTD}(t) \leq R_{idMTD}(t)$ *and* $S_{idMTD}(t) \leq S_{MTD}(t) \leq S_{alt}(t) \leq S_{noTreat}(t)$, *where the comparisons between MTD and the alternative treatment are only valid if* $C_{alt}(t) \leq C_{max}$ *for all* $t \geq 0$.
b) *If* $S_{alt}(t_{alt}) = 0$, *then* $t_{alt} \geq t_{idMTD}$

Proof. a) Immediate by Proposition 1; b) if $S(t_{alt}) = 0$, then $N_{tol} = N_{alt}(t_{alt}) = R_{alt}(t_{alt}) \leq R_{idMTD}(t_{alt})$ by a), hence $t_{idMTD} \leq t_{alt}$. □

Proposition 1 also implies that ideal containment leads to a smaller resistant population than under any alternative treatment that has not yet failed, and maximizes time to treatment failure.

Proposition 3. *(comparison with ideal containment)*

a) *For all* t *in* $[0, t_{alt}]$, $R_{idCont}(t) \leq R_{alt}(t)$ *and* $S_{idCont}(t) \geq S_{alt}(t)$.
b) $t_{idCont} \geq t_{alt}$

Proof. a) Let t_0 be the first time such that $N_{idCont}(t_0) = N_{tol}$. On $[0, t_0]$, ideal containment does not treat, so these inequalities hold by Proposition 2. If $t_0 \leq t_{alt}$, then on $[t_0, t_{alt}]$, $N_{idCont}(t) \geq N_{alt}(t)$. Since the inequalities hold for $t = t_0$, it follows from Proposition 1 that they still hold on $[t_0, t_{alt}]$.

b) Therefore, $N_{tol} = N_{alt}(t_{alt}) \geq R_{alt}(t_{alt}) \geq R_{idCont}(t_{alt})$, which implies that $t_{idCont} \geq t_{alt}$, since under ideal containment, failure occurs when $R = N_{tol}$. □

Under a maximal instantaneous dose constraint, containment at N_{tol} does not exactly maximize time to treatment failure. Indeed, contrary to what happens with ideal containment, there are still sensitive cells at treatment failure. For this reason, switching to MTD slightly before containment fails would slightly delay treatment failure.[10] However, containment leads to a lower resistant population than any treatment that treats at C_{max} after failing, in particular than ideal containment.

Proposition 4. *(containment) For all* $t \geq 0$, $R_{Cont}(t) \leq R_{alt}(t)$ *and* $S_{Cont}(t) \geq S_{alt}(t)$.

Proof. Let t_0 be the first time such that $N_{idCont}(t_0) = N_{tol}$. On $[0, t_0]$, containment does not treat, so these inequalities hold by Proposition 2. For $t \geq t_0$, $N_{cont}(t) \geq N_{tol}$, so $N_{cont}(t) \geq N_{alt}(t)$ or $C_{alt}(t) \geq C_{cont}(t)$, or both. Therefore, repeated application of Proposition 1 on time intervals where $N_{cont}(t) \geq N_{alt}(t)$ and on time intervals where $C_{alt}(t) \geq C_{cont}(t)$ show that the desired inequalities still hold at all later times. □

We now compare intermittent containment between N_{tol} and $N_{min} < N_{tol}$ to containment at the higher threshold N_{tol} and containment at the lower threshold N_{min}. The latter lets tumour grow to N_{min} (or treats at C_{max} until $N = N_{min}$ if $N_0 > N_{min}$), then stabilizes tumour size at N_{min} as long as possible with a dose $C(t) \leq C_{max}$, and then treats at C_{max} (unless tumour size goes back to N_{min}, in which case containment at N_{min} again tries to stabilize tumour size at N_{min} as long as possible). In the idealized version, tumour size is stabilized at N_{min} as long as some sensitive cells remain (and tumour size is instantly reduced to N_{min} at time 0 if $N_0 > N_{min}$). The subscripts used for containment and ideal containment at N_{min} are ContNmin and idContNmin, respectively.

The next result shows that idealized intermittent containment is, in a precise sense, intermediate between ideal containment at the lower and at the higher level. It is illustrated by Extended Data Fig. 1.

Proposition 5. *(intermittent versus continuous containment: idealized treatments)*

a) *For all* $t \geq 0$, $R_{idCont}(t) \leq R_{idInt}(t) \leq R_{idContNmin}(t)$ *and* $S_{idContNmin}(t) \leq S_{idInt}(t) \leq S_{idCont}(t)$
b) $t_{idContNmin} \leq t_{idInt} \leq t_{idCont}$.

[9]The latter result should be seen as a comparison between idealized treatments. Indeed, under the constraint $C(t) \leq C_{max}$, the sensitive population size would never be exactly 0.

[10]The omitted proof of this result is easy. It simply exploits the fact that, in the short run, increasing treatment decreases both the sensitive population and tumour size. In the long run, this would lead to a quicker development of resistant cells and typically a larger tumour size, but increasing treatment only shortly before t_{Cont} ensures that the short-run effect dominates until t_{Cont}. We assumed here that the sensitive population growth-rate is decreasing in C, and not only non-increasing.

c) *For all* $t \geq t_{idInt}$, $N_{idCont}(t) \leq N_{idInt}(t) \leq N_{idContNmin}(t)$.

Proof. The comparison with ideal containment at N_{tol} (idCont) follows from Proposition 3. Let us compare ideal intermittent containment and ideal containment at N_{min}. Let

$$t^* = \sup\{\tau \geq 0, N_{idContNmin}(t) \leq N_{idInt}(t) \text{ on } [0,\tau]\}$$

and

$$\hat{t} = \sup\{t \geq 0, N_{idContNmin}(t) \leq N_{min}\}$$

and note that $\hat{t} \leq t^*$. For $t \in [0, t^*]$, it follows from Proposition 1 that $R_{idContNmin}(t) \geq R_{idInt}(t)$ and $S_{idContNmin}(t) \leq S_{idInt}(t)$. In particular, this holds at $\hat{t}$. But for $t \geq \hat{t}$, $S_{idContNmin}(t) = 0 \leq S_{idInt}(t)$. Therefore, the above inequalities are still valid at all later times by Proposition 1, and are thus valid for all positive times. In particular, at t_{idInt}, $N_{tol} = R_{idInt} \leq R_{idContNmin}$, hence $t_{idContNmin} \leq t_{idInt}$. Finally, for $t \geq t_{idInt}$, $N_{idInt} = R_{idInt} \leq R_{idContNmin} \leq N_{idContNmin}$. This concludes the proof. □

The next proposition is a partial analog for non-idealized treatments. The proof uses that containment at N_{min} treats at C_{max} when $N > N_{min}$.

Proposition 6. *(intermittent containment: bounded instantaneous dose)*
For all $t \geq 0$, $R_{Cont}(t) \leq R_{Int}(t) \leq R_{ContNmin}(t)$ *and* $S_{ContNmin}(t) \leq S_{Int}(t) \leq S_{Cont}(t)$

Proof. The comparison with containment at N_{tol} follows from Proposition 4. If $N_{min} \geq N_0$, then the comparison with containment at N_{min} is similar to the comparison with ideal containment at N_{min} in Proposition 5, but replacing $S_{idContNmin} \leq S_{idInt}$ by $C_{ContNmin} \geq C_{Int}$ when $N_{ContNmin} > N_{min}$. If $N_{min} < N_0$, then as long as $N_{Contmin} > N_0$, $C_{Contmin} = C_{max} \geq C_{Int}$, hence the result holds by Proposition 1; if at some time $\tilde{t}$, $N_{Contmin} = N_{min}$, the proof that the required inequalities hold also for $t \geq \tilde{t}$ is as in the case $N_0 \geq N_{min}$. □

Contrary to what happens for idealized treatments, time to treatment failure could be larger under intermittent containment than under containment at the upper level. This is because when intermittent containment does not manage to bring back tumour size to N_{min}, it starts treating continuously at C_{max}: by quickly diminishing the sensitive population, this may delay treatment failure, to the cost of a larger resistant population. This is further discussed in Section 4.3 and illustrated in Extended Data Fig. 4, see also Table 1 in the main text.

Our final result compares all reference treatments, including delayed MTD and its idealized version.

Proposition 7. *(comparison between all reference treatments) For all* $t \geq 0$*:*

a) $S_{idMTD}(t) \leq S_{del-idMTD}(t) \leq S_{idInt}(t) \leq S_{idCont}(t) \leq S_{noTreat}(t)$
b) $R_{idMTD}(t) \geq R_{del-idMTD}(t) \geq R_{idInt}(t) \geq R_{idCont}(t) \geq R_{noTreat}(t)$
c) $t_{idMTD} \leq t_{del-idMTD} \leq t_{idInt} \leq t_{idCont}$
d) $S_{MTD}(t) \leq S_{del-MTD}(t) \leq S_{Int}(t) \leq S_{Cont}(t) \leq S_{noTreat}(t)$
e) $R_{MTD}(t) \geq R_{del-MTD}(t) \geq R_{Int}(t) \geq R_{Cont}(t) \geq R_{noTreat}(t)$

Moreover, for all $t \geq t_{idCont}$, $N_{idMTD}(t) \geq N_{del-idMTD}(t) \geq N_{idInt}(t) \geq N_{idCont}(t)$

Proof. a) The first two inequalities are immediate from the definition of these treatments. The inequality $S_{idInt}(t) \leq S_{idCont}(t)$ was proved in Proposition 5. The last inequality is immediate from Proposition 1.

b) Immediate from a) and Proposition 1.

c) Immediate from b), since for idealized treatments, $S = 0$ when treatment fails.

d) The first two inequalities are immediate from the definition of these treatments and Proposition 1 (since $C_{MTD}(t) \geq C_{del-idMTD}(t) \geq C_{Int}(t)$ for all t). The inequality $S_{Int}(t) \leq S_{Cont}(t)$ was proved in Proposition 6. The last inequality is immediate from Proposition 1.

e) Immediate from d) and Proposition 1.

Finally, the last result is due to b) and to the fact that, by c) and definition of reference idealized treatments, for $t \geq t_{idCont}$, $S = 0$ hence $N = R$ for all these treatments. □

2.4. **Models with a Norton-Simon kill-rate.** To derive Proposition 1, the growth-rate $g_s(S, R, C)$ of sensitive cells was assumed non-increasing in R. In general, this assumption does not hold for Model 2 of the main text. More precisely, it holds for models with a log-kill rate, that is, $g(N, C) = g(N) - \lambda C$, with g nonincreasing, but not for Norton-Simon models:

$$\begin{aligned} \dot{S} &= Sg(N)(1 - \lambda C) \\ \dot{R} &= Rg(N) \qquad \text{with } g \text{ decreasing,} \end{aligned}$$

such as the model we use for simulations (Model 3). Indeed, in the absence of treatment, or as long as $\lambda C < 1$, an increase in the resistant population size decreases the growth-rate of sensitive cells, but if $\lambda C > 1$, the opposite happens. This makes sense: an increase in the number of resistant cells might make more sensitive cells quiescent, which may protect them from the drug.[11].

There is no hope to completely rescue Proposition 1. Indeed, for such models, if $S_1(t_0) = S_2(t_0)$, $R_1(t_0) > R_2(t_0)$, and $C_1(t) = C_2(t) > 1/\lambda$ on $[t_0, t_1]$, then $S_1(t) < S_2(t)$ for all $t = t_0 + h$ with $h > 0$ small enough. This contradicts Proposition 1, when the extra-assumption is iiic), i.e., $C_1(t) \leq C_2(t)$.

Nevertheless, the assumption that g_s is decreasing in R is not crucial. The key-reason to impose it was to make sure that not treating maximizes the number of sensitive cells, which is important when considering containment at a larger size than N_0. However, it is not difficult to see that this property always holds in Model 2 (hence in Model 3). Furthermore, the results in Proposition 1 still hold when the extra-assumption is iiia) or iiib). A close examination of the proofs then shows that all results of Section 2.3 on idealized treatments still hold for Model 2. In particular, ideal containment at N_{tol} still maximizes the time it takes for tumour size to exceed N_{tol} (Proposition 3b). Actually, for Model 3 and more general models, it may be shown that almost all of our results on non-idealized treatments still hold as well, but this requires more sophisticated arguments. This will be the topic of a companion paper.

2.5. **The case $N_0 > N_{tol}$.** It could be that at the beginning of treatment, tumour size is already intolerable, that is, $N_0 > N_{tol}$. In that case, maximizing the time at which treatment fails is not an appropriate objective, since, with our definition of treatment failure, treatment fails before beginning. Another possible objective is to maximize the total time spent at tumour sizes below N_{tol}; that is, the quantity

$$\tau = \int_0^{+\infty} \mathbb{1}_{N(t)\leq N_{tol}}\, dt$$

where $\mathbb{1}_{N(t)\leq N_{tol}} = 1$ if $N(t) \leq N_{tol}$ and 0 otherwise.

Containment could be thought of as first treating at MTD until tumour size is tolerable, and then trying to stabilize tumour size at N_{tol} for as long as possible. In the idealized version – our definition of ideal containment when $N_0 > N_{tol}$ – tumour size is instantly reduced from N_0 to N_{tol}, and then stabilized at this size as long as $R(t) \leq N_{tol}$. Our next result is that ideal containment is optimal for the above objective, under the additional assumption that the resistant population may be slowed down by the presence of sensitive cells, but nonetheless keeps increasing. This is equivalent to assuming that any tumour containing fully resistant cells is eventually lethal.

The intuition is as follows: first, since the resistant population keeps growing, tumour size should be reduced as quickly as possible, to minimize the size of the resistant population when tumour size becomes tolerable. For the same reason, once tumour burden is tolerable, there is no advantage in letting tumour burden become temporarily intolerable (this would not contribute to the time spent with a tolerable tumour burden, and while $N > N_{tol}$, the resistant population would still grow, making the situation worse when going back to $N \leq N_{tol}$). It follows that, to be optimal, it suffices to bring tumour size back to N_{tol} as quickly as possible, and then maximize time to treatment failure from that point on. This is precisely what ideal containment does.

Proposition 8. *Let τ_{idCont} and τ_{alt} denote the total time spent at tumour sizes below N_{tol} under ideal containment and an alternative treatment, respectively. Assume that as long as the patient is alive, the resistant population keeps growing: for all $R \leq N \leq N_{crit}$, $g_r(R, N-R) > 0$, where N_{crit} is the lethal tumour size. Then $\tau_{idCont} \geq \tau_{alt}$.*

Proof. First note that, since $R'_{idCont} = g_r(R_{idCont}, N_{tol} - R_{idCont})$ for $0 < t \leq \tau_{idCont}$:

$$\tau_{idCont} = \int_0^{\tau_{idCont}} 1\, dt = \int_0^1 \frac{R'_{idCont}(t)}{g_r(R_{idCont}(t), N_{tol} - R_{idCont}(t))}\, dt = \int_{R_0}^{N_{tol}} \frac{du}{g_r(u, N_{tol} - u)} \tag{4}$$

where we made the change of variables $u = R_{idCont}(t)$ and used that $R_{idCont}(0) = R_0$ and $R_{idCont}(\tau_{idCont}) = N_{tol}$. Second, let t_0 and t_1 be the first and last times such that $N_{alt}(t) = N_{tol}$ under the alternative treatment. For all $t \leq t_1$, $R_{alt}(t) \leq N_{tol}$ and

$$\mathbb{1}_{N_{alt}(t)\leq N_{tol}} = \frac{R'_{alt}(t)}{g_r(R_{alt}(t), N_{alt}(t) - R_{alt}(t))} \mathbb{1}_{N_{alt}(t)\leq N_{tol}} \leq \frac{R'_{alt}(t)}{g_r(R_{alt}(t), N_{tol} - R_{alt}(t))}$$

[11] We thank Frank Ernesto Alvarez Borges for pointing out this issue to us.

Indeed, the Left-Hand-Side is 0 if $N_{alt}(t) > N_{tol}$, and is not larger than the Right-Hand-Side otherwise, since $R'_{alt}(t)$ is positive, and g_r is positive and decreasing in its second argument. Therefore, the change of variable $u = R_{alt}(t)$ leads to:

$$\tau_{alt} = \int_{t_0}^{t_1} \mathbb{1}_{N_{alt}(t) \leq N_{tol}} \, dt \leq \int_{t_0}^{t_1} \frac{R'_{alt}(t)}{g_r(R_{alt}(t), N_{tol} - R_{alt}(t))} dt = \int_{R(t_0)}^{R(t_1)} \frac{du}{g_r(u, N_{tol} - u)} \leq \tau_{idCont}$$

by (4), since $R(t_0) \geq R_0$ and $R(t_1) \leq N_{tol}$. □

A similar reasoning could also be applied to the case $R_0 < N_{tol}$. The result is then that ideal containment not only maximises the first time at which tumour burden becomes larger than N_{tol}, but also maximizes the total time spent at tumour sizes below N_{tol} (that is, even considering treatments that would temporarily let tumour grow above N_{tol}, then reduce tumour size below this threshold, any number of times, ideal containment maximizes the total time spent at tumour sizes non-larger than N_{tol}). This requires the additional assumption that the resistant population may be slowed down by sensitive cells, but keeps increasing as long as the patient is alive, even for very large sensitive population sizes. Otherwise, a possible strategy would be to first let the sensitive population grow so much that the size of the resistant population decreases, and start treating heavily only when the resistant population has almost been eliminated. If this allows obtaining a tumour of size N_{tol} with a resistant population smaller than R_0, then this allows obtaining a larger total time spent at tumour sizes below N_{tol}. Similar strategies are discussed by Carrère (2017), Pouchol *et al.* (2018), and Carrère and Zidani (2019) [3–5].

2.6. **Reminder on differential equations and proof of Proposition 1.** For completeness, we recall differential equation tools used to prove Proposition 1, which can be found in any good advanced textbook. The reader familiar with differential equations and Gronwall's inequalities (which we call here "comparison principles") can jump to Section 2.6.2.

2.6.1. *Reminder on differential equations.* Consider the differential equation

$$\dot{x}(t) = f(t, x(t)) \tag{5}$$

with $f : \mathbb{R}^2 \to \mathbb{R}$. Assume that:

- f is continuous, and admits a continuous partial derivative $\partial f / \partial x$ with respect to its second variable.
- there exist constants A and B such that $|f(t, x)| \leq A|x| + B$ for all (t, x) in $\mathbb{R}^2$.

This ensures that for any (t_0, x_0) in $\mathbb{R}^2$, there is a unique solution such that $x(t_0) = x_0$, and that this solution is defined for all times. The first part also implies that a solution starting below another stays below it.

Property 9. *Let x and y be solutions of (5). If there exists a time t_0 such that $x(t_0) < y(t_0)$, then $x(t) < y(t)$ for all t in $\mathbb{R}$.*

A subsolution of (5) is a differentiable function u such that $u'(t) \leq f(t, u(t))$. A supersolution is a differentiable function u such that $u'(t) \geq f(t, u(t))$. A solution is both a subsolution and a supersolution. The most important tool for our proofs is the following *comparison principle*, a variant of Gronwall's lemma. It says that if a subsolution starts below a solution (or a supersolution), it stays below at all later times (strictly so if it starts strictly below).

Property 10. (comparison principle) *Let $t_0 \in \mathbb{R}$. Let u be a subsolution and v a supersolution of (5), defined at t_0. Assume that $u(t_0) \leq y(t_0)$. Then for all $t \geq t_0$ such that both u and v are defined, $u(t) \leq y(t)$, with a strict inequality if $u(t_0) < v(t_0)$.*

Finally, let $\phi_t(x_0)$ denote the value $x(t)$ of the solution of (5) with initial condition $x(t_0) = x_0$.

Property 11. (solutions of differential equations depend continuously on initial conditions) *Function ϕ_t is continuous.*

Similar results may be obtained under less demanding assumptions, allowing for generalizations of our results under similarly less demanding assumptions on the regularity of treatment level and of the sensitive population size. In particular, we may assume that treatment level $C(t)$ is only piecewise continuous.

2.6.2. *Proof of Proposition 1.* Assume that conditions i) and ii) hold, and then distinguish three cases.

Case 1: if iiia) holds. Let $f(t,R) = Rg_r(S_1(t),R)$, so that $\dot{R}_1(t) = f(t,R_1(t))$. Since $S_1 \geq S_2$ and g_r is non-increasing in S, it follows that:

$$\dot{R}_2(t) = R_2(t)g_r(S_2(t),R_2(t)) \geq R_2(t)g_r(S_1(t),R_2(t)) = f(t,R_2(t))$$

Since $R_1(t_0) \leq R_2(t_0)$, the comparison principle implies that $R_1 \leq R_2$ on $[t_0,t_1]$

Case 2: if iiib) holds. The proof that $R_1 \leq R_2$ on $[t_0,t_1]$ is as in the proof of a) but with $f(t,R) = Rg_r(N_1(t)-R,R)$. Since by assumption, $N_1 \geq N_2$, it follows that $S_1 \leq S_2$ on $[t_0,t_1]$.

Case 3: if iiic) holds. The idea of the proof is as follows: in forward time, as long as $S_1 \geq S_2$, the comparison principle implies $R_1 \leq R_2$. Similarly, as long as $R_1 \leq R_2$, since we also have $C_1 \leq C_2$, the comparison principle implies $S_1 \geq S_2$. Thus, as long as we have one of the properties that we want, we have the other. However, there is a chicken and egg problem. To solve it, we slightly perturb initial conditions to make sure that both properties hold strictly initially, and then use the fact that solutions of differential equations depend continuously on initial conditions.

Let $\varepsilon > 0$. Let $(S_1^\varepsilon, R_1^\varepsilon)$ be solution of (3) for the same treatment $C(t) = C_1(t)$ as (S_1,R_1), but with initial conditions $S_1^\varepsilon(t_0) = S_1(t_0) + \varepsilon > S_2(t_0)$, and $R_1^\varepsilon(t_0) = R_1(t_0) - \varepsilon < R_2(t_0)$. Let $\tau \in [t_0,t_1]$. A variant of case 1 leads to:

Lemma 12. *If $S_1^\varepsilon(t) \geq S_2(t)$ on $[t_0,\tau]$, then $R_1^\varepsilon(t) < R_2(t)$ on $[t_0,\tau]$.*

A similar argument, using that g_s is non-increasing in R and in C, implies the following lemma:

Lemma 13. *If $R_1^\varepsilon(t) \leq R_2(t)$ on $[t_0,\tau]$, then $S_1^\varepsilon(t) > S_2(t)$ on $[t_0,\tau]$.*

Putting both lemmas together, we obtain:

Lemma 14. *For all t in $[t_0,t_1]$, $R_1^\varepsilon(t) < R_2(t)$ and $S_1^\varepsilon(t) > S_2(t)$.*

Proof. Otherwise there exists a first time τ in $[t_0,t_1]$ such that $R_1^\varepsilon(\tau) \geq R_2(\tau)$ or $S_1^\varepsilon(\tau) \leq S_2(\tau)$. But on $[0,\tau]$, $R_1^\varepsilon(t) \leq R_2(t)$ and $S_1^\varepsilon(t) \geq S_2(t)$. Thus, by Lemmas 12 and 13, $R_1^\varepsilon(\tau) < R_2(\tau)$ and $S_1^\varepsilon(\tau) > S_2(\tau)$. This contradicts the definition of τ. □

Since solutions of differential equations depend continuously on initial conditions, it follows from Lemma 14 that, for any t in $[t_0,t_1]$

$$R_1(t) = \lim_{\varepsilon \to 0} R_1^\varepsilon(t) \leq R_2(t)$$

and similarly $S_1(t) \geq S_2(t)$.

3. Explicit formulas

We compute below, for various treatments and models, the time it takes for tumour size to become strictly larger than an arbitrary threshold $N^* \geq N_0$. This time is denoted by $t_{N^*}(treatment)$. Times to progression, to treatment failure, and survival times are obtained by taking N^* equal to N_0, N_{tol}, and N_{crit}, respectively. Section 3.1 studies general density-dependent models, and Section 3.2 some frequency-dependent ones. Formulas for Gompertzian growth are given in Section 3.3. Treatments considered were defined in Section 2.1.

3.1. The purely density-dependent case.

This section studies Model 2, that is, the particular case of Model 1 in the main text (Eq. (3) in this supplementary material) where $g_s(S,R,C) = g(N,C)$ and $g_r(S,R) = g(N,0)$, with g non-increasing both in N and in C, and $g(N,0) > 0$ for all $N \leq N_{crit}$. We will refer to this as the purely density-dependent case[12]. Thus:

$$\left\{ \begin{array}{rcl} \dot{S}(t) & = & S(t)g(N(t),C(t)) \quad ; \quad S(0) = S_0 \geq 0 \\ \dot{R}(t) & = & R(t)g(N(t),0) \quad ; \quad R(0) = R_0 > 0 \end{array} \right. \tag{6}$$

Henceforth, we let $g(N) := g(N,0)$. Note that there is no cost of resistance, so that the resistant population keeps increasing. Moreover, the treatment level needed to stabilize the tumour at a given size is easily seen to be increasing in R. It follows that during the stabilization phase of containment (when such a stabilization is possible), treatment level gradually increases until $C(t) = C_{max}$, at which point containment at that size is no longer possible. It also follows that once the size of a tumour treated at C_{max} starts

[12]The term density-dependent here refers to the density of tumour within the body. In the following models, as in standard Gompertz models, the growth rates depend on the total number of tumour cells in the patient, so the product of the tumour volume and the number of cells per unit volume (rather than just the number of tumour cells per unit volume).

increasing, it keeps increasing until the patient dies, so there is no possibility that under containment tumour size progresses beyond the stabilization size but then goes back to it, as could happen in the more general Model 1.

3.1.1. *No treatment, ideal MTD, delayed ideal MTD.* For an untreated of fully resistant tumour, $\dot{N} = Ng(N)$. This equation may be solved by separation of variables. The time it takes for tumour size to grow from N_1 to $N_2 > N_1$ is:

$$t_{N_1 \to N_2} = \int_{N_1}^{N_2} \frac{dN}{Ng(N)}$$

Supplementary Table 2 gives an explicit expression of $t_{N_1 \to N_2}$ for various tumour growth-models.

With the above notation, the time it takes for an untreated tumour to become larger than N^* is:

$$t_{N^*}(noTreat) = t_{N_0 \to N^*} = \int_{N_0}^{N^*} \frac{dN}{Ng(N)}$$

Under ideal MTD, the tumour is first reduced to size R_0 and then grows as an untreated tumour. Thus:

$$t_{N^*}(idMTD) = t_{R_0 \to N^*} = t_{N^*}(noTreat) + t_{R_0 \to N_0}$$

Under delayed ideal MTD, with treatment starting at some size $N_{ref} \geq N_0$, the tumour first grows to size N_{ref}, then is reduced to the current resistant population size R_1, and then grows back as a fully resistant tumour. Due to the absence of resistance cost, the frequency of resistant cells does not change during no treatment phases, so that $R_1 = R_0 \frac{N_{ref}}{N_0} \geq R_0$. For $N^* \geq N_{ref} \geq N_0$, this leads to:

$$t_{N^*}(del\text{-}idMTD) = t_{N_0 \to N_{ref}} + t_{R_1 \to N^*} = t_{N^*}(noTreat) + t_{R_0 N_{ref}/N_0 \to N_{ref}}$$

3.1.2. *Ideal containment at $N_{ref} \geq N_0$.* The tumour grows as an untreated or fully resistant tumour before and after the stabilization phase. For $N^* < N_{ref}$, $t_{N^*}(idCont) = t_{N^*}(noTreat)$. For $N^* \geq N_{ref}$, the absolute benefit of ideal containment with respect to no treatment is the duration of the stabilization phase. This is the time it takes for the resistant population to grow from $R_1 = R_0 \frac{N_{ref}}{N_0}$ to $R_2 = N_{ref}$ at a constant per-cell growth-rate $g(N_{ref})$. This leads to:

$$t_{N^*}(idCont) = t_{N^*}(noTreat) + \frac{\ln(N_0/R_0)}{g(N_{ref})}$$

3.1.3. *Constant dose, MTD, and delayed constant dose with a Norton-Simon kill rate.* Assume a Norton-Simon kill-rate: $g(N, C) = g(N)(1 - \lambda C)$. Then under a constant dose treatment, $\frac{dS}{S} = (1 - \lambda C)\frac{dR}{R}$ so that $SR^{\lambda C - 1}$ is constant. Thus, $S = S_0 \left(\frac{R_0}{R}\right)^{\lambda C - 1}$, and when $N = N^*$ for the last time, the resistant population size is the largest solution R^* of:[13]

$$N(R^*) = N^*,\ R^* \geq R_0,\ \text{with } N(R) = R + S_0 \left(\frac{R_0}{R}\right)^{\lambda C - 1} \tag{7}$$

[13]The solution to (7) is easily seen to be unique unless both $N^* = N_0$ and $S_0(1 - \lambda C) + R_0 < 0$ (i.e. tumour size initially decreases), in which case R^* is the unique solution strictly greater than R_0.

SUPPLEMENTARY TABLE 2. **Time in which an untreated tumour grows from N_1 to N_2.**

Model name	Per-cell growth-rate $g(N)$	$t_{N_1 \to N_2}$
Exponential	ρ	$\frac{1}{\rho} \ln\left(\frac{N_2}{N_1}\right)$
Gompertz	$\rho \ln(K/N)$	$\frac{1}{\rho} \ln\left(\frac{\ln(K/N_1)}{\ln(K/N_2)}\right)$
Logistic	$\rho(1 - N/K)$	$\frac{1}{\rho}\left[\ln\left(\frac{N_2}{N_1}\right) + \ln\left(\frac{K - N_1}{K - N_2}\right)\right]$
Power-Law	$\rho N^{-\gamma}$; $0 < \gamma < 1$	$\frac{1}{\rho\gamma}(N_2^\gamma - N_1^\gamma)$
von Bertalanffy	$\rho(N^{-\gamma} - K^{-\gamma})$; $0 < \gamma < 1$	$\frac{1}{\rho\gamma K^{-\gamma}} \ln\left(\frac{K^\gamma - N_1^\gamma}{K^\gamma - N_2^\gamma}\right)$

This leads to:

$$t_{N^*}(\text{Constant dose } C) = \int_{R_0}^{R^*} \frac{dR}{Rg(N(R))}$$

with R^* and $N(R)$ defined by (7). A formula for MTD is obtained by taking $C = C_{max}$.

More generally, if at some point $N = N_1$, $R = R_1$, and tumour is then treated at a constant dose C, then the time it takes for the tumour to exceed size $N_2 \geq N_1$ is:

$$t(N_1 \to N_2 | R_1, C) = \int_{R_1}^{R_2} \frac{dR}{Rg(\tilde{N}(R))} \text{ with } \tilde{N}(R) = R + S_1 \left(\frac{R_1}{R}\right)^{\lambda C - 1} \tag{8}$$

where R_2 is the largest solution of $R_2 + S_1 \left(\frac{R_1}{R_2}\right)^{\lambda C - 1} = N_2$. However, except in very special cases, R_2 and the integral can only be computed numerically.

If treatment is delayed until $N = N_{ref}$ and a constant dose C is then applied, the time at which tumour size increases beyond N^*, assuming $N^* \geq N_{ref}$, is equal to

$$t_{N^*}(\text{delayed constant dose } C) = t_{N_0 \to N_{ref}} + t(N_{ref} \to N^* | R_1, C), \text{ with } R_1 = R_0 N_0 / N_{ref}$$

where the second term is defined by (8). Taking $C = C_{max}$ gives a formula for delayed MTD, though again with an integral to be computed numerically.

3.1.4. *Containment at N_{ref}.* If $N^* < N_{ref}$, then $t_{N^*}(Cont) = t_{N^*}(noTreat)$. If $N^* = N_{ref}$, then as for ideal containment:

$$t_{N_{ref}}(Cont) = t_{N_{ref}}(noTreat) + \frac{\ln(R_2/R_1)}{g(N_{ref})}$$

where $R_1 = R_0 \frac{N_{ref}}{N_0}$ and R_2 are the resistant population sizes at the beginning and at the end of the stabilization phase. However, R_2 is no longer equal to N_{ref}, and needs to be computed. To do so, let $\tilde{R}_2$ be the solution of:

$$(N_{ref} - R) g(N_{ref}, C_{max}) + R g(N_{ref}) = 0$$

that is, if $N = N_{ref}$, $R = \tilde{R}_2$ and $C = C_{max}$, then $dN/dt = 0$. There are two cases: if $R_1 \geq \tilde{R}_2$, or equivalently $R_0 \geq \frac{N_0}{N_{ref}} \tilde{R}_2$, then when the tumour reaches the stabilization size N_{ref}, treating at C_{max} does not decrease tumour size: there is then no stabilization phase, $R_2 = R_1$ and $t_{N^*}(Cont) = t_{N^*}(noTreat)$. Otherwise, there is a stabilization phase that lasts until $R = \tilde{R}_2$. Thus, $R_2 = \max(R_1, \tilde{R}_2)$. In the case $R_1 < \tilde{R}_2$ (existence of a stabilization phase), we get:

$$t_{N_{ref}}(Cont) = t_{N_{ref}}(noTreat) + \frac{\ln(N_0/R_0)}{g(N_{ref})} - \frac{\ln\left(1 + g(N_{ref})/|g(N_{ref}, C_{max})|\right)}{g(N_{ref})}$$

For a Norton-Simon kill rate: $g(N, C) = g(N)(1 - \lambda C)$, this boils down to:

$$t_{N_{ref}}(Cont) = t_{N_{ref}}(noTreat) + \frac{\ln(N_0/R_0)}{g(N_{ref})} - \frac{\ln\left(\lambda C_{max}/[\lambda C_{max} - 1]\right)}{g(N_{ref})}$$

For $N^* \geq N_{ref}$, still assuming a Norton-Simon kill rate and the existence of a stabilization phase,

$$t_{N^*}(Cont) = t_{N_{ref}}(noTreat) + \frac{\ln(N_0/R_0)}{g(N_{ref})} - \frac{\ln\left(\lambda C_{max}/[\lambda C_{max} - 1]\right)}{g(N_{ref})} + t(N_{ref} \to N^* | \tilde{R}_2, C_{max}) \tag{9}$$

where the last term is defined by (8). The difference with ideal containment is:

$$t_{N^*}(Cont) - t_{N^*}(idCont) = -\frac{\ln\left(\lambda C_{max}/[\lambda C_{max} - 1]\right)}{g(N_{ref})} + \left[t(N_{ref} \to N^* | \tilde{R}_2, C_{max}) - t_{N_{ref} \to N^*}\right]$$

The first term is the difference in the durations of the stabilization phases. It is smaller if C_{max} is large. The second term (the bracket) is the difference between the time it takes for the tumour to progress from N_{ref} to N^* under containment and under ideal containment. It is positive and increasing in N^*. This expresses the fact that, under containment, after the stabilization phase, the tumour is still partially sensitive, hence progresses more slowly than under ideal containment.

3.1.5. *Ideal intermittent containment between N_{min} and N_{max}.* To fix ideas, assume $N_0 \leq N_{max} \leq N^*$. Under ideal intermittent containment, the tumour grows as an untreated or fully resistant tumour, except that each time it reaches size N_{max} and is still partially sensitive the sensitive population is decreased by $N_{max} - N_{min}$, or by $N_{max} - R$ if $R > N_{min}$. Letting $t_{stab}(idInt)$ be the duration of the (dynamic) stabilization phase, that is, the time between the first and the last time such that $N = N_{max}$,

$$t_{N^*}(idInt) = t_{N^*}(noTreat) + t_{stab}(idInt)$$

We now compute t_{stab}. Let t_k denote the kth time that $N = N_{max}$. Let t_{q+1} denote the first time at which $N = N_{max}$ and N cannot be reduced to N_{min} (that is, $R > N_{min}$). Let $R_{q+1} = R(t_{q+1})$. During the stabilization phase, the tumour size changes q times from N_{min} to N_{max}, and once from R_{q+1} to N_{max}. Therefore:

$$t_{stab} = q\, t_{N_{min} \to N_{max}} + t_{R_{q+1} \to N_{max}}$$

It remains to compute q and R_{q+1}. Due to the absence of resistance cost, the proportion of resistant cells does not change during a no-treatment phase. This implies that:

$$R_{q+1} = R_0 \times \frac{N_{max}}{N_0} \times \left(\frac{N_{max}}{N_{min}}\right)^q \tag{10}$$

so it only remains to compute q. The fact that, by definition of q, $N_{min} < R_{q+1} \leq N_{max}$ implies that q is the integer part of (i.e., the greatest integer no greater than)

$$\frac{\ln(N_0/R_0)}{\ln(N_{max}/N_{min})} \tag{11}$$

It may be checked that if $N_{min} < R_0$, so that $q = 0$, we obtain the formula for delayed ideal MTD (let the tumour grow until N_{max}, then eliminate all sensitive cells). Similarly, in the limit $N_{min} \to N_{max}$, we recover the formula for ideal (continuous) containment.

The explicit formula for ideal intermittent containment is plotted in Extended Data Fig. 1 in the case of a Gompertzian growth-model (Model 3 in the main text). This figure compares time to progression for ideal containment at N_0, ideal containment at $N_{min} < N_0$, and intermittent containment between N_0 and $N_{min} < N_0$. The value of N_{min} is varied from R_0 to N_0. This illustrates two important points: first, for idealized treatments, time to progression for intermittent containment is in-between time to progression for containment at the lower level and for containment at the upper level (this is actually true for time to progression beyond any level $N^* \geq N_{max}$, see Proposition 5); second, though ideal containment at the upper level is superior to ideal intermittent containment, the difference is small when N_{min} is a substantial fraction of N_{max}.

3.1.6. *Summary.* Supplementary Table 3 summarizes absolute benefits of various treatments compared to not treating:

$$t_{N^*}(treatment) - t_{N^*}(noTreat),$$

in the case $N^* \geq N_{ref} \geq N_0$. The formula for containment is given in the case of a Norton-Simon kill rate, and assuming that some stabilization is possible (for other cases, see Section 3.1.4). The inequality in this formula indicates that the benefit is greater that this quantity (with equality for $N^* = N_{ref}$). In simulations, for large values of N^*, we find the benefit of containment to be similar to the benefit of ideal containment, and even slightly greater in some cases when the endpoint tumour size is larger than the containment size.

3.2. **Frequency-dependent models and models with resistance costs.** Models where the resistant population follows a frequency-dependent dynamic $\dot{R} = Rf(R/N)$, or more generally a frequency and density-dependent dynamic,

$$\dot{R} = Rf(R/N)g(N), \text{ with } f \text{ increasing and } f(1) = 1 \tag{12}$$

SUPPLEMENTARY TABLE 3. **Absolute benefits compared to not treating in Model** (6)

Treatment	idMTD	del-idMTD	idCont	Cont
Absolute benefit	$t_{R_0 \to N_0}$	$t_{R_0 \frac{N_{ref}}{N_0} \to N_{ref}}$	$\frac{\ln(N_0/R_0)}{g(N_{ref})}$	$\geq \frac{\ln(N_0/R_0) - \ln(1 + 1/[\lambda C_{max} - 1])}{g(N_{ref})}$

have been considered in the literature, e.g., Silva *et al.* (2012) [13], Bacevic *et al.* (2017) [14]. Another possibility is to keep an essentially density dependent model, but to introduce a resistance cost, e.g., $\dot{S} = \rho_s S g(N)$, $\dot{R} = \rho_r R g(N)$, with $\rho_r \leq \rho_s$. Under such models, the frequencies of resistant and sensitive cells continuously change even in an untreated tumour. This makes it difficult to obtain useful explicit formulas for treatments that begin by letting the tumour grow, such as containment at tumour sizes higher than the initial size. But for ideal MTD and ideal containment at the initial size N_0, explicit formulas are readily obtained for general models where $\dot{R} = R g_r(R, S)$. Indeed, under ideal MTD, the tumour becomes immediately fully resistant, hence the frequency-dependence disappears. Thus, for $N^* \geq N_0$, we still have

$$t_{N^*}(idMTD) = t_{R_0 \to N^*}, \text{ with } t_{N_1 \to N_2} = \int_{N_1}^{N_2} \frac{dN}{N g(N)} \text{ for Model (12)},$$

or more generally $t_{N_1 \to N_2} = \int_{N_1}^{N_2} \frac{dN}{N g_r(N,0)}$.

For ideal containment at N_0, the stabilization phase lasts:

$$t_{stab}(idContN_0) = \frac{1}{g(N_0)} \int_{R_0}^{N_0} \frac{dR}{R f(R/N_0)} \text{ for Model (12)},$$

and more generally, $t_{stab}(idContN_0) = \int_{R_0}^{N_0} \frac{dR}{R g_r(R, N_0 - R)}$. After the stabilization phase, the tumour is fully resistant. Thus,

$$t_{N^*}(idContN_0) = t_{stab}(idContN_0) + t_{N_0 \to N^*}.$$

For containment at the initial size N_0, the stabilization phase lasts:

$$t_{stab}(ContN_0) = \frac{1}{g(N_0)} \int_{R_0}^{R_{end}} \frac{dR}{R f(R/N_0)} \text{ for Model (12)},$$

and more generally, $t_{stab}(ContN_0) = \int_{R_0}^{R_{end}} \frac{dR}{R g_r(R, N_0 - R)}$, where R_{end} is the resistant population size when the stabilization treatment level reaches C_{max}. The value of R_{end} is easy to compute once the sensitive population dynamics are specified. For $N^* \geq N_0$,

$$t_{N^*}(ContN_0) \geq t_{stab}(ContN_0) + t_{N_0 \to N^*}.$$

The expression for $t_{N_1 \to N_2}$ no longer corresponds to the growth of an untreated tumour, but to the growth of a fully resistant tumour. Thus, the formulas do not permit easy comparison with no treatment, but they allow comparison of ideal MTD and ideal containment (or containment). For the same function $g(N)$ as in Section 3.1, frequency-dependence as modeled in (12) provides an additional rationale to containment, increasing its benefit with respect to ideal MTD.

3.3. **Application to Gompertzian growth.** We now consider the case of a Gompertz model: $g(N) = \rho \ln(K/N)$, for which:

$$t_{N_1 \to N_2} = \frac{1}{\rho} \ln \left[\frac{\ln(K/N_1)}{\ln(K/N_2)} \right] = \frac{1}{\rho} \ln \left[\frac{\log(K/N_1)}{\log(K/N_2)} \right]$$

where ln denotes the natural logarithm ($\ln(2.718...) = 1$), while log denotes the base 10 logarithm ($\log(10) = 1$). For readability, time units are chosen so that $\rho = 1$ (otherwise, all times should be divided by ρ). Assume $N_0 \leq N_{tol} \leq N_{crit} \leq K$, and let a, b, c, d be nonnegative real numbers such that

$$K = 10^a R_0 = 10^b N_0 = 10^c N_{tol} = 10^d N_{crit}.$$

Note that $a \geq b \geq c \geq d$. For ideal intermittent containment, let $N_{max} = 10^\alpha N_{min}$. *With time units such that* $\rho = 1$, the time to progression, the time to treatment failure, and the survival time in the absence of treatment are respectively 0, $\ln(b/c)$ and $\ln(b/d)$. Supplementary Table 4 gives the *absolute benefit* compared to no treatment in terms of time to progression, time to treatment failure, and survival time. The formulas for ideal intermittent containment are approximations (exact when the last cycle is complete), see Section 3.1.5. Formulas for other models are easily obtained by using the values of $g(N)$ and $t_{N_1 \to N_2}$ in Supplementary Table 2.

Supplementary Tables 5 and 6 give numerical values of time to progression, time to treatment failure, and survival time with parameters from Monro and Gaffney (2009) [11] (main text Table 2).[14] Note that contrary to Supplementary Table 4, these are not the benefits with respect to no treatment, but the actual times to progression, times to treatment failure and survival times. This is why we add a row for no treatment in Supplementary Table 6. Note also that, although it leads in our model to a large survival

[14] In [11], simulations start with $S = 1$, $R = 0$, so the value of R at treatment initiation, i.e., when $N = 10^{10}$, is not explicitly given. However, it may be derived from a well-known formula, see, e.g., Goldie and Coldman, 1979 [20].

SUPPLEMENTARY TABLE 4. **Absolute benefit over no treatment for a Gompertz model: formulas.** Parameters satisfy $K = 10^a R_0 = 10^b N_0 = 10^c N_{tol} = 10^d N_{crit}$, and $N_{max} = 10^\alpha N_{min}$. Time units exceptionally chosen so that $\rho = 1$ (otherwise all times should be divided by ρ). Time to progression, to treatment failure, and survival time in the absence of treatment are respectively 0, $\ln(b/c)$ and $\ln(b/d)$, which should be added to the values of the table to obtain the corresponding times for the treatment of interest.

Treatment	Progression benefit	Treatment failure benefit	Survival benefit
ideal MTD	$\ln\left(1+\frac{a-b}{b}\right)$	$\ln\left(1+\frac{a-b}{b}\right)$	$\ln\left(1+\frac{a-b}{b}\right)$
del-idMTD $N_{ref}=N_{tol}$	0	$\ln\left(1+\frac{a-b}{c}\right)$	$\ln\left(1+\frac{a-b}{c}\right)$
del-idMTD $N_{ref}=N_{crit}$	0	0	$\ln\left(1+\frac{a-b}{d}\right)$
idContN_0	$\frac{a-b}{b}$	$\frac{a-b}{b}$	$\frac{a-b}{b}$
idContN_{tol}	0	$\frac{a-b}{c}$	$\frac{a-b}{c}$
idContN_{crit}	0	0	$\frac{a-b}{d}$
idIntN_0	$\frac{a-b}{b}\times\frac{\ln(1+\alpha/b)}{\alpha/b}$	$\frac{a-b}{b}\times\frac{\ln(1+\alpha/b)}{\alpha/b}$	$\frac{a-b}{b}\times\frac{\ln(1+\alpha/b)}{\alpha/b}$
idIntN_{tol}	0	$\frac{a-b}{c}\times\frac{\ln(1+\alpha/c)}{\alpha/c}$	$\frac{a-b}{c}\times\frac{\ln(1+\alpha/c)}{\alpha/c}$
idIntN_{crit}	0	0	$\frac{a-b}{d}\times\frac{\ln(1+\alpha/d)}{\alpha/d}$
ContN_0	$\frac{a-b-\log\left(\frac{\lambda C_{max}}{\lambda C_{max}-1}\right)}{b}$	semi-explicit formula, see Eq. (9)	semi-explicit formula, see Eq. (9)
ContN_{tol}	0	$\frac{a-b-\log\left(\frac{\lambda C_{max}}{\lambda C_{max}-1}\right)}{c}$	semi-explicit formula, see Eq. (9)
ContN_{crit}	0	0	$\frac{a-b-\log\left(\frac{\lambda C_{max}}{\lambda C_{max}-1}\right)}{d}$

time, we do not advocate containment at the critical size N_{crit} as such a strategy would be extremely risky and harmful to quality of life.

SUPPLEMENTARY TABLE 5. **Times to progression, to treatment failure, and survival time for a Gompertz model: idealized treatments and containment** The model is Model 3 from the main text, with parameters from Table 2. Time is measured in days. Numbers with an asterisk are estimated from simulations, others are calculated from formulas.

Treatment	t_{prog}	t_{fail}	t_{surv}
ideal MTD	186	263	412
delayed ideal MTD (at N_{tol})	0	319	468
delayed ideal MTD (at N_{crit})	0	77	591
ideal containment at N_0	340	417	566
ideal containment at N_{tol}	0	615	764
ideal containment at N_{crit}	0	77	1526
idInt between N_0 and $N_0/2$	320	397	546
idInt between N_{tol} and $N_{tol}/2$	0	566	715
idInt between N_{crit} and $N_{crit}/2$	0	77	1280
Containment at N_0 ($C_{max} = 2$)	318	418*	568*
Containment at N_{tol} ($C_{max} = 2$)	0	580	767*
Containment at N_{crit} ($C_{max} = 2$)	0	77	1441

SUPPLEMENTARY TABLE 6. **Times to progression, to treatment failure, and survival time for a Gompertz model: constant doses and delayed constant doses** Same model and parameters as in Supplementary Table 5. Numbers in parentheses (given only when different) are for the original Monro and Gaffney model [11], with mutations and back mutations at rate 10^{-6} (this does not change optimal doses, given our precision level). Bold squares correspond to optimal results given the starting time, e.g., the dose $C = 0.74$ maximizes survival time among all constant dose treatments starting immediately. $C = 2$ corresponds to MTD in most of our simulations. For visual representation of survival time for constant doses starting immediately, see Figure 1 in [11].

C	Starting size	t_{prog}	t_{fail}	t_{surv}
2 (MTD)	N_0	236	314	463
1.09	N_0	**303 (302)**	397 (396)	549 (548)
1	N_0	0	421 (420)	578 (579)
0.89	N_0	0	**443 (442)**	634 (632)
0.74	N_0	0	296	**730 (727)**
0	irrelevant	0	77	226
2 (MTD)	N_{tol}	0	400 (398)	549 (547)
1.07	N_{tol}	0	**543 (537)**	731 (726)
1	N_{tol}	0	77	780 (774)
0.86	N_{tol}	0	77	**885 (877)**
2 (MTD)	N_{crit}	0	77	762 (758)
1.04	N_{crit}	0	77	**1276 (1255)**

4. Comparison between treatments

Building on findings of Sections 2 and 3, this section compares treatments for a purely density-dependent model with no resistance cost, as defined in Section 3.1, Eq. (6) (or equivalently, in Model 2 of the main text). Except when discussing exponential and superexponential tumour growth in Section 4.1.1, we always assume negative density-dependence; that is, the per-cell growth-rate function g in Eq. (6) is decreasing in N.

4.1. **Idealized treatments.**

4.1.1. *Impact of tumour growth model.* To fix ideas, assume $N^* \geq N_{ref} = N_{max} \geq N_0$. Recall that $t_{N^*}(treatment)$ denote the time at which tumour size exceeds size N^* under the treatment considered. It

follows from Proposition 7 that already in the general model of Section 2,

$$t_{N^*}(idMTD) \leq t_{N^*}(del\text{-}idMTD) \leq t_{N^*}(idInt) \leq t_{N^*}(idCont) \tag{13}$$

Considering a purely density-dependent model leads to further insights. In this case, the benefits of ideal MTD, delayed ideal MTD, ideal intermittent containment, and ideal containment, compared to not treating, are each the time taken for the resistant population to grow by a factor N_0/R_0, but in different circumstances: from R_0 to N_0 in the absence of competition for ideal MTD; from $R_1 = \frac{R_0}{N_0} N_{ref}$ to N_{ref} with no, some, or strong competition for delayed ideal MTD, ideal intermittent containment, and ideal containment, respectively. Since doubling times are assumed longer at higher tumour sizes, we obtain another proof of (13). Moreover, the duration of the stabilization phase is inversely proportional to $g(N_{ref})$, hence the larger the stabilization size, the longer the stabilization phase, and the greater the benefits of ideal containment. (Figs. 1f, 1h; Supplementary Tables 3, 4, 5).

These qualitative findings are very general. However, the magnitude of clinical benefits vary considerably depending on the precise model [6]. As easily seen, assuming negative density-dependence, a general bound on the relative benefits of ideal containment over ideal MTD in terms of time to progression is given by:

$$\frac{t_{prog}(idContN_0)}{t_{prog}(idMTD)} \leq \frac{g(R_0)}{g(N_{ref})}$$

For logistic growth, $g(N) = 1 - N/K$, so that:

$$\frac{t_{prog}(idContN_0)}{t_{prog}(idMTD)} \leq \frac{1 - R_0/K}{1 - N_0/K} \leq \frac{1}{1 - N_0/K} \simeq 1 + \frac{N_0}{K}$$

for N_0/K small. With the parameters from main text Table 2, $N_0/K = 1/200$, so that ideal containment improves on ideal MTD by less than 0.5%, a very tiny gain. To take into account the fact that the value of the carrying capacity K was chosen for a Gompertz model [11], we may want to modify this value (see Extended Data Fig. 2). But as long as $K \geq N_{crit}$, and $N_{crit} = 50N_0$ as in main text Table 2, we still have $N_0/K \leq 0.02$ so that ideal containment improves on ideal MTD by less than about 2%. By contrast, with parameters from Table 2 but a Gompertz model, the time to progression under ideal containment at the initial size is 84% higher than under ideal MTD (Supplementary Table 5). Moreover, relative benefits of ideal containment for a von Bertalanffy model are even higher than for a Gompertz model (Fig. 2c). Thus, these three standard tumour growth models lead to very different quantitative predictions.

Extended Data Fig. 2 illustrates these findings, as well as the cases of exponential and superexponential tumour growth. As discussed in the main text, if the resistant population grows exponentially then ideal MTD and ideal containment at any size no larger than N_{tol} both lead to the same time to treatment failure: the relative benefit of ideal containment is thus equal to 1 (yellow curve). If tumour growth is superexponential and sensitive and resistant cells do not differ except with respect to their reaction to treatment then the presence of sensitive cells boosts the growth of resistant cells. Aggressive treatments then have the double advantage of eliminating sensitive cells and reducing the growth rate of the resistant population. This leads to a strong advantage of ideal MTD over ideal containment in the superexponential case (grey line in Extended Data Fig. 2). We plan to extend our study of the influence of the model on predicted benefits of containment in a companion paper.

4.1.2. *Impact of parameters.* We discuss here the effect of varying parameters on absolute and relative benefits of ideal containment over ideal MTD, for the Gompertzian Model 3 of the main text. Changing the baseline growth-rate ρ just changes the time-scale. Halving ρ doubles absolute differences between treatments, hence absolute benefits of ideal containment, but does not change relative benefits. To investigate the effect of other parameters, let $x = \ln(K/R_0)/\ln(K/N_0)$. As follows from Section 3, the absolute benefit of ideal containment at N_0, and its relative benefit in terms of time to progression, are given by $[x - \ln(1+x)]/\rho$ and by $x/\ln(1+x)$, respectively (Supplementary Table 4). These are two increasing functions of x, so any change of parameter that increases the value of x increases both of these benefits. It is easy to see that this is the case of a decrease in K or in R_0 (with N_0 fixed), or of an increase in N_0 (with R_0 fixed, and also with R_0/N_0 fixed). The absolute benefit of ideal containment at N_{tol} with respect to ideal MTD is also easy to study. Results are summed up in Supplementary Table 7.

Extended Data Fig. 3 illustrates the impact of increasing the initial fraction of resistant cells on times to progression in Model 3 of the main text (see also Fig. 2 and Extended Data Fig. 6). For a given average per-cell growth rate, increasing R_0 reduces the time it takes for the resistant population to increase from R_0 to N_0. This tends to decrease absolute difference between treatments. Moreover, while this does not change the per-cell growth rate of resistant cells during the stabilization phase of containment or ideal

SUPPLEMENTARY TABLE 7. **Qualitative effect of parameters on absolute benefits of ideal containment over ideal MTD in main text Model 3.** The table should be read as follows: a "+" means an increase, an "=" no change, and a "-" a decrease.

Parameter increased	K	N_{tol}	N_0 (R_0 fixed)	N_0 (N_0/R_0 fixed)	R_0 (N_0 fixed)
Effect on $t_{prog}(idContN0) - t_{prog}(idMTD)$	-	=	+	+	-
Effect on $t_{fail}(idContN_{tol}) - t_{fail}(idMTD)$	-	+	+	-	-

containment, increasing R_0 increases the per-cell growth rate during the regrowth phase of MTD or ideal MTD, so that the differences in growth rates is smaller. This is because a higher initial resistant population leads to a higher average tumour size during this regrowth phase. This further reduces absolute benefits of ideal containment, and also reduces relative benefits.

The impact of varying parameters on *relative benefits* in terms of *time to treatment failure* or survival time is more complex. Indeed, varying a parameter may increase the absolute benefit of ideal containment over ideal MTD, yet reduce its relative benefit. This may happen for instance if it also increases the duration of growth phases that are common to ideal containment and ideal MTD. Indeed, a long common phase attenuates relative differences between treatments.

Consider for instance the impact of a lower initial tumour size N_0 for a fixed initial fraction of resistant cells R_0/N_0. Assuming $N_0 < N_{tol}$, this does not change the duration of the stabilization phase under ideal containment at N_{tol}, but decreases the duration of the phase of regrowth from R_0 to N_0 under ideal MTD. As a result, this increases the absolute benefit of ideal containment at N_{tol} over ideal MTD in terms of time to treatment failure. But this also increases the duration of the phase of growth from N_0 to N_{tol}, which is common to both treatments. The net effect on the ratio of times to treatment failure $t_{fail}(idContN_{tol})/t_{fail}(idMTD)$ is unclear. This is apparent from Fig. 2b in the main text, where we see that for a fixed initial fraction of resistant cells, a higher initial tumour size sometimes increases and sometimes decreases the relative benefit of ideal containment at N_{tol}.

4.2. **Containment and ideal containment.** As we saw in Section 2, Proposition 3, the tumour progresses beyond the stabilization size faster under containment than under ideal containment. However, the resistant population under containment is always smaller, leading intuitively to a survival time that is longer or at least comparable to that under ideal containment. For the purely density-dependent Model 2 of the main text (that is, Eq. (6) in Section 3.1), we may be more precise. In the case of a Norton-Simon kill rate, for instance, it follows from Section 3 that the ratio of the duration of the stabilization phases of containment and ideal containment is given by:

$$\frac{t_{stab}(Cont)}{t_{stab}(idCont)} = 1 + \frac{\ln\left(1 - 1/\lambda C_{max}\right)}{\ln\left(N_0/R_0\right)}$$

(this ratio is the same independently of the stabilization size). Supplementary Table 8 gives this ratio for various initial proportions of resistant cells and efficiency λC_{max} of the MTD treatment (for a visual representation, see Fig. 2g in main text).[15] When sensitive cells are not very sensitive and resistant cells are initially abundant, this ratio is substantially smaller than 1. However, if the drug is quite effective or resistant cells are initially rare, this ratio is quite high. In that case, containment is not far from maximizing the time at which tumour size grows above the stabilization level (see also Figs. 1a, 1d, 2d, 2h, 2g, Supplementary Tables 4 and 5, Extended Data Fig. 6).[16]

Moreover, the reason why containment progresses beyond N_{ref} before ideal containment is that this happens before all sensitive cells have been eliminated. With a Norton-Simon kill rate, this may be made precise: the proportion of sensitive cells when the tumour can no longer be stabilized (whatever

[15]If $\lambda C_{max} = 2$, the speed at which a purely sensitive tumour size decreases under MTD is equal to the speed at which it would increase if untreated. This is roughly consistent with the fact that, in preliminary results of a clinical trial of intermittent containment (Zhang et al, 2017 [1]), treatment was applied, on average, 47% of the time (this average later decreased to 41%, as stated by Robert A. Gatenby in a seminar on July 22, 2020). For this reason, and due to the simple interpretation it offers, we chose $\lambda C_{max} = 2$ as our reference value in simulations.

[16]If we take the constraint $C \leq C_{max}$ into account then containment is closer to optimal than the numbers seem to indicate. This is because the optimal strategy then begins as containment and switches to MTD before progression or failure occurs. Comparing containment to ideal containment gives us a non-tight upper bound on how far we are from optimality, given the constraint on C_{max}.

SUPPLEMENTARY TABLE 8. **Ratio of times to progression under containment vs ideal containment for various initial fractions of resistant cells and treatment efficiencies.**

		λC_{max}		
		1.5	2	5
$\frac{R_0}{N_0}$	10%	0.52	0.70	0.90
	1%	0.76	0.85	0.95
	0.1%	0.84	0.90	0.97
	0.01%	0.88	0.92	0.96
	0.005%	0.90	0.94	0.98

the stabilization level) is either the initial proportion (when the tumour cannot be stabilized at all) or $1/\lambda C_{max}$: 50% if $\lambda C_{max} = 2$; 33% if $\lambda C_{max} = 3$; and so on.

These remaining sensitive cells slow down the expansion of resistant cells. This is why, as shown in Section 2, the resistant population is always smaller for containment than for ideal containment. A sufficient condition for containment to be at least comparable to ideal containment in terms of survival time is thus that, by the time tumour size reaches N_{crit}, almost all sensitive cells have been eliminated. This is more likely if the treatment is quite efficient against sensitive cells (λC_{max} high) and if the tumour is stabilized at a relatively low size, leaving more time after the end of the stabilization phase to eliminate the remaining sensitive cells. However, we now argue that even if containment is made at a relatively high tumour size, and treatment effect is relatively modest, it is likely that by the time of death, the proportion of sensitive cells will be very low.

To see this, consider the post-stabilization phase during which containment treats at C_{max} and assume a Norton-Simon kill rate: $\dot{S} = Sg(N)(1 - \lambda C)$. As we saw in Section 3.1.3, if the tumour is treated at a constant dose C, then the quantity $SR^{\lambda C-1}$ is constant. It follows that if $\lambda C = 2$ (resp. 3), then each time the resistant population is multiplied by 10, the sensitive population is divided by 10 (resp. 100). Since we also know that the proportion of sensitive cells at the end of the stabilization phase is $1/\lambda C_{max}$, this allows us to estimate the remaining sensitive population at the time of death. For instance, assuming that containment is made at $N_{tol} = 7 \times 10^{10}$, that $N_{crit} = 5 \times 10^{11}$ (about 7 times larger than N_{tol}) and that $\lambda C_{max} = 2$, the proportion of sensitive cells at the time of death is only about 0.5%. This is true for any instance of Model 2 in the main text.

We conclude that in terms of survival time, containment is bound to be at least as good as ideal containment, and possibly slightly better. This is what we observe in simulations (Figs. 1a, 1c, 1d, 2f, 2i, Supplementary Table 5, and Extended Data Fig. 6).

4.3. **Continuous and intermittent containment.** As mentioned in the main text, when the constraint on the maximal tolerated dose is taken into account, containment does not exactly maximize time to treatment failure. Indeed, at least in Model 2, treatment failure can be slightly delayed by switching from containment to MTD slightly before the stabilization dose reaches C_{max}. This is achieved through a greater reduction of the number of sensitive cells than under containment, which leads to a larger resistant population and subsequently faster tumour growth.

Similarly, contrary to what happens with idealized treatments (Section 2.3, Proposition 5), intermittent containment between N_{min} and N_{max} may lead to a longer time to progression beyond the upper threshold N_{max} than containment at N_{max}, especially when N_{min} is a relatively large fraction of N_{max}. This is because intermittent containment commences indefinite treatment at dose C_{max} before containment does, which potentially prolongs the time to progression beyond N_{max}, as evidenced by Extended Data Fig. 4. As before, this gain comes at the cost of a larger resistant population (Section 2.3, Proposition 6). This reinforces the fact that even before intermittent containment commences indefinite treatment at dose C_{max}, it already leads to a larger resistant population than containment at the upper threshold, because it initially leads to a lower average tumour burden.

Even more than for ideal containment (Section 4.2), it is thus expected that as the fraction of sensitive cells decreases, tumour size becomes higher under intermittent containment than under containment at the upper threshold, leading to a lower survival time under intermittent containment than under containment. This is observed in simulations of the Gompertzian Model 3 (Extended Data Fig. 4, Table 1 from main text).

It should be noted however that, for reasons not modeled here, it might be more difficult for the tumour to adapt to changing conditions generated by intermittent treatment than to the more stable conditions generated by continuous containment. This, or PKPD considerations, could make intermittent containment theoretically more promising than continuous containment. Investigating these issues is however beyond the scope of this article.

4.4. **MTD and ideal MTD.** To facilitate the comparison between MTD and ideal MTD, let us first estimate the remaining sensitive population at the time of progression under the MTD treatment. Assume a Norton-Simon kill rate. Then, as discussed in Section 4.2, if $\lambda C_{max} = 2$ (resp. 3; 1.5), each time the resistant population is multiplied by 10, the sensitive population is divided by 10 (resp. 100; $\sqrt{10} \simeq 3.2$). So if there were 1% resistant cells initially, then at time to progression, there will be 1% sensitive cells (resp. about 0.01%; about 10.5%). This shows that unless the initial proportion of resistant cells is very large, or treatment is very inefficient against sensitive cells, the MTD treatment will eliminate the vast majority of sensitive cells before progression.

Thus, the difference in times to progression mostly comes from the difference in resistant populations. Under the MTD treatment, the sensitive population disappears more slowly than under its idealized counterpart. As a consequence, the resistant population still somewhat competes with sensitive cells, and develops more slowly (Fig. 1c). The MTD treatment is thus expected to lead to a longer time to progression than its idealized version. This is especially true if treatment is relatively inefficient. In that case, by the time sensitive cells have been crushed, resistant cells are already abundant. It follows that tumour size is never very low, so that resistant cells never develop very quickly.

To quantify this phenomenon in the case of a Norton-Simon kill rate, recall that under MTD, the quantity $SR^{\lambda C_{max}}$ is constant. It follows that the tumour reaches its smallest size when $S = R/(\lambda C_{max} - 1)$. Its size is then:

$$N = \frac{\lambda C}{\lambda C - 1} \times \left[(\lambda C - 1) S_0 R_0^{\lambda C - 1}\right]^{1/\lambda C}, \text{ with } C = C_{max}$$

Some values of this minimal size are given in Supplementary Table 9, assuming $S_0 = 10^{10}$ and $R_0 = 10^6$. It confirms that, for modest treatment effects ($C_{max} \leq 2$), the minimal tumour size under MTD is much higher than under ideal MTD (that is, than the initial resistant population).

Finally, the fact that few sensitive cells remain at the time of progression implies that, after progression, MTD and ideal MTD have similar dynamics. As a result, the difference in survival times should not be much higher than the difference in times to progression. This is what we observe in simulations (Table 1, Figs. 2d, 2f, Extended Data Figs. 7 and 6)

4.5. **MTD and containment.** Ideal containment at N_0 always leads to a higher time to progression than ideal MTD, and with a Gompertz model, typically substantially so, unless the tumour is initially very resistant. The difference in time to progression between the more realistic versions – containment at N_0 and MTD – is smaller. If treatment is not very efficient, MTD may even lead to a higher time to progression than containment. For instance, in main text Model 3, if parameter values (other than R_0) are as in main text Table 2, this occurs whenever the initial fraction of resistant cells is higher than about 1% if $\lambda C_{max} = 2$ (Fig. 2d) and than about 0.1% if $\lambda C_{max} = 1.5$.

There are two explanations. First, low treatment efficiency decreases time to progression under containment. Indeed, progression then occurs as the tumour is still quite sensitive (see Fig. 2g, and Section 4.2). Second, as discussed in Section 4.4, low treatment efficiency makes MTD less problematic. Supplementary Table 9 shows that, for $\lambda C_{max} = 1.5$, the minimal tumour size under MTD is only slightly below 10^9. The average size before progression will be substantially higher than 10^9, compared to $N_0 = 10^{10} + 10^6 \simeq 10^{10}$ for containment at the initial size. In log-scale, this is not a huge difference. Thus, resistant cells would develop only slightly slower under containment than under MTD. With a higher initial resistant population, this advantage of containment is even lower, and need not compensate the fact that under containment, progression requires a lower resistant population size than under MTD, due to the larger remaining sensitive population.

SUPPLEMENTARY TABLE 9. **Minimal tumour size under MTD.** These numbers are valid for any density-dependent model (6), assuming $S_0 = 10^{10}$ and $R_0 = 10^6$

λC_{max}	1.1	1.25	1.5	2	3	5	10
Minimal N	5.9×10^9	2.6×10^9	8.7×10^8	2×10^8	4.1×10^7	1.0×10^7	3.5×10^6

However, if containment is made at a higher level, the average tumour burden during the stabilization phase is larger, and the benefit of containment over MTD in terms of the time to progress beyond size N_{ref} is expected to be greater (compare Figs. 2d and 2h). Moreover, even when MTD and containment at N_0 are comparable in terms of time to progression, the resistant population is always smaller under containment, leading to longer times to treatment failure and longer survival times under containment than under MTD. This is seen in simulations (Figs.2d, 2e, 2f).

Finally, Extended Data Fig. 5 compares containment and MTD in a Gompertzian growth model, with and without mutations after treatment initiation, for two different mutation rates. It suggests that, while complicating the analysis and the obtention of explicit or semi-explicit formulas, taking into account ongoing mutations does not substantially affect outcomes (see also Supplementary Table 6).

4.6. **Impact of varying C_{max}.** Extended Data Fig. 6 further explores the impact of varying the resistant population size R_0 and the maximal tolerated dose C_{max} on containment at the maximal tolerable size, MTD, and idealized versions. The doses considered have the following interpretation: If $C_{max} = 0.8$ then the sensitive cell population keeps growing under MTD, but 5 times slower than in the absence of treatment. If $C_{max} = 1.5$ (respectively 5) then the sensitive population decreases twice as slowly (respectively, four times faster) under MTD than it would increase in the absence of treatment.

In the first row, $R_0 = 2.3 \times 10^5$. If $C_{max} = 0.8$ (panel a) then there is no stabilization phase under containment. Containment at N_{tol} then boils down to delayed MTD. The time to treatment failure is the same as under no treatment, and much lower than under MTD. Nevertheless, survival time is still higher than under MTD (though this would not be true for even lower values of C_{max}). Tumour composition at the time of death is very different between treatments: less than 5% of cells are resistant under containment at N_{tol}, versus 66% for MTD. Thus, under MTD, even though the sensitive population always grows, death occurs mostly due to resistant cells. Since tumour size is never reduced under MTD in this scenario, resistant cells develop much slower than under ideal MTD, leading to a much larger survival time.

If $C_{max} = 1.5$ (panel b), the sensitive population size decreases under MTD but relatively slowly. The minimal tumour size under MTD is much higher than under ideal MTD, leading to a substantial difference between the two treatments. Under containment, there is a stabilization phase that lasts until the tumour is 1/3 resistant. Given the low initial resistant population, there is little difference between growing from R_0 to $N_0/3$ and growing from R_0 to N_0, and so there is little difference between containment and ideal containment. Under all treatments, the tumour is almost fully resistant at the time of death (2% of cells are sensitive under containment, and 0.001% under MTD).

If $C_{max} = 5$ (panel c), the sensitive population decreases much faster than the resistant population increases, and there is very little difference between idealized and non-idealized treatments.

In the second row, $R_0 = 10^8$. Since the tumour is initially much more resistant, the tumour size never becomes very low, even under ideal MTD. As a result, there are smaller differences between treatments, but otherwise the impact of varying C_{max} is similar. For $C_{max} = 0.8$, tumour composition at the time of death depends substantially on treatment: 89% of cells are resistant under MTD, but only 54% under containment at N_{tol}. For $C_{max} = 1.5$ and $C_{max} = 5$, the tumour is almost fully resistant by the time of death under all treatments.

4.7. **Constant dose and containment.** Survival time under constant dose and delayed constant dose treatments in main text Model 3 have been studied by Monro and Gaffney (2009) [11]. A key insight is that there is an optimal balance between limiting the expansion of sensitive cells, and keeping enough of them to slow down the growth of resistant cells. In other words, a tradeoff between dying from sensitive cells and dying from resistant cells. Constant doses that lead to high survival time are such that at the time of death, the populations of resistant and sensitive cells are of the same order of magnitude. Here we are also interested in time to progression and time to treatment failure, and in comparing with containment.

In Model 3, among constant dose treatments, survival time is maximized by the dose $C = 0.74$ (Supplementary Table 6 and Extended Data Fig. 7).[17] Being smaller than the dose used for containment (which is always greater than 1), the optimal constant dose leads to a smaller resistant population, while still significantly slowing down the growth of sensitive cells. This treatment strategy turns out to prolong survival more than either containment or ideal containment at the initial size N_0 (Supplementary Table 5). This

[17]According to our simulations, the dose that maximizes survival time among doses given immediately is $C = 0.74$ instead of the dose $C = 0.9$ reported by Monro and Gaffney (2009), which however is not consistent with the curves of their Fig. 1. This seems to be a simple typo: in Fig 1 of [11], point A visually seems to corresponds to $C \simeq 0.5$ and point B (the optimum) to $C = 0.74$ as we find. There seem to be also typos in their description of Figs. 2 and 6. This does not change the study's key messages, which we agree with.

does not violate our optimality results because ideal containment at N_0 maximizes time to progression, not survival time. The dose $C = 0.74$, however, is far from maximizing survival time among all possible treatments (Supplementary Table 5): treating even less initially represses resistant cells more efficiently, while treating more eventually prolongs survival by diminishing the sensitive population once this becomes necessary. Containment at a high threshold does both, leading to longer survival.

As discussed in the main text, containment may be mimicked by delaying treatment and then applying a dose $C = 1/\lambda$, or slightly higher. There are however two issues. First, as mentioned in the main text, the dose that allows stabilizing tumour size is bound to be patient-dependent. By adjusting the dose as a function of patient's response, containment allows the clinician to arrive at the right dose without foreknowledge. Second, treatment response, in practice, is likely to be much less predictable than our model suggests. In a pre-clinical trial, it was found that, possibly due to normalization of tumour vasculature, tumour control could be achieved by applying progressively lower doses [12]. In a clinical trial of intermittent containment (adaptive therapy) for patients suffering from metastatic castration resistant prostate cancer, tumour size cycled less regularly than models predicted [1]. This suggests that even for a given patient with known tumour characteristics, delayed constant doses might not mimic containment as well as our model suggests, and hence an adaptive protocol is necessary to even approximately stabilize tumour size.

5. Impact of resistance costs on the best possible outcome and on clinical benefits of containment

5.1. **Justification of main text Figure 4b.** We discuss here the impact of competition and resistance costs on the best possible outcome for the following model (Model 4 in the main text):

$$\begin{aligned}\dot{S}(t) &= \rho_s \left[\ln\left(\frac{K_s}{S(t)+\alpha R(t)}\right)\right](1-\lambda C(t))S(t),\\ \dot{R}(t) &= \rho_r \ln\left(\frac{K_r}{R(t)+\beta S(t)}\right)R(t).\end{aligned}$$

If sensitive cells are eliminated by a high-dose treatment, then the resistant population size, hence tumour size, will grow to K_r, unless the patient dies before. Such a treatment would thus result in a tolerable long-run outcome (i.e. tumour size always below N_{tol}) only if $K_r \leq N_{tol}$. If $N_{tol} < K_r < N_{crit}$, the long-run tumour size would be non-lethal, but intolerable. If $K_r > N_{crit}$, a high dose treatment leads to death.

Whether containment strategies can do better depends on whether β is greater than 1, that is, whether additional sensitive cells inhibit the growth of resistant cells more than additional resistant cells would. If $\beta \leq 1$, then $R + \beta S \leq R + S = N$. Thus, as long as $N < K_r$, $R + \beta S < K_r$, and the resistant population grows ($\dot{R} > 0$). In that case, containment strategies may gain time, but cannot change the long-run outcome.

If $\beta > 1$, then provided that the initial resistant population is low enough, the tumour could be stabilized around $S = K_r/\beta$, $R = 0$, hence a total tumour size of $N = K_r/\beta$. The tumour cannot be stabilized at a lower size. Indeed, if $N < K_r/\beta$, then since $\beta \geq 1$, $R + \beta S \leq \beta N < K_r$, hence the resistant population grows. The best long-run outcome is thus a tolerable tumour size if $K_r/\beta < N_{tol}$, a non-lethal but intolerable tumour size if $N_{tol} < K_r/\beta < N_{crit}$, and eventual death if $K_r/\beta > N_{crit}$.[18]

If β is very high, that is, if sensitive cells strongly inhibit the growth of resistant cells, then it could be that $K_r/\beta < N_{tol}$ though $K_r > N_{crit}$. In that case, an aggressive treatment would lead to death, even though a containment strategy would have allowed stabilizing tumour size at a tolerable level forever.

Of course, any conclusion that under some circumstances containment could last forever is dubious, as our model then loses validity. If containment is expected to last for a very long time, a model that better accounts for the long-term evolution of the tumour should be developed, taking into account the appearance of new cell phenotypes.

5.2. **Approximate formula for the benefit of containment with resistance costs.** We derive here an approximate formula for the relative benefit of ideal containment versus ideal MTD in terms of time to treatment failure:

$$\frac{t_{fail}(idContN_{tol})}{t_{fail}(idMTD)},$$

[18]Favourable outcomes need not be attainable if the initial tumour is too resistant.

for the above model (Model 4 in the main text). This formula is used to plot Fig. 4a in the main text. The approximation is valid if resistant cells are initially very rare and do not grow much more quickly than sensitive cells in the absence of treatment. Since ideal MTD instantly eliminates sensitive cells, resistant costs introduce no difficulty. The time to treatment failure is given by (see Section 3):

$$t_{fail}(idMTD) = \frac{1}{\rho_r} \ln\left(\frac{\ln(K_r/R_0)}{\ln(K_r/N_{tol})}\right)$$

(unless $K_r \leq N_{tol}$, that is, $\gamma \geq K_s/N_{tol} \simeq 28.6$, in which case a resistant tumour is benign, always tolerable, and time to treatment failure is infinite).

To compute the time to treatment failure of ideal containment, we distinguish two phases: the growth until N_{tol}, and the stabilization phase. Consider the first phase. Assuming that the initial frequency of resistant cells is very small, and that they do not expand much faster than sensitive cells, then the tumour remains almost fully sensitive during this phase. The dynamics of the total population N may then be approximated by the dynamics of a fully sensitive tumour:

$$\dot{N} = \rho_s N \ln(K_s/N).$$

It follows that the time it takes for the tumour to grow from N_0 to N_{tol} is approximately:

$$t_{N_0 \to N_{tol}} \simeq \frac{1}{\rho_s} \ln\left(\frac{\ln(K_s/N_0)}{\ln(K_s/N_{tol})}\right). \tag{14}$$

Moreover, during this phase (with the approximation $S = N$, $R = 0$, to compute the per-cell growth rates),

$$\frac{1}{\rho_r}\frac{\dot{R}}{R} - \frac{1}{\rho_s}\frac{\dot{S}}{S} \simeq -\ln(K_s/K_r).$$

A new approximation $S = N$ leads to:

$$R \simeq R_0 \left(\frac{N}{N_0}\right)^{\rho_r/\rho_s} \exp(-t\rho_r \ln(\beta K_s/K_r))$$

so that, letting R_1 denote the resistant population size at the beginning of the stabilization phase:

$$R_1 \simeq R_0 \left(\frac{N_{tol}}{N_0}\right)^{\rho_r/\rho_s} \exp(-t_{N_0 \to N_{tol}}\rho_r \ln(\beta K_s/K_r)).$$

That is,

$$R_1 \simeq R_0 \left(\frac{N_{tol}}{N_0}\right)^{\rho_r/\rho_s} \exp\left(-\frac{\rho_r}{\rho_s} \ln\left(\frac{\ln(K_s/N_0)}{\ln(K_s/N_{tol})}\right) \ln(\beta\gamma)\right) \tag{15}$$

with $\gamma = K_s/K_r$. Finally, the length t_{stab} of the stabilization phase depends on whether the resistant population grows or not when the tumour reaches N_{tol}. If it decreases (which is the case if $(1-\beta)R_1 + \beta N_{tol} \geq K_r$, which essentially boils down to $\beta\gamma > K_s/N_{tol} \simeq 28,6$ for initially rare resistant cells), then the treatment never fails:

$$t_{stab} = +\infty.$$

Otherwise,

$$t_{stab} = \frac{1}{\rho_r} \int_{R_1}^{N_{tol}} \frac{dR}{Rg(R)} \text{ with } g(R) = \ln\left(\frac{K_r}{R + \beta(N_{tol} - R)}\right) \tag{16}$$

and R_1 is given approximately by (15). Summing the terms in (14) and (16) leads to an approximation of time to treatment failure under ideal containment at N_{tol} since:

$$t_{fail}(idContNtol) = t_{N_0 \to N_{tol}} + t_{stab}.$$

The formula is not precise for very low values of β, because resistant cells then grow much more quickly than sensitive cells as long as they are rare, so that the approximation of an almost fully sensitive tumour during the growth phase from N_0 to N_{tol} need not be appropriate. The comparison of Fig. 4a and Extended Data Fig. 8 shows that the figure obtained from this approximate formula in a Gompertzian growth model is similar to figures obtained by simulations, which require heavy computation.

Remark: Integrating from R_1 to R_2 in (16), where R_2 is the resistant population size when containment fails (see Section 3.1.4) leads to a formula for time to treatment failure under containment (as opposed to ideal containment). Moreover, the same method (approximating tumour growth by the growth of a fully

sensitive tumour in the initial phase) allows one to find approximate formulas for time to treatment failure for more general models.

The case $\beta = 1$. For $\beta \neq 1$, we were unable to solve explicitly the integral in (16) and had to evaluate it numerically. But if $\beta = 1$, computing this integral is easy, since $g(R)$ is then constant. This leads to:

$$(\text{Case } \beta = 1) \quad t_{stab} = \frac{1}{\rho_r} \frac{\ln(N_{tol}/R_1)}{\ln(K_r/N_{tol})}.$$

We then obtain an explicit approximate formula for the time to treatment failure under ideal containment. This formula is simpler when $\rho_r = \rho_s = 1$. Letting

$$A = \ln\left(\frac{\ln(K_s/N_0)}{\ln(K_s/N_{tol})}\right),$$

we then find:

$$(\text{Case } \beta = 1,\ \rho_r = \rho_s = 1) \quad t_{fail}(idCont) \simeq A + \frac{\ln(N_0/R_0) + A\ln(\gamma)}{\ln(K_r/N_{tol})}.$$

The ratio is then approximately:

$$(\text{Case } \beta = 1, \rho_r = \rho_s = 1) \quad \frac{t_{fail}(idCont)}{t_{fail}(idMTD)} \simeq \frac{A + \frac{\ln(N_0/R_0) + A\ln(\gamma)}{\ln(K_r/N_{tol})}}{\ln\left(\frac{\ln(K_r/R_0)}{\ln(K_r/N_{tol})}\right)}.$$

6. Issues with containment

As mentioned in the main text, by identifying general assumptions ensuring that containment is superior to more aggressive strategies, we also clarify that if these assumptions are not satisfied, containment might do worse than MTD.[19] We discuss here what would happen if three of our assumptions are relaxed: what if there is no competition between sensitive and resistant cells? what if ongoing mutations are taken into account? and what if all tumour cells are partially sensitive to treatment? Other potential issues with containment are pointed out in the Discussion section and in [24].

6.1. What if there is no competition between sensitive and resistant cells?

Although low-dose therapy might have various advantages – such as reduced toxicity and stabilization of the tumour microenvironment – the essential motivation for containment strategies is to exploit competition between sensitive and resistant cells. Accordingly, we have assumed that the growth rate of resistant cells decreases as the number of sensitive cells increases. The growth of every tumour is ultimately limited by available resources such as space, glucose and oxygen. A longstanding consensus view is that human tumour growth rates begin to slow by the time of treatment initiation [21, 25]. Yet it has also been suggested that some tumours sustain longterm exponential or even superexponential growth via processes such as the accumulation of driver mutations, niche construction, and immune escape [23].

If the growth of the resistant population is exponential ($\dot{R}(t) = \rho_r\, R(t)$, a limit case of our assumptions) then the resistant population dynamics are independent of treatment. It follows that ideal MTD and ideal containment at the initial size lead to the same time to progression: $\frac{1}{\rho}\ln(N_0/R_0)$, which is the time it takes for the resistant population to increase by a factor of N_0/R_0. Ideal MTD and ideal containment also lead to the same time to treatment failure and the same survival time (Extended Data Fig. 2). When a constraint on the maximal tolerated dose is taken into account, MTD is predicted to be better than containment, since it results in the same resistant population but fewer sensitive cells. However, the gain is mostly in terms of time to progression. For survival time, provided that the tumour eventually becomes mostly resistant, the difference between treatments, and in particular between containment and MTD, remains modest.

If tumour growth is superexponential ($\dot{R}(t) = \rho g(N(t))\, R(t)$, with $g(N)$ increasing in N) then containment can be substantially inferior to MTD – even for idealized treatment strategies – in terms of both time to progression and survival time (Extended Data Fig. 2). For particular functions g, the magnitude of the advantage of MTD over containment can be examined using the explicit formulas in our Supplementary material (Section 3), which remain valid in this case.

Another scenario that permits aggressive treatments to be considerably better than containment is when sensitive cells benefit resistant cells via mutualism, parasitism, or commensalism more than they

[19] In other words, one of the reasons why several authors, including ourselves, found that containment is superior to MTD might be that they used similar models, which do not take enough into account factors that might be detrimental to containment.

harm them via competition. Beneficial interactions between cancer cells have been identified [26, 27] but their importance in human tumour development remains to be determined.

In summary, although it can be argued that there is probably little to lose and potentially much to gain from using containment strategies even when intra-tumour dynamics are poorly characterized [6], a more prudent approach would be to use containment strategies only when cell-cell competition is believed to be strong. This will require developing ways of characterizing cell-cell interactions and measuring intra-tumour competition.

6.2. **What if all tumour cells are partially sensitive to treatment?** If resistant cells retain some sensitivity to treatment then the basic logic changes in two ways. First, if resistant cells are sufficiently sensitive, then MTD can cure the tumour. This is not a case that concerns us, since our goal is to find alternative treatments when MTD is expected to fail. Second, even if a cure is impossible, there are now two ways to fight resistant cells: treating at low dose (to maintain competition with sensitive cells) or aggressively (to exploit partial sensitivity). Since competition with sensitive cells weakens as the sensitive population is depleted, treatment failure can be delayed by switching from a containment strategy to MTD at an appropriate time before treatment failure, but at the cost of increased toxicity. Whether the gain from switching to MTD is typically small or substantial remains to be investigated but, in general, the difference in outcomes for containment versus MTD is smaller when all cells are partially sensitive to treatment. If resistant cells are sufficiently sensitive then MTD may even be superior to pure containment.

If resistant cell frequency and sensitivity are unknown then we face a conundrum. Should we treat at high dose after low dose treatment failure? If the tumour is already fully resistant then any further treatment will incur needless toxicity. If resistant cells are fully resistant but some sensitive cells remain then it might be better to maintain a low dose. But if resistant cells retain some sensitivity then treating at high dose after initial treatment failure may be the best option, subject to treatment toxicity. To make the best choice, clinicians will require new methods for assessing tumour composition and sensitivity during therapy. Determining optimal strategies in the case of partial or unknown treatment sensitivity is an important topic for future theoretical research. In particular, when it may be proved that it is optimal to first contain the tumour and then switch to MTD, clinically implementable methods to determine a close to optimal switching time should be developed.

6.3. **What if ongoing mutations are taken into account?** Resistance mutations occurring after treatment initiation result in a trade-off: sensitive cells inhibit the resistant population via competition, but boost it via mutation. Due to this trade-off, it has been shown that ideal containment is theoretically worse than ideal MTD if the initial resistant population is below a certain threshold, which depends on the mutation rate and the nature of competition [8]. The question then is whether this scenario is plausible.

Assuming Model 2 with the addition of random mutation, our own analysis (to be further developed in a companion paper) reveals that if the initial resistant population size is consistent with the mutation rate then mutations occurring after treatment initiation have very little impact on the clinical gains due to containment (less than 1% in a model with no resistant costs). This is supported by numerical simulations (Extended Data Fig. 5). Unless the predicted benefits of containment versus MTD are already very small then ongoing mutation can be neglected. Our analysis is however limited to two-type models with random mutation from the sensitive to the resistant phenotype (as in previous studies [6, 8, 11]). Other types of mutation (e.g., drug-induced mutations, driver mutations) may have more substantial effects [28, 29].

7. Containment at the initial size in practice

One of our findings is that, at least for our simple models, the precise way to implement containment treatments is not essential. Nevertheless, we discuss here how containment at the initial tumour size N_0 could be attempted in practice: how should the initial dose be chosen? how to adapt the dose during the course of treatment? how many measurements are likely to be needed before finding a dose that approximately stabilizes tumour size? We assume that some biomarker allows us to estimate tumour size (or its variation). This biomarker level is measured at times t_0, t_1,...,t_k,..., leading to an estimated tumour size of N_k at time t_k (or an estimated ratio N_k/N_0). A constant dose C_k is given between times t_k and t_{k+1}. Though the timing of the measurements is important, we focus on the choice of the doses C_k.[20]

[20]It makes sense to have shorter time intervals between the first measurements, in order to assess patient's specific reaction to treatment, and also when recent measurements suggest a quick evolution of tumour size, or measurements errors.

7.1. **Some simple protocols.** We first discuss some simple protocols, before proposing a slightly more elaborated one.

Downward titration: start with the maximal tolerated dose, and then decrease the dose by a certain fraction of the maximal tolerated dose until tumour size (or rather, the biomarker level) starts increasing. E.g. use initially the dose $C = C_{max}$, then $C = 0.9\,C_{max}$, then $C = 0.8\,C_{max}$ and so on, until the dose is low enough for tumour size to increase again. At that point, the dose would remain constant until tumour size becomes higher than at the beginning of treatment (or could be decreased again if for some reason tumour size starts decreasing while it is still below its initial level N_0). Once tumour size becomes higher than N_0, the dose would be incremented upwards until tumour size starts decreasing, and so on. A variant is to use increments that are not a certain fraction of C_{max} but of the current dose. For instance, if the dose C_k at step k is too weak, the next dose could be $C_{k+1} = 1.1C_k$, instead of $C_{k+1} = C_k + 0.1C_{max}$.

Upward titration: similar, but starting with a low dose instead of a high dose, and gradually increasing it until a dose is found that allows to decrease tumour size.

The Gallaher et al. (2018) protocol: Jill Gallaher and collaborators consider a protocol that is essentially a downward titration method but with some twists. First, a treatment vacation occurs if tumour size becomes smaller than half the initial size. Second, the dose does not change if tumour size varied little since the last measurement. With our notation, the protocol may be described as follows: initially, $C_0 = C_{max}$. Later, if $N_{k+1} < N_0/2$, a treatment vacation occurs: $C_{k+1} = 0$. Otherwise,

$$C_{k+1} = \begin{cases} \min(C_{max}, (1+\alpha)C_k^*) & \text{if } N_{k+1}/N_k > 1+\beta \\ C_k^* & \text{if } 1-\beta < N_{k+1}/N_k \leq 1+\beta \\ (1-\alpha)C_k & \text{if } N_{k+1}/N_k \leq (1-\beta) \end{cases}$$

where α and β are parameters (e.g., $\alpha = 0.25$, $\beta = 0.05$), and $C_k^* = C_k$ unless $C_k = 0$, in which case C_k^* denotes the last positive dose given. In other words, if a treatment vacation occurs, the reference dose to determine further modulations does not become zero but remains equal to the last positive dose.[21]

Titration methods have the advantage of being conceptually simple. However, they might be slow in determining an approximately stabilizing dose. For downward titration, this could result in too strong an initial treatment, and competitive release. For upward titration, this could result in the tumour growing very large before treatment is increased sufficiently to stabilize it.

Moreover, the methods we described do not fully take into account how far the current tumour size is from its target, and how much tumour size decreased or increased since the last measurement. For instance, assume that in the Gallaher et al. protocol, $\alpha = 0.25$ and $\beta = 0.05$, so that the dose is increased by 25% if tumour size increased by more than 5%, but does not change if tumour size changed by less than 5% since the last measurement. Except when a treatment vacation occurs, this rule does not depend on whether tumour size if close or far from some target[22]. More importantly, the modulation rule does not differentiate between a tumour that increased by 4% and a tumour that decreased by the same amount, nor does it differentiate between a tumour that increased by 6% and a tumour that increased by 60%. Finally, Gallaher et al.'s protocol is sensitive to the time interval between two measurements and the speed of evolution of the tumour, which may be patient specific: if measurements are frequent, if tumour evolution is slow, or if β is large, then it may be that tumour size never evolves sufficiently between two successive measurements to trigger dose modulation, though in the long run tumour size may evolve substantially.

We now propose some ideas to improve these methods. First, starting from an intermediate dose rather than from a very high or very low dose should somewhat speed up the process of determining a stabilizing dose. How large the initial dose should be depends on how large the tumour currently is, that is, whether the main issue is to quickly avoid tumour size growing larger, or to avoid triggering competitive release.

Second, if, e.g., the first dose is too high, then instead of slightly decreasing it again and again until the tumour starts to rebounce, we suggest to decrease it relatively sharply. It is then more likely that the second dose will be lower than the stabilizing dose, helping tumour size not to drift too far away from its target. Large initial adjustments also help to adapt the treatment sufficiently quickly when patient's reaction is untypical (e.g., the patient is particularly responsive or unresponsive). How sharply the dose should be changed between the first and the second dose would depend on whether tumour size evolved a lot or just a little between the first two measurements.

[21]The description in the original article is somewhat different, but Jill Gallaher kindly confirmed that what was meant and implemented is the above described protocol.

[22]This need not be a defect, it depends whether the emphasis is on stabilizing the tumour at any level, or on stabilizing it close to its initial size.

Third, once the effect of the first two doses is observed, that is, after three measurements, an educated guess for a stabilizing dose could be achieved by building on simple models of tumour growth. This is explained below in Section 7.3. Based on the above considerations, we now propose a protocol taking into account how far tumour size is from target and how much it recently increased or decreased.

7.2. **A new protocol.** A basic family of protocols is as follows (see remarks afterwards for details and refinements). The first two doses are somewhat arbitrary.

1. At time t_0: choose an initial dose expected to at least stabilize tumour size in most similar patients (e.g. in 75% of similar patients).[23]

2. At time t_1: given patient's response to the first dose, choose a dose expected to bring tumour size back towards N_0.

3. From time t_2 on: compute an estimation C_{guess} of the dose that would currently stabilize the tumour, based on recent measurements and a standard tumour growth model, e.g., using formulas of Section 7.3 below. Deliver this dose if $N = N_0$, a higher dose if $N > N_0$, and a lower one if $N < N_0$.

A concrete example is to fix a low and a high threshold, $N_l < N_0$ and $N_h > N_0$, positive parameters γ_1 and γ_2, and to deliver the following dose between time t_k and t_{k+1}:

$$C_k = \begin{cases} 0 & \text{if } N_k \leq N_l; \\ C_{guess}\left[1 - \left(\frac{N_0 - N}{N_0 - N_l}\right)^{\gamma_1}\right] & \text{if } N_l \leq N_k \leq N_0; \\ C_{guess} + (C_{max} - C_{guess})\left(\frac{N - N_0}{N_h - N_0}\right)^{\gamma_2} & \text{if } N_0 \leq N_k \leq N_h; \\ C_{max} & \text{if } N_k \geq N_h \end{cases}$$

Thus, the dose given depends both on the estimated stabilizing dose and on how far tumour size is to its target N_0. A treatment vacation occurs if tumour size falls below the low threshold, and the tumour is treated at the maximal tolerated dose if tumour size increases beyond the high threshold. In between, the dose is a continuously increasing function of tumour size, equal to the estimated stabilizing dose if tumour size is equal to its target N_0. The parameters γ_1 and γ_2 tune whether the emphasis is on stabilizing tumour size ($\gamma_i > 1$) or bringing it back to N_0 ($\gamma_i < 1$). For instance, if γ_2 is significantly larger than 1, then it is only when tumour size approaches the higher threshold N_h that the dose given becomes substantially different from the estimated stabilizing dose.

Some remarks are in order:

a) The above protocol is for containment at the initial size, but may easily be adapted for containment at another target size.

b) A target size, whether absolute or relative to initial tumour size, may prove too large for some patients, in the sense of leading to a low quality of life or other adverse effects. To deal with this issue, the target size could be defined as the minimum of an a priori target size (e.g., the initial size) and the largest tumour size compatible with a satisfying quality of life.

c) Protocols should be adapted to each tumour type and biomarker. If the link between tumour size and biomarker level is known to evolve with time, the protocol should be modified accordingly. [24]

d) If containment treatments become common, data on previous patients should allow to determine the percentage of tumours stabilized by a given dose. This would help choosing the initial dose. For initial clinical trials, an educated guess could be made using the ideas of Section 7.3, provided tumour growth data is available in the absence of treatment and under standard of care.

e) If tumour growth data in the absence of treatment is available for the current patient, then an educated guess of the stabilizing dose for this specific patient could be computed already for the second dose (at time t_1).

f) The second measurement should be made shortly after the first one, since the first dose might be well off the mark due to patients' heterogeneity. The third measurement should also be made quickly if the second one revealed quick evolution of tumour size. Once an approximately stabilizing dose

[23]The choice of 75% of patients is arbitrary, but at least in initial clinical trials, patients and physicians are likely to feel more comfortable with not too low an initial dose. In theory, whether choosing a first dose that would work for an average patient, or for a large majority of patients, depends on whether current tumour size is considered worrying large or not. If the initial tumour size seems way below our hypothetical maximal tolerable size, then starting with a relatively low dose is reasonable. If the initial tumour size is quite large, then starting with a relatively high dose is bound to be preferable.

[24]In Zhang et al.'s (2017) clinical trial of adaptive therapy on metastatic castrate resistance prostate cancer, the biomarker used is prostate specific antigen (PSA). An issue is that cells resistant to the drug used, Abiraterone, may contribute much more to PSA production than sensitive cells, thus an increase in PSA might signal an increase in tumour size or an increase in the fraction of resistant cells.

has been found, tumour should evolve more slowly, and monitoring could become rarer. However, tumour's response to treatment is likely to evolve with time. Thus, regular monitoring remains needed.

g) Tumour's true response, measurements of biomarkers, and the relation between tumour size and biomarkers are likely to be noisy. In order not to rely excessively on a very small number of possibly wrong data points, and to smooth out the noise, methods could be developed to base the estimate of the current stabilizing dose not only on the last three data points but on all available data points. These methods should nevertheless give a greater weight to recent data, to take into account tumour evolution. Here is a simple possibility. Let $C_{guess}(t_k)$ denote the stabilizing dose between t_k and t_{k+1} suggested by the last three data points (from times t_{k-2}, t_{k-1} and t_k). Define the smoothed stabilizing dose by $C_{smooth}(t_2) = C_{guess}(t_2)$, and for $k \geq 3$,

$$C_{smooth}(t_k) = (1-\delta)C_{guess}(t_k) + \delta C_{smooth}(t_{k-1}),$$

where $\delta \in (0,1)$ is a parameter tuning the importance given to recent data compared to older data. More involved methods with an explicit modeling of the noise could also be considered.

h) Different models might give different estimates of the current stabilizing dose. To eventually rely on the best models, a possibility is to use as our estimates for the stabilizing dose a weighted average of estimates produced by a number of different models, with larger weights put on models that fit well previous data points. There is a large literature in statistics and game theory on how to choose the best "expert", in our case, the best model [30].

Complementary considerations on practical implementation of containment treatments may be found in the forthcoming Ph.D. dissertation of Jessica Cunningham.

7.3. **How to make an educated guess for the current stabilizing dose?** We conclude by explaining how to make an educated guess for the stabilizing dose based on the last three measurements. Assume to begin with that a tumour growth-model of the form

$$\dot{N} = Ng(N)(1-\lambda C) \tag{17}$$

is deemed reasonable. Assume also that between t_{k-2} and t_k, tumour size does not evolve too much so that the natural net growth-rate $g(N)$ can be considered approximately equal to some constant g. Denote by $\rho_{k-2} = \frac{1}{t_{k-1}-t_{k-2}} \ln(N_{k-1}/N_{k-2})$ and $\rho_{k-1} = \frac{1}{t_k - t_{k-1}} \ln(N_k/N_{k-1})$ the average per-cell growth-rate on the time intervals $[t_0, t_1]$ and $[t_1, t_2]$, respectively. This leads to:

$$\begin{cases} \rho_{k-2} = g(1-\lambda C_{k-2}) \\ \rho_{k-1} = g(1-\lambda C_{k-1}) \end{cases}$$

Solving this system and noting that for Model (17) the stabilizing dose is $C = 1/\lambda$ leads to:[25]

$$C_{guess} = \frac{\rho_{k-1}C_{k-2} - \rho_{k-2}C_{k-1}}{\rho_{k-1} - \rho_{k-2}} \tag{18}$$

If the kill-rate is not assumed proportional to the dose but to some function of the dose:

$$\dot{N} = Ng(N)(1-\lambda f(C))$$

for instance due to some saturation effect, then the estimated stabilizing dose is such that:

$$f(C_{guess}) = \frac{\rho_{k-1}f(C_{k-2}) - \rho_{k-2}f(C_{k-1})}{\rho_{k-1} - \rho_{k-2}} \tag{19}$$

and can be found by inverting the function f. This formula may also be expressed in terms of doubling times: letting $DT_{k-2} = (\ln 2)/\rho_{k-2}$ and $DT_{k-1} = (\ln 2)/\rho_{k-1}$ denote the tumour's doubling time on the time-intervals $[t_{k-2}, t_{k-1}]$ and $[t_{k-1}, t_k]$ leads to:

$$f(C_{guess}) = \frac{DT_{k-1}f(C_{k-1}) - DT_{k-2}f(C_{k-2})}{DT_{k-1} - DT_{k-2}}$$

The important point is that the exact same formulas are obtained for a variety of other models. For instance, if we use a log-kill rate instead of a Norton-Simon kill rate:

$$\dot{N} = N[g(N) - \tilde{\lambda}f(C)]$$

[25]Note that only relative variations matter, that is, quotients N_{k+1}/N_k. This is handy when the evolution of biomarker level is correlated to the evolution of tumour size but the initial biomarker level is not much informative in itself, as is the case for prostate specific antigen level in prostate cancer.

then we still obtain (19). This remains true with birth-death models, with a Norton-Simon kill rate

$$\dot{N} = N[b(N)(1 - \lambda f(C) - d(N)]$$

or a log-kill rate

$$\dot{N} = N[b(N) - d(N) - \tilde{\lambda} f(C)]$$

under the assumption that the birth and death rates $b(N)$, $d(N)$ are approximately constant.This is because, under these simplifying assumptions, the above four class of models are equivalent. Variants of these models with sensitive and resistant tumour cells, e.g., Model 3, also lead to the same formulas if the frequencies of each cell type may be considered constant between t_{k-2} and t_k. Though we do not expect them to work perfectly, we conclude that the above formulas could provide reasonable initial guesses for stabilizing doses.[26]

[26]Due to measurement errors or some unexpected phenomenon, it might be that though the dose was recently increased: $C_{k-1} > C_{k-2}$, the estimated tumour growth rate also increased: $\rho_{k-1} > \rho_{k-2}$. This is incompatible with our deterministic models and the assumption that the frequency of resistant cells may be considered constant on $[t_{k-2}, t_k]$. The above formulas then should not be used directly, though a smoothened version of the estimated stabilizing dose, as discussed in Section 7.2, could still be a useful indicator.

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