

**Figure 1 | Computer simulations of mCRPC growth during conventional and adaptive application of abiraterone.** *Top panel*, computer simulation of conventional abiraterone treatment at MTD until progression. This strategy selects for the resistant subclones and eliminates competitors to accelerate progression – an evolutionary phenomenon coined “competitive release.” *Bottom panel*, model of a strategy in which therapy-sensitive cells are preserved by withdrawing abiraterone when the PSA reaches half of its pre-treatment value. This permits the tumor to regrow but, in the absence of therapy, the sensitive cells are fitter and thus remain the dominant population. This permits retreatment with abiraterone to maintain tumor control over multiple cycles. Note, however, that at the PSA trough of each cycle there is a small increase of the T- cells. This permits a slow but monotonic increase in the population of resistant cells that will eventually lead to treatment failure. The number of cycles until failure is dependent on the size of the original T- population and their growth rate. Model predictions suggest the number of observed cycles will range from 2 to 20. Importantly the model predicts cycle length can vary depending on initial conditions (*i.e.*, the pretreatment size of the subpopulations) and the relative fitness difference values of each phenotype.

Macintosh HD:Users:cunningham:Dropbox:ProstateCancerModel:CurrentCode:PSAManuscriptFigures:FinalFigures_Version2:Figure2_SlowVsFast.eps

**Figure 2 |** **Computer simulations of mCRPC growth during conventional and adaptive application of abiraterone.** *Top row*, a strategy is modeled in which therapy-sensitive cells are preserved by withdrawing abiraterone when the PSA reaches 0.5 of its pre-treatment value. This permits the tumor to regrow but, in the absence of therapy, the sensitive cells are fitter and remain the dominant population. This permits retreatment with abiraterone to maintain tumor control over multiple cycles, which can be protracted or relatively fast. Model predictions suggest the number of observed cycle will range from 2 to 20 and that cycle length varies depending on initial conditions (*i.e.*, the pretreatment size of the subpopulations) and the relative fitness difference values of each phenotype. *Bottom row*, the actual PSA fluctuations in 2 patients with associated abiraterone administration. Clearly, incorporation of evolutionary dynamics into treatment elicits a wide range of patient-specific outcomes. In one patient, the PSA has not changed following withdrawal of therapy for over 2 years. In the others, as predicted by the model, the cycle length varies from about 3 months to over 1 year**.**

In the bottom row, the actual PSA fluctuations in 2 patients with associated abiraterone administration. Clearly, incorporation of evolutionary dynamics into treatment elicits a wide range of patient-specific outcomes. In one patient, the PSA has not changed following withdrawal of therapy for over 2 years. In the others, cycles as predicted by the model are observed but the cycle length varies from about 3 months to over 1 year**.**

****

**Figure 3 | TP and T+ cells are manifest in mCRPC prior to initiating ADT**. Immunohistochemical analyses of androgen receptor (AR, *top panels*) and CYP17A1 (*bottom panel*) expression in primary radical prostatectomy sample (*left panels*) and lymph node biopsy (*right panels*) from subject 1001 in the current clinical trial. TP cells have positive nuclear staining for AR (brown top panels) and positive cytoplasmic and membrane staining for CYP17A1. T+ cells have only positive AR staining. T- cells (negative for both AR and CYP17A1) were detected in the lymph node biopsy.

Macintosh HD:Users:cunningham:Dropbox:ProstateCancerModel:CurrentCode:PSAManuscriptFigures:FinalFigures_Version2:Figure4_Swimmers.eps

**Figure 4 | Status of the first 10 patients in the mCRPC adaptive therapy trial.** Black in the bar indicates time during which abiraterone was withheld and red is time during which therapy was administered. 9 of the patients remain on study with controlled tumor. Mean follow up time is 15.6 months. Mean progression free survival has not been reached but already exceeds the best reported PFS (11.1 months). Because of the adaptive application of treatment, the mean cumulative dose for the cohort is only 40% of standard of care.