1 Supplementary Information

Table S1: Competition parameters for Lupron and Abiraterone treatment

$c > e$	TP cells have a higher fitness than T- cells when interacting with few T+ (absence of competition)
$a > f$	Interacting with mostly TP cells, T+ gains from the public good and from the new available space in low vasculature regions
$b < d$	Interacting with mostly T- cells, TP cells see little competition near vasculature. Payoffs to T+ cells, b, may be small or zero
$a > b = 0$	T+ cells need the TP cells to succeed in the absence of systemic testosterone
$c > d$	c is likely the largest parameter as TP cells have the highest fitness in a mostly T- tumor without systemic testosterone
$e > f$	Again, TP cells outcompete T- cells in the absence of systemic testosterone

Table S2: Competition parameters for no treatment

$c < e$	T- cells have a higher fitness than TP cells when interacting with many T+, especially in low vasculature regions. Testosterone production by TP production comes at some cost to provide public good to both self (TP) and neighbor (T+). Both c and e should decrease in the pre-treatment condition
$a > f$	T+ cells have a higher fitness than T- cells when interacting with many TP, receiving advantage from the public good. The parameter a should increase in the pre-treatment condition f slightly decrease
$b > d$	T+ cells have a higher fitness than TP cells when interacting with many T- because there is lack of spatial competition near vasculature for T+ cells as testosterone is not being used
$a < b$	T+ cells have a higher fitness competing with T- over competition with TP
$c < d$	Similarly, TP cells have a higher fitness competing with T- over competition with T+
$e > f$	T- cells have less competition for space in a tumor with mostly T+ than with mostly TP. The parameter f should decrease in the pre-treatment condition slightly

Population dynamics

Briefly, we restate a previously published Lotka-Volterra mathematical model used to characterize adaptive treatment of metastatic castrate resistant prostate cancer in figure 3. The model describes competition among three cell types: testosterone-dependent (T+), testosterone-producing (TP), and testosterone-independent (T-), $i = 1, 2, 3$, respectively.

$$\frac{dy_i}{dt} = r_i y_i \left(1 - \frac{\sum_{j=1}^{3} a_{ij} y_j}{K_i} \right) \tag{4}$$

where the intrinsic growth rates, r_i, were parameterized from in vitro cell data ($\vec{r} = [0.0278, 0.0355, 0.0665]$; see (26)). Carrying capacities represent the contribution of each subpopulation to changes in PSA, not the overall cell count of each subpopulation. Under Lupron treatment only, the carrying capacities are given by: $K_1 = 1.5 \cdot 10^4$; $K_2 = 10^4$; $K_3 = 10^4$. Lupron & Abiraterone carrying capacities

are given by: $K_1 = 0.5 \cdot 10^4$; $K_2 = 10^2$; $K_3 = 10^4$ (26). Carrying capacities for dynamics under no treatment are given by: $K_1 = 1.5 \cdot 10^4$, $K_2 = 10^4$, $K_3 = 10^2$. Competitive interactions between these three cell types are summarized in the payoff matrix, A, below.

$$
\begin{array}{c}
\begin{array}{ccc} T^+ & T^P & T^- \end{array} \\
\begin{array}{c} T^+ \\ T^P \\ T^- \end{array}
\begin{pmatrix}
0 & a_{1,2} & a_{1,3} \\
a_{2,1} & 0 & a_{2,3} \\
a_{3,1} & a_{3,2} & 0
\end{pmatrix}
\end{array}
\tag{5}
$$

Competition parameters are described by certain inequalities for given treatment dynamics. We summarize these inequalities in Supplemental Materials for convenience: Table S1 (under treatment) and Table S2 (no treatment) (26, 46, 60). Since there is cell-cell competition and niche partitioning with respect to association with surrounding vasculature, we assume that all coefficients are positive and bounded between 0 and 1. Consistent with ref. (26), two general rules are used to determine the relative values of inter-cell type interactions: 1) T+ cells with no exogenous testosterone are the least competitive cell type and 2) the competitive effect of T- cells is stronger on TP cells than on T+ cells. Unless otherwise noted parameters for untreated dynamics are: $a_{1,2} = 0.8$; $a_{1,3} = 0.4$; $a_{2,1} = 0.7$; $a_{2,3} = 0.5$; $a_{3,1} = 0.6$; $a_{3,2} = 0.9$, for Lupron only are: $a_{1,2} = 0.6$; $a_{1,3} = 0.7$; $a_{2,1} = 0.4$; $a_{2,3} = 0.5$; $a_{3,1} = 0.8$; $a_{3,2} = 0.9$, and for Lupron & Abirateron are: $a_{1,2} = 0.5$; $a_{1,3} = 0.9$; $a_{2,1} = 0.4$; $a_{2,3} = 0.8$; $a_{3,1} = 0.6$; $a_{3,2} = 0.7$.
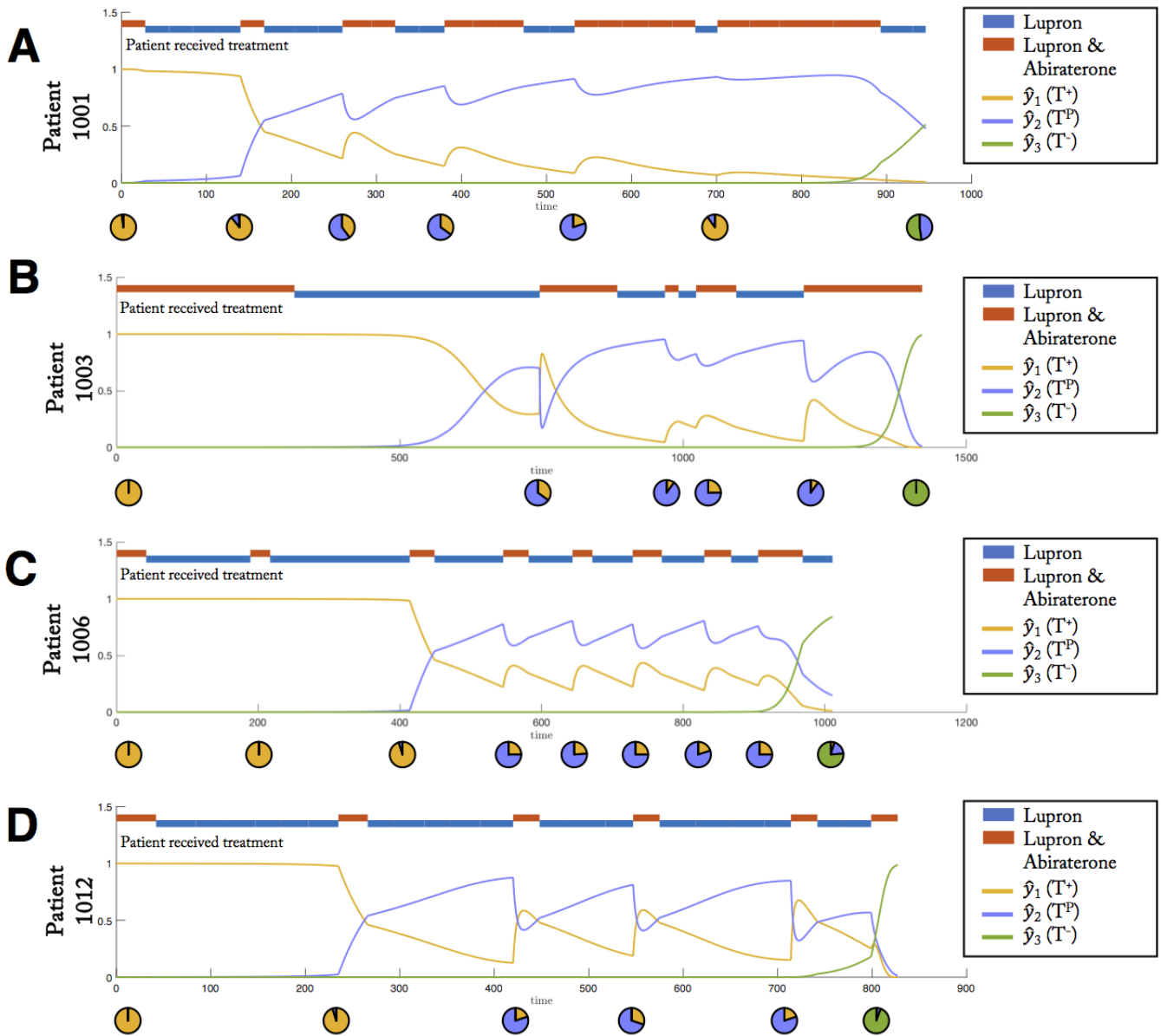
Figure S1: **After-action analysis of patient-specific subpopulations** Normalized subpopulations over time (equation 4) for testosterone-dependent (T+, yellow), testosterone-producing (TP, blue), and testosterone-independent cells (T-, green). Timing of treatment received under clinical protocol is indicated (top) for Lupron & Abiraterone (red) and Lupron only (blue). Parameterization of the model is performed by least-squares fit to PSA data from clinical trial NCT02415621 (see figure 3).