Supplemental Figures

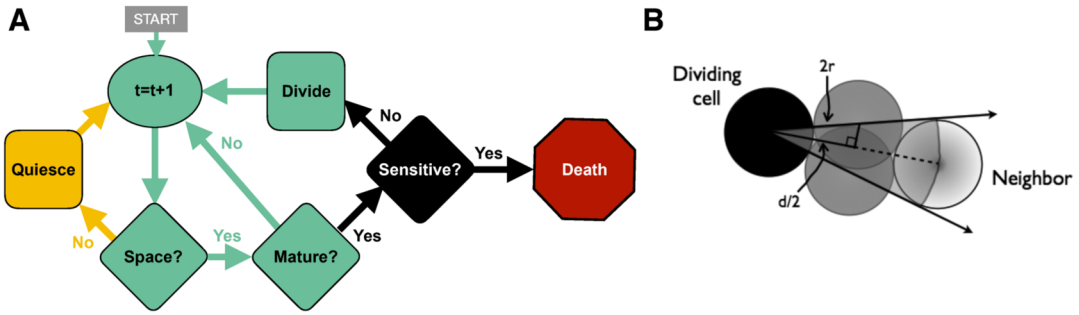

Figure S1. Mathematical model rules. A) Decision-making flowchart for each cell over each time step. Proliferation steps are shown in green, quiescence in yellow, and drug-induced death in black and red. During growth, the green dashed arrow is followed, and during drug application, the black dashed arrows are followed to check whether the drug kills the cell. B) The off-lattice model assumes space limited proliferation, such that a dividing cell with insufficient space for non-overlapping offspring enters a quiescent state.

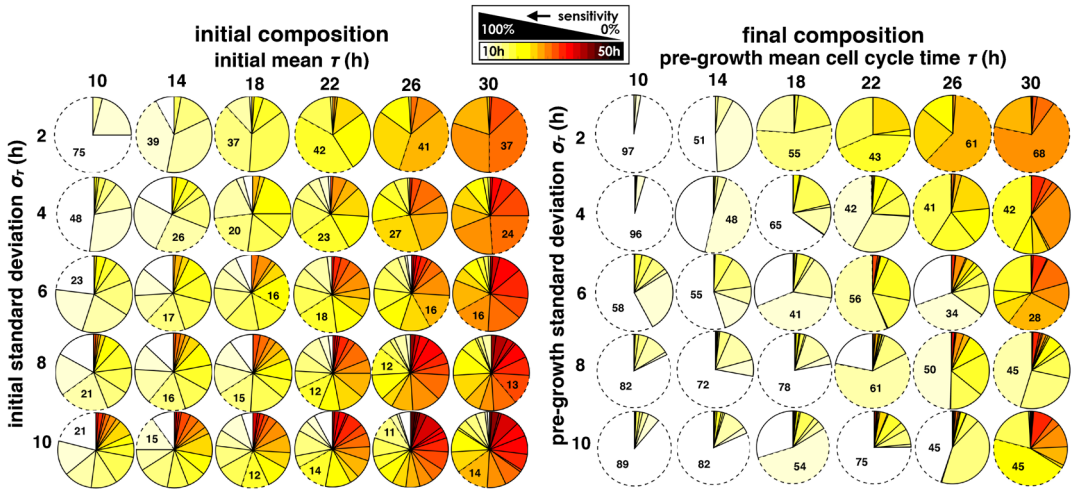

Figure S2. Phenotype distributions before and after growth period. Initial compositions of cell phenotypes are defined by a mean cycle time τ and a standard deviation in cycle time σ_τ. We display in pie charts the fraction of the population occupied by cells with different cell cycle times at the beginning (left) and end (right) of the simulation. The color key gives the cycle time and corresponding drug sensitivity. A pie piece with a dashed border and a number shows the dominant clone and the percent occupied at that time point.

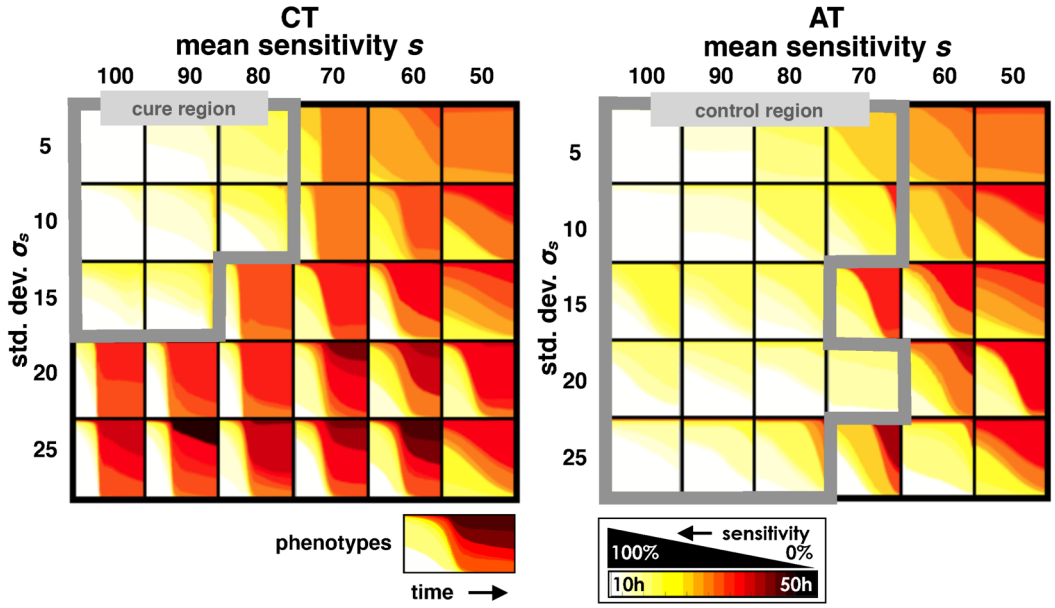

Figure S3. Phenotype distribution dynamics during continuous treatment (CT) and adaptive therapy (AT). Each tumor treated was grown with a normal distribution of sensitivities ranging from 50-100% and heterogeneity (standard deviation in sensitivity) ranging from 5-25%. For each, the relative proportions of phenotypes over time is shown, as depicted by the key shown below the figure. For CT, the tumors cured are outlined in gray. For AT (α=0.25, β=0.05), the tumors controlled are outlined in gray.

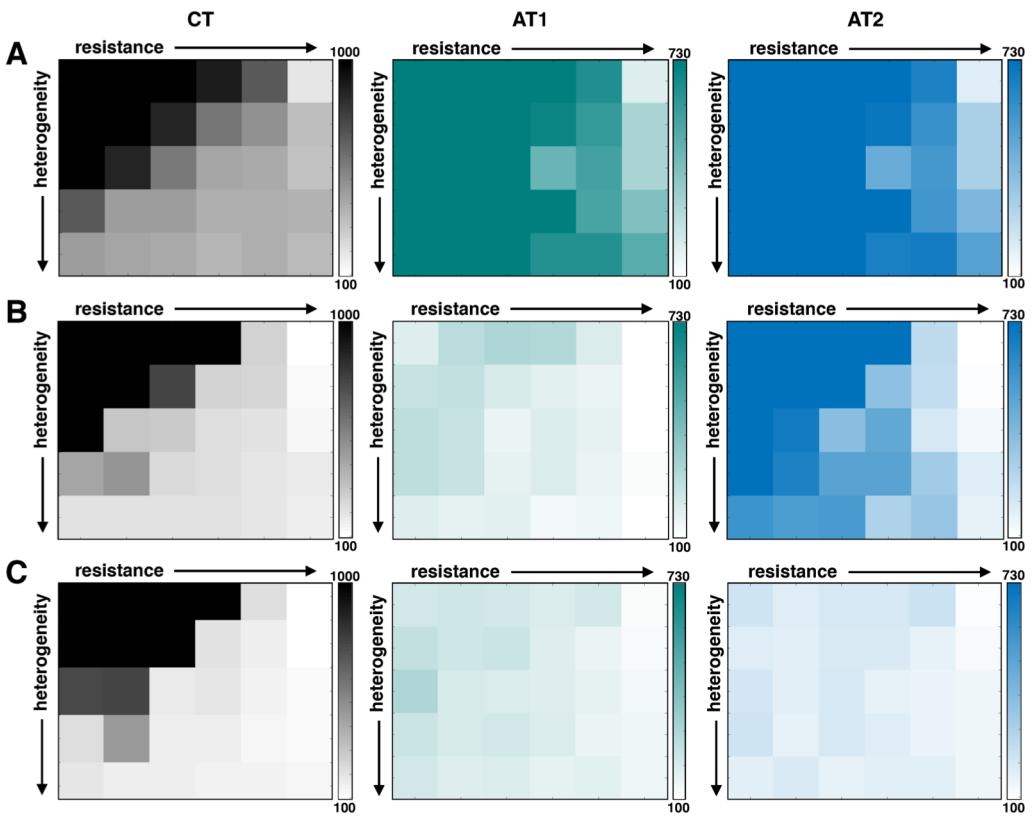

Figure S4. The mean time until recurrence (TTR) for treatment schedules CT, AT1, and AT2 for different migration speeds. A) Cells do not migrate. B) Cells have migration speeds of 5 μm/h. C) Cells have migration speeds of 10 μm/h. The heat map averages 3 runs for each tumor composition and the color key to the right of each heat map shows the TTR in days. For CT, the TTR is set to 1000 if the tumor is cured. For both AT schedules, if the tumor is controlled, the TTR is the end of the simulation: 730 days.

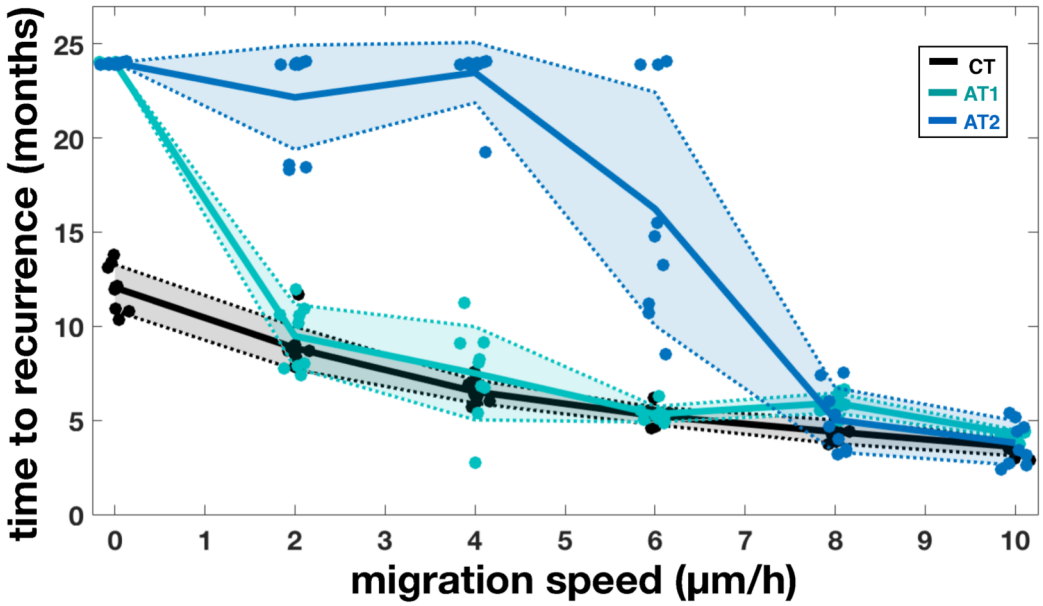

Figure S5. The effect of intermediate migration speeds on time to recurrence given treatment schedules CT, AT1, and AT2. For 10 different tumors grown with the same initial conditions (s=100% and σ_s=25%), each treatment was given until the tumor recurred or the time reached 2 years. The lines represent mean values, the shaded areas around the lines represent standard deviations, and the points are individual simulations.

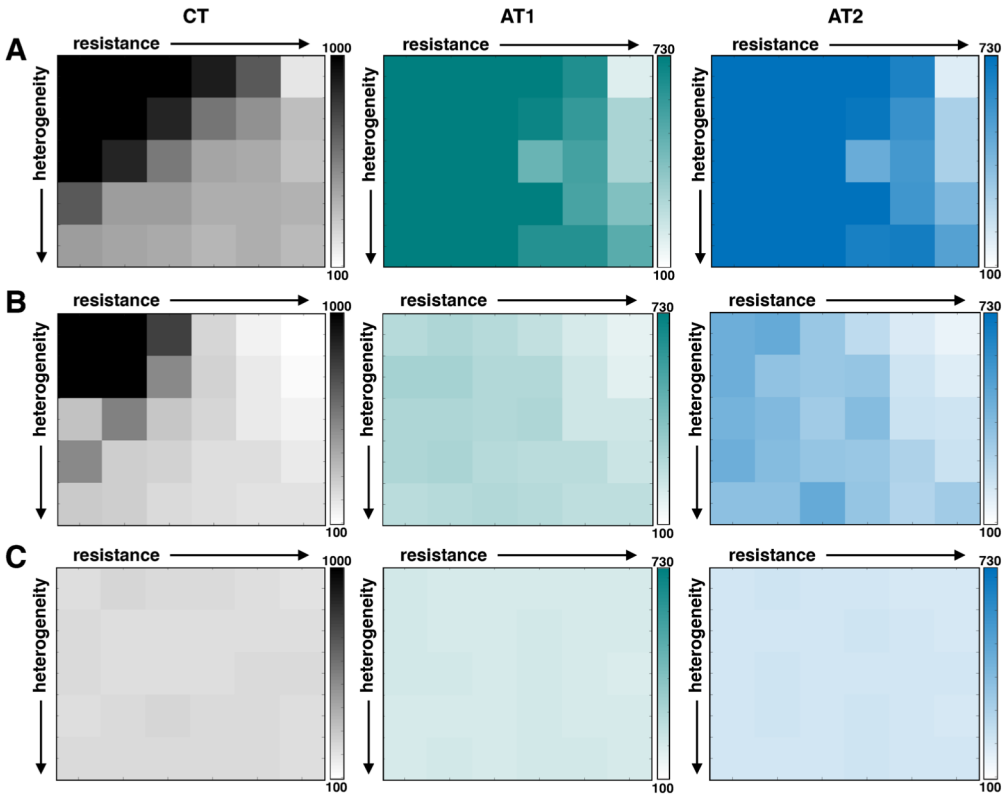

Figure S6. The mean time until recurrence (TTR) for treatment schedules CT, AT1, and AT2 for different phenotypic drift rates. A) Cells do not have phenotypic drift. B) Cells have phenotypic drift; there is a 10% probability at each division that a cell will alter its cycle time by ±1 h or stay the same (ensuring that the IMT stays within the allowed range of 10-50h). C) Cells have phenotypic drift; there is a 100% probability at each division a cell will alter its cycle time by ±1 h or stay the same (ensuring that the IMT stays within the allowed range of 10-50h). The heat map averages 3 runs for each tumor composition and the color key to the right of each heat map shows the TTR in days. For CT, the TTR is set to 1000 if the tumor is cured. For both AT schedules, if the tumor is controlled, the TTR is the end of the simulation: 730 days.

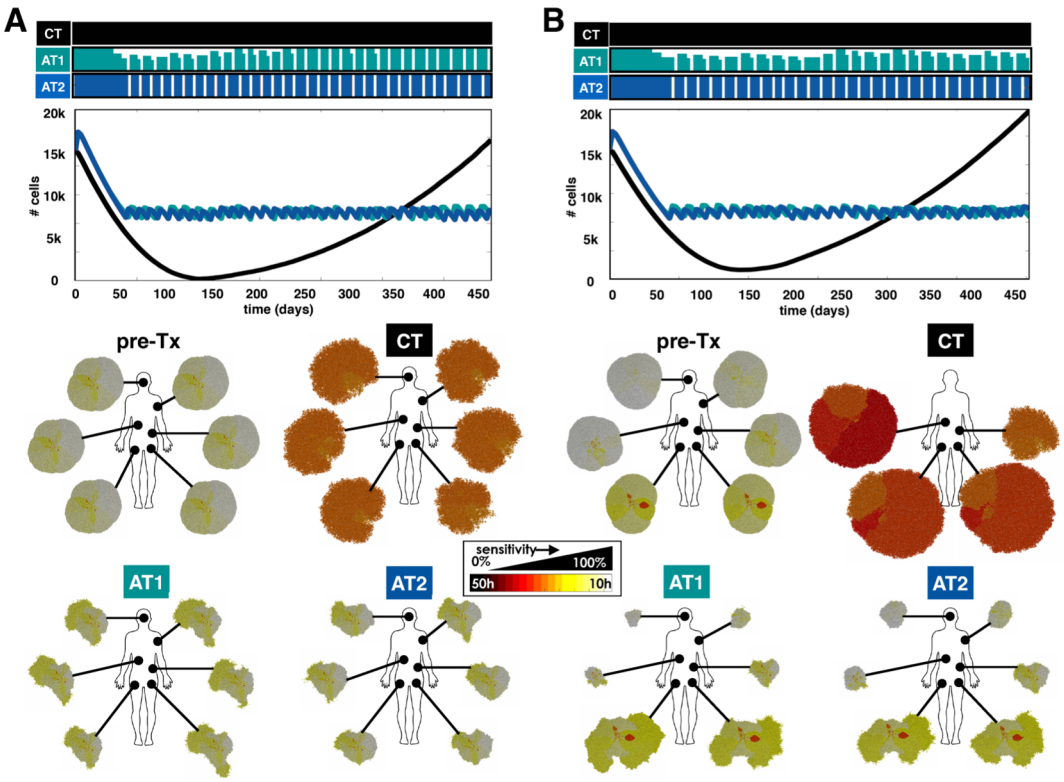

Figure S7. Multiple metastases treated at the same time with CT, AT1, and AT2. A) Metastases of the same composition are treated. B) Metastases with different compositions are treated. The top panels show the dose schedule for each strategy with the bar height representing the percentage of MTD given over time. The middle panel shows the population dynamics for the total burden (sum of all metastases). The bottom portion shows the pre-treatment spatial configuration for all metastases and their final spatial configurations after each treatment.