Supplemental Information

Supplemental Methods

Calculate druggability of a cell. Instead of modelling the dynamics of the drug explicitly, such as diffusion, uptake, decay, and perfusion into the tumor, we made the simplifying assumption that the drug will only reach the outer periphery of the tumor. In previous versions of this model [37], this was achieved by only allowing the proliferating cells access to the drug, which were always on the boundary due to quiescence when there was no space to divide. However, adding cell turnover means that cells can die in the middle of the tumor, which opens up space for cells to reenter the proliferation state and therefore be exposed to the drug. Here, we apply the following algorithm for ensuring that only the cells on the periphery of the tumor will be subjected to drug exposure.

At the start of each cell loop, cells are assigned a position in a coarse grid (18x18 pixel grid over a 2700x2700 pixel domain) to determine an approximate neighborhood, which is used to narrow the range of possible neighbor interactions and speed up computation. This same grid structure is used to determine if a cell is on the periphery of the tumor. If the cell is on the periphery, it will be druggable. The peripheral cells are those cells that are on the edge of the mass of cells, which we define explicitly by either 1) there is more than 1 neighboring grid point that has less than 2 cells, or 2) there is only 1 grid point with fewer than 2 cells but those cells are at least a half of a grid length away from the cell in question. Further, the cell must be in the proliferating state to be affected by the drug.

Gleason Classification. The simulation data are classified into a Gleason group (high, mid, and low) based on how several metrics compare to the those from the patient data (from Fig. 6A). First, the virtual patient (simulation) data are grouped into a possible Gleason group based on the change in the number of metastases over the first cycle of adaptive therapy. If there is a decrease in metastases, the virtual patient may only be in the low Gleason group. If there is no change in the number of metastases over the first cycle, it may be classified into any group, and if there is an increase in metastases, it may only be in the high Gleason group. Further, we check the probability that each virtual patient may fit in either group based on the distributions of the other 3 metrics (number of total cycles, drug response time, and regrowth time). Because the patient's tumors sizes are on a much larger scale than those simulated, the time scales will be shorter. This will change the scale of all 3 metrics that we are comparing. Therefore, we do not compare absolute values, but rather we normalize the values in both the patient data set and the simulated data set by their maximum to compare. We assume that the distribution of each metric follows a normal distribution so that we can compute the probability density that a value x_i from the simulated data lies within the distribution of the metric *i* as:

$$\phi_i(x_i, \sigma_i) = \frac{1}{\sigma_i\sqrt{2\pi}} e^{-(x_i-\mu_i)^2/(2{\sigma_i}^2)},$$

where μ_I and σ_I are the mean and standard deviation of the patient distribution. Then for each virtual patient, we calculate the probability that it belongs to a Gleason category as the mean of probabilities over the 3 metrics. If the probability is below 70%, it may exist in that group. If it can exist in multiple groups, it will be classified into the group that has the highest probability. If it does not meet any of these criteria, it will be deemed as not belonging to any group and will be removed from the analysis.

Supplemental Tables

Subject ID	Gleason Score	Pre Abi PSA (ng/ml)	Metastasis sites	1st cycle Δ*m*	1st cycle drug on time (d)	1st cycle drug off time (d)	Number of cycles
1001	8(4+4)	6.06	bone, soft tissue	0	28	112	6
1002	8(4+4)	58.57	bone	unknown	65	84	4
1003	9 (5+4)	68	bone, LN	0	314	402	3
1004	10(5+5)	1.64	bone	1	63	273	1
1005	7(4+3)	95.86	LN	-1	254	110	1
1006	8(4+4)	15.25	bone	0	42	147	8
1007	6(3+3)	109.4	bone	-3	280	552	1
1009	6(3+3)	13.55	bone	-3	228	217	1
1010	7(3+4)	17.33	bone	-6	28	182	1
1011	9(4+5)	2.42	LN, soft tissue	0	150	141	4
1012	8(4+4)	4.17	bone	0	42	193	10
1014	7(4+3)	11.83	bone	0	204	234	2
1015	8 (4+4)	7.25	bone	0	113	88	2
1016	7 (3+4)	34.02	bone	0	85	286	3
1017	9(4+5)	21.59	bone	2	115	619	1
1018	unknown	36.54	bone	4	72	95	1

Table S1. Individual patient metrics collected and analyzed in the adaptive therapy cohort.

Description	**Value or Range**	**Reference**
proliferation rates	0.12-0.48 d^{-1}	estimated
cell diameter	20 μm	estimated
probability of cell death by cell cycle-independent drug	0.6 d^{-1}	estimated
Initial number of cells in metastasis seed	30	set

Table S2. Other parameters that do not vary.

Supplemental Figures

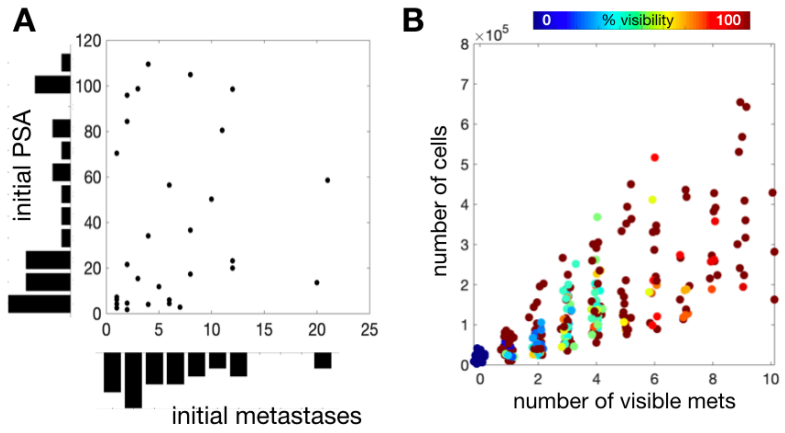

Figure S1. Burden vs. number of visible metastases for A) patients in the mCRPC the adaptive therapy trial (n=16) combined with the historical cohort (n=15) and B) the cohort of 1000 model simulations from Fig. 2E-F. While the patient data shows no apparent correlation between burden (PSA) and initial number of metastases, the simulated cohort does not have data points in the high burden, low metastases region.

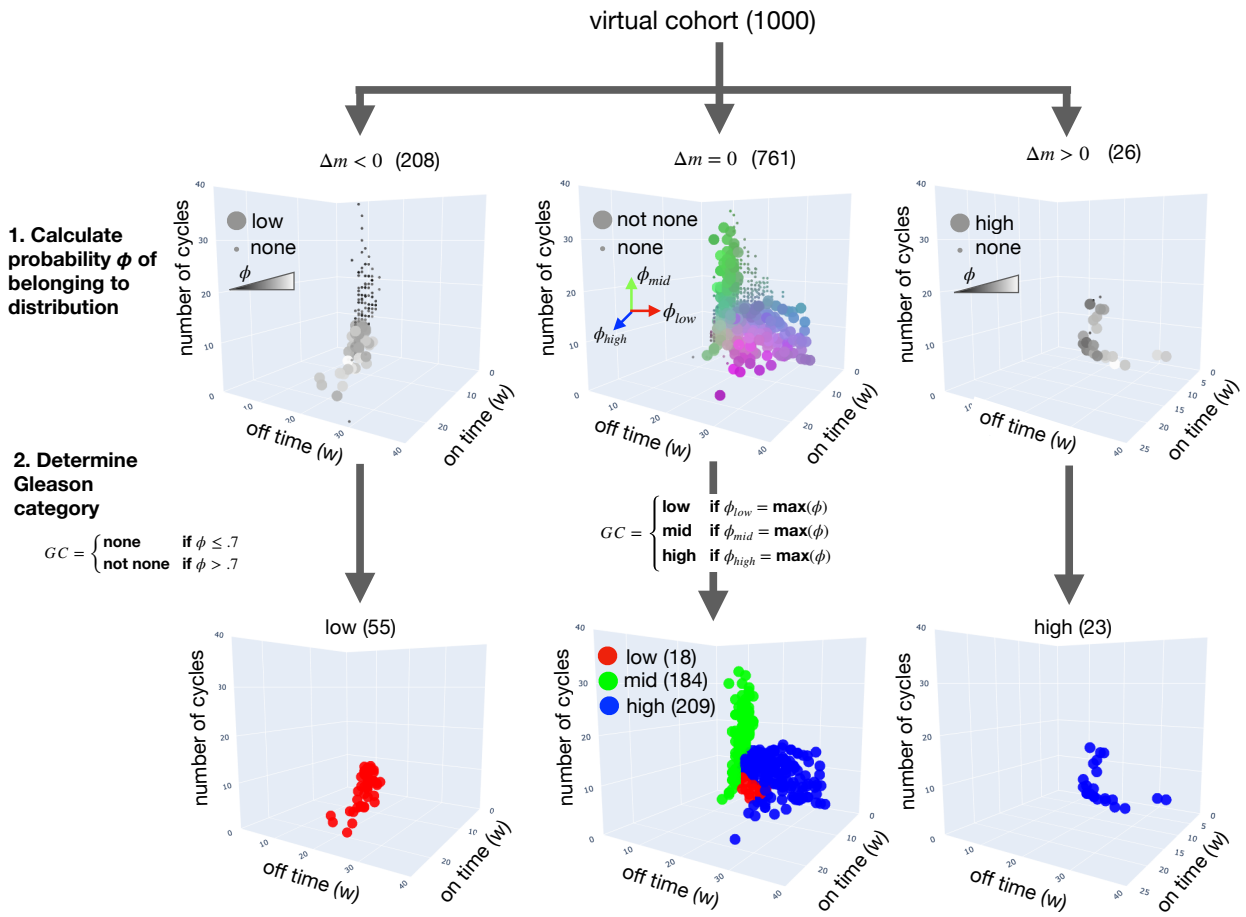

Figure S2. Gleason classification of simulation data. In a 2-step process, each simulation is attempted to be matched to either the low, mid, or high Gleason group observed in the clinical data. In the first step, a simulation is categorized by the change in number of metastases over the first cycle (Δm). Subsequently, a combination of three factors is used to classify the simulation: 1) the total number of cycles, 2) the drug on time during the first cycle, and 3) the drug off time during the first cycle. Specifically, if there is a decrease in m, the simulations may be classified as belonging to the low Gleason group if within 70% of the distribution determined by the data. If there is an increase, the simulations may be classified as belonging to the high Gleason group if within 70% of the distribution determined by the data. If there is no change in the number of metastases, the simulations may be classified as belonging to any Gleason group if within 70% of the distribution determined by the data and will be categorized as the group with the highest probability if they meet the criteria for several groups. The simulation will not be categorized if there is less than 70% probability of belonging to a group (these are shown in each plot as smaller points). The colors in the top row represent the probability of belonging to the group (for the left and right columns lighter is higher and for the middle an RGB color is used based on the probability for existing in the low (R), high (B), or mid (C) groups).

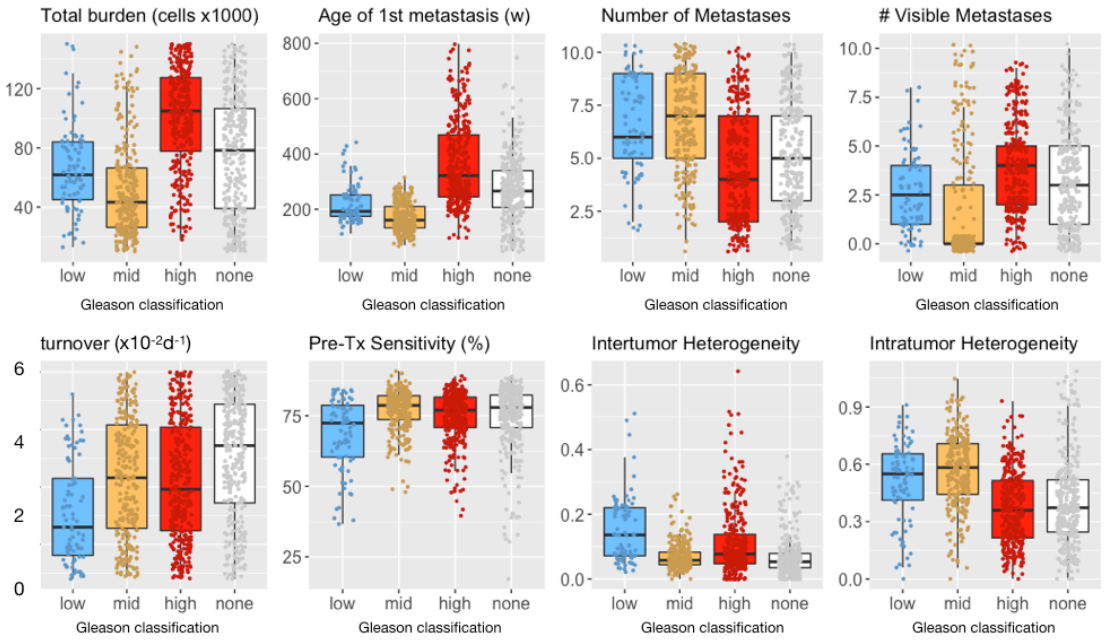

Figure S3. Comparison of the classified Gleason groups for the simulated data over different metrics. The classification is determined using the algorithm in the Supplemental Methods, which is based on data separated into Gleason Score (low=6-7, mid=8, and high=9-10). The category "none" did not fit the criteria to fit into any Gleason classification. The percent of samples in each group are 7.3 %, 18.4%, 23.2%, and 51.1% in the low, mid, high, and none Gleason groups, respectively.

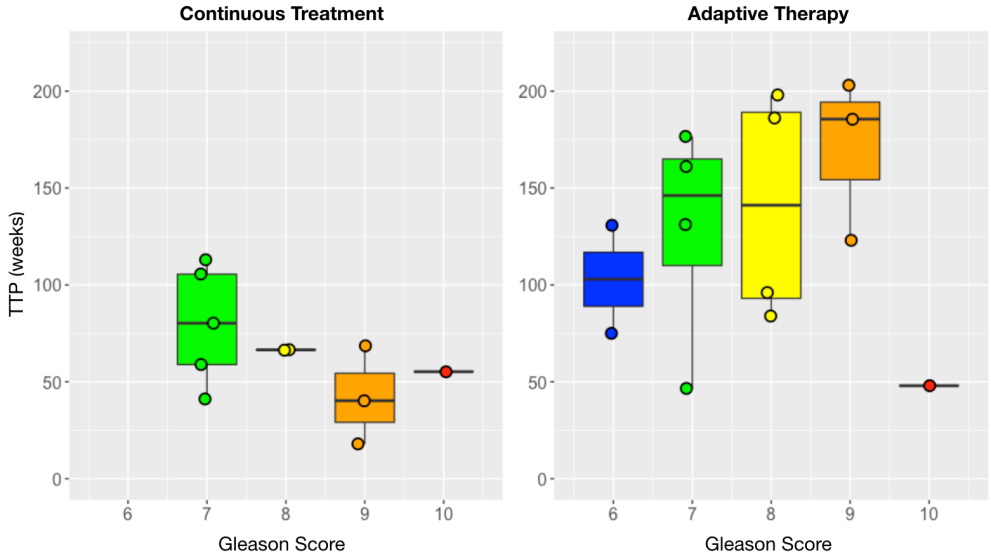

Figure S4. Comparison of time to progression (TTP) over different Gleason scores for continuous treatment (left) and adaptive therapy (right). A historical cohort is used for the continuous treatment patient data (n=12), and the mCRPC trial is used for the adaptive therapy patient data (n=15).