Evolutionary Dynamics in Cancer Control and Cure

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IMAGING RESEARCH
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Personalized oncology focuses on matching treatment to molecular targets. But, …

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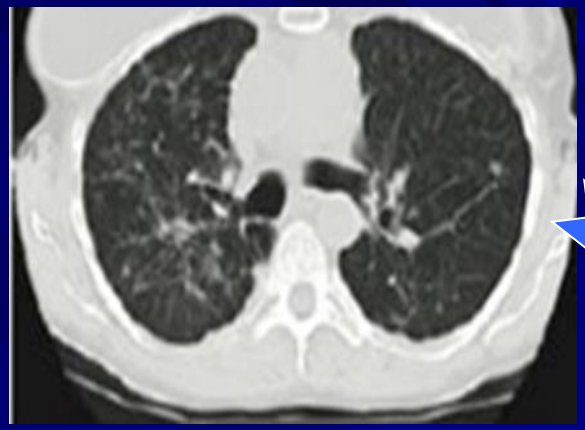

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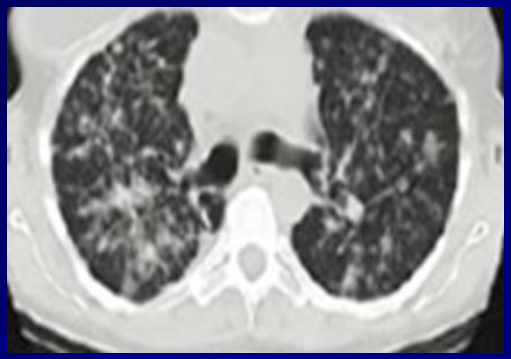
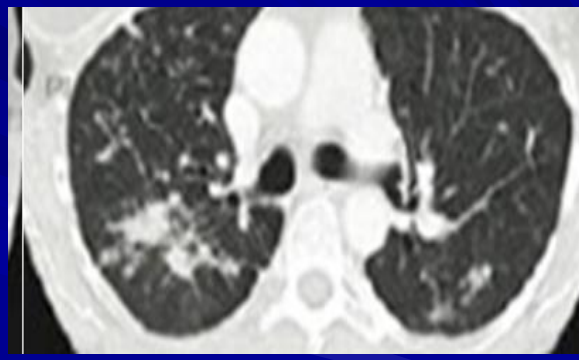




General principle: Resistant phenotypes are inevitable but clinical resistance requires the population to proliferate, which is governed by Darwinian forces

Second principle: Treatment as a game between the oncologist (treatment) and cancer (adaptation)

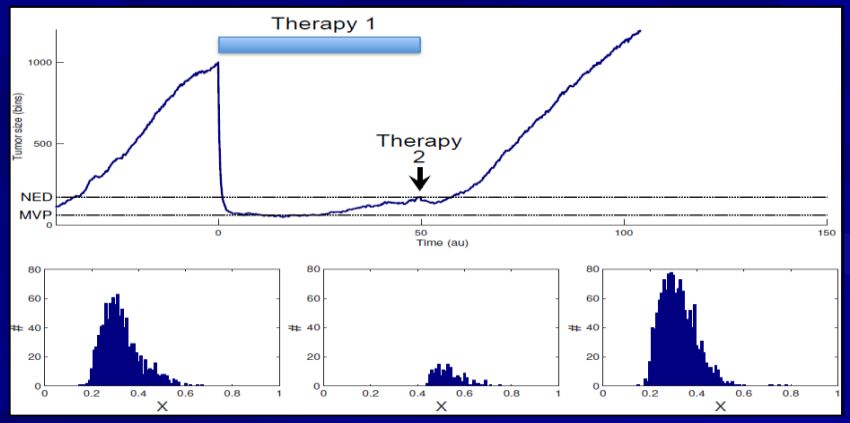
JAMA Oncol. 2019 January 01; 5(1): 96–103. doi:10.1001/jamaoncol.2018.3395.

Optimizing Cancer Treatment Using Game Theory

Kateřina Staňková, PhD, Joel S. Brown, PhD, William S. Dalton, MD, PhD, Robert A. Gatenby, MD

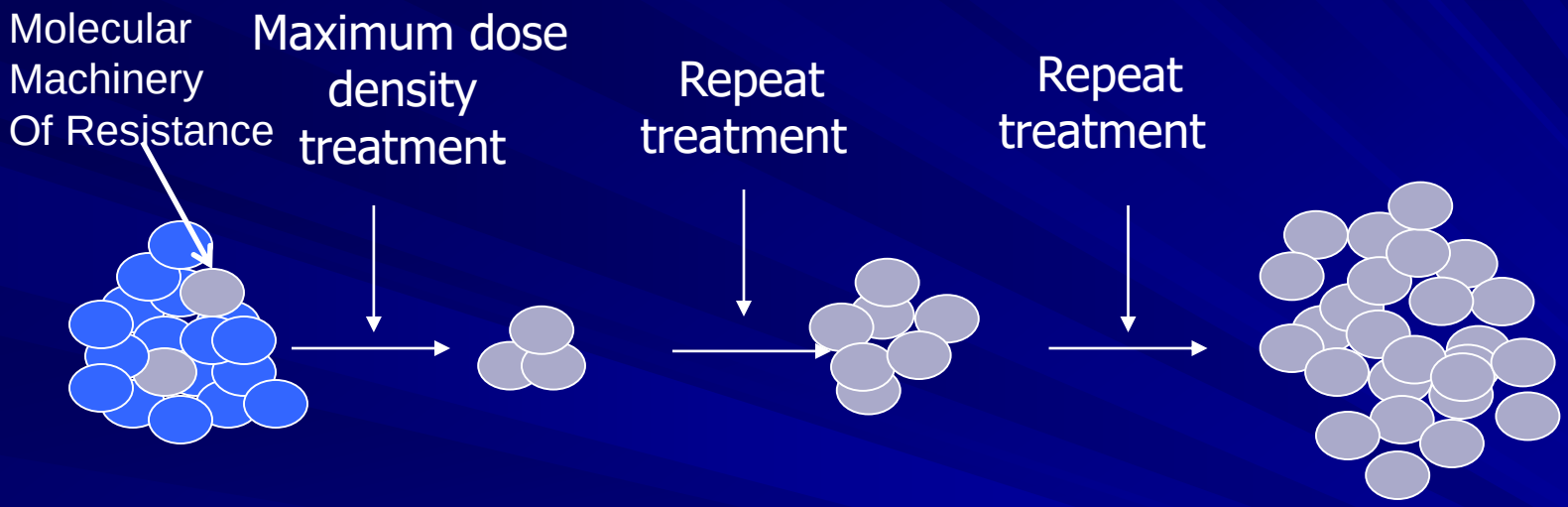
The oncologist has 2 large game theoretic advantages:

1. He/she plays first (Stackelberg dynamics – i.e. white pieces in chess)
2. He/she is sentient and can play dynamically while an evolving cancer population can never anticipate the future.



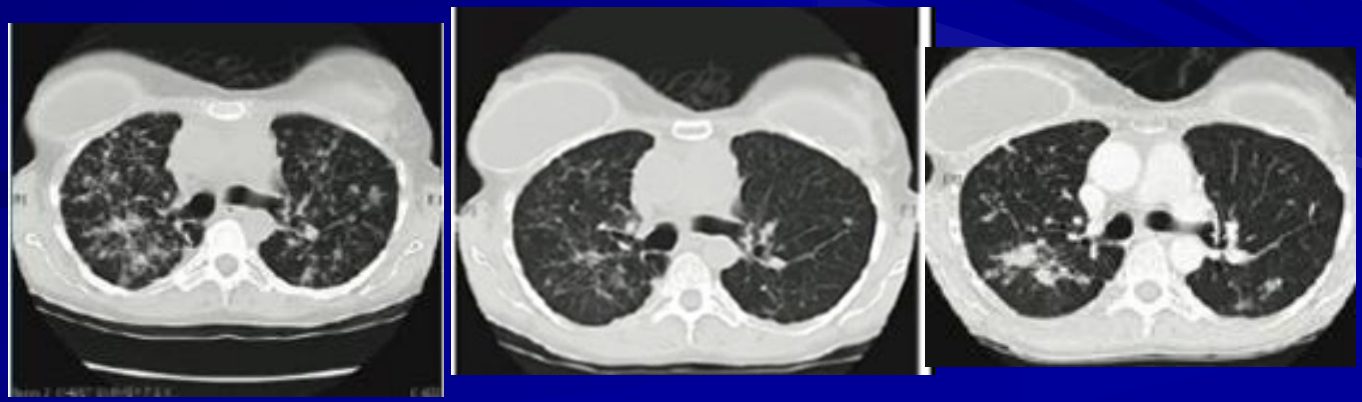
By “playing” the same treatment continuously until progression, oncologists lose both advantages

Combining personalized medicine and game theory models: MTD kills maximum numbers of cancer cells but selects for resistance and eliminates competitors – "competitive release"

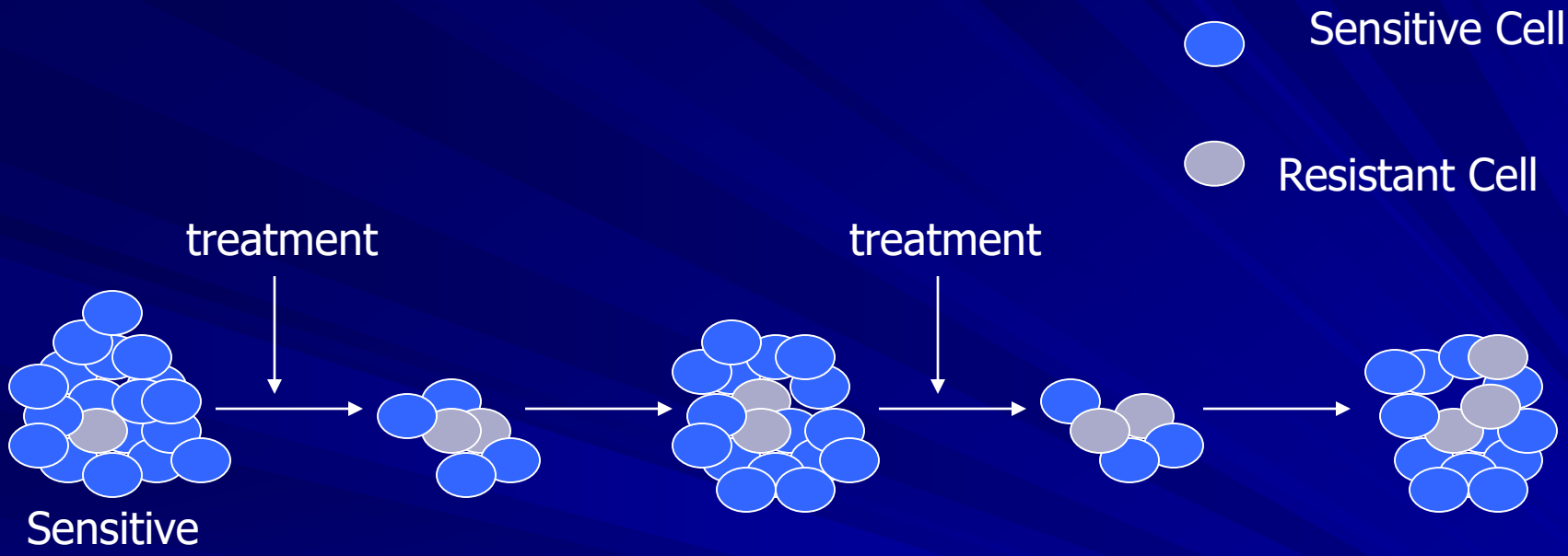


Sensitive Cell

Resistant Cell



Adaptive therapy - exploiting the cost of resistance in clinical cancer treatment



- Limited administration of therapy to maintain sensitive cell population
- Sensitive cells, without the phenotypic cost of resistance, suppress resistant cells during no treatment. Treatment is a *forcing function* that, *when applied at the correct time,* induces oscillating near steady state

First clinical application: Abiraterone blocks androgen synthesis in mCRPC. In large trials 62% of men with mCRPC respond (radiographic TTP 8 to 16 months)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

ABSTRACT

BACKGROUND

The androgen-receptor isoform encoded by splice variant 7 lacks the ligand-binding domain, which is the target of enzalutamide and abiraterone, but remains constitutively active as a transcription factor. We hypothesized that detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells from men with advanced prostate cancer would be associated with resistance to enzalutamide and abiraterone.

From the Departments of Oncology (E.S.A., H.W., B.L., J.T.I., R.N., C.J.P., S.R.D., M.A.C., M.A.E.), Pathology (H.L.F., T.L.L., Q.Z., A.M.D.M.), and Urology (C.L., M.N., J.C.R., Yan Chen, W.B.I., J.L.), Johns Hopkins University School of Medicine, Baltimore; and Greehey Children's Cancer Research Institute (T.A.M., Yidong Chen)

Evolution-based mathematical models to design trial

Define mCRPC subpopulations based on androgen dynamics:

- T+ cells require exogenous testosterone (sensitive to ADT)
- TP cells produce testosterone (sensitive to Abi) and promote T+ cells
- T- cells proliferate independent of testosterone (bad guys!)

Evolution mathematical models define intratumoral Darwinian dynamics during therapy

The oncologist-tumor "game" is modeled as a payoff matrix

The fitness function is set up as follows:

$$G_i = r_i\left(\frac{K_i - (1 - E_i)\sum x_j}{K_i}\right)$$

where $\sum x_j = x_1 + x_2 + x_3$.

The population dynamics are a simple difference equation.

$$\Delta x_i = x_i G_i$$

The PSA dynamics are shown below.

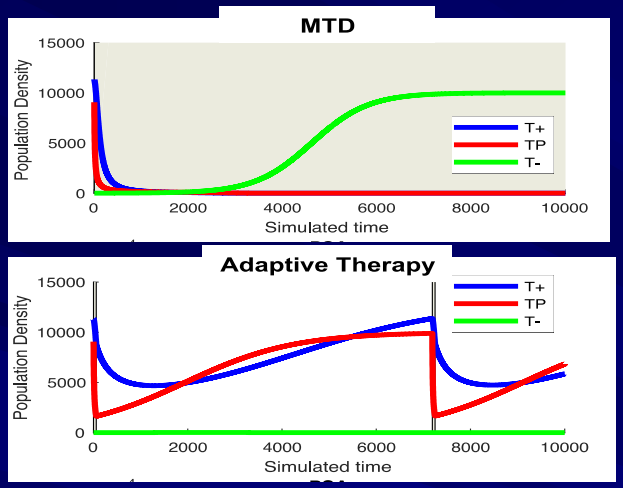
$$\frac{dPSA}{dt} = f_1 x_1 + f_2 x_2 + f_3 x_3 - \sigma_{PSA} \cdot PSA$$

where $\sigma_{PSA} = 0.3$ and
where f_i is the PSA production per cell based on the frequency of TP cells.

	T+	TP	T-
T+	0	*a*	*b*
TP	*c*	*0*	*d*
T-	*e*	*f*	0

ADT Inequalities	
c > e	a > b
a > f	c > d
b < d	e > f

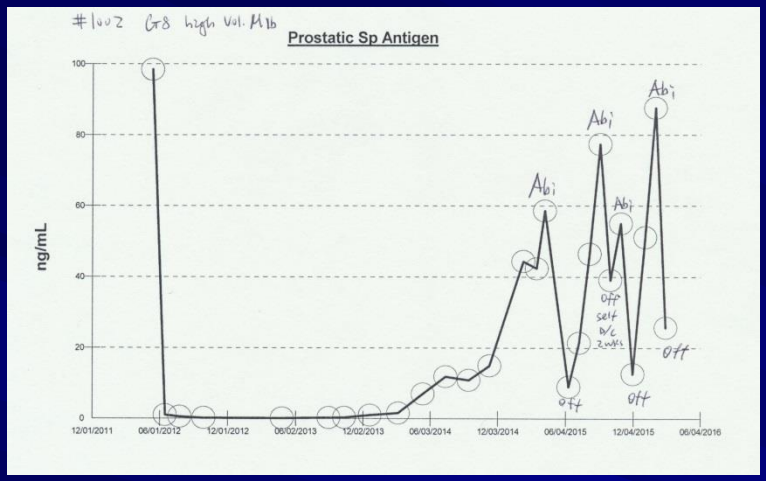
Integrating adaptive therapy mathematical model into clinical oncology practice

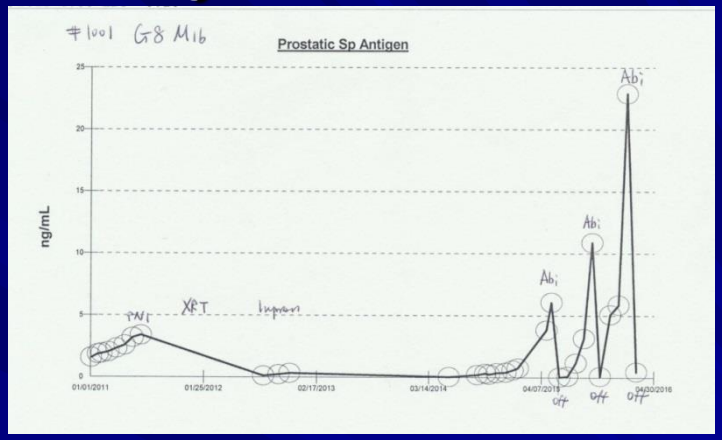


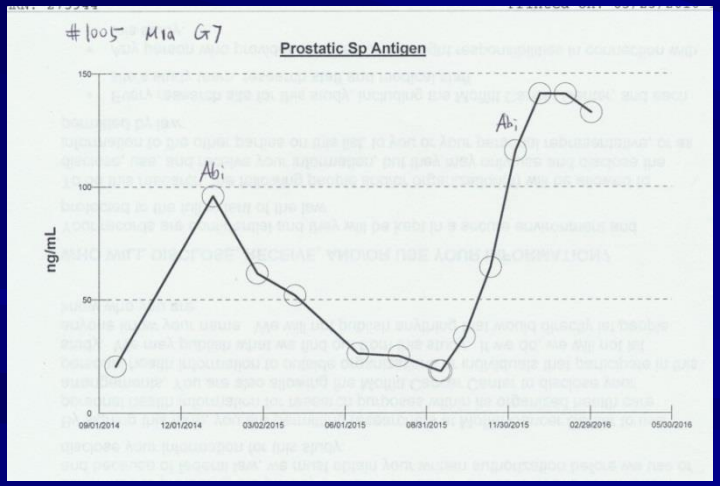
Jingsong Zhang, MD PhD

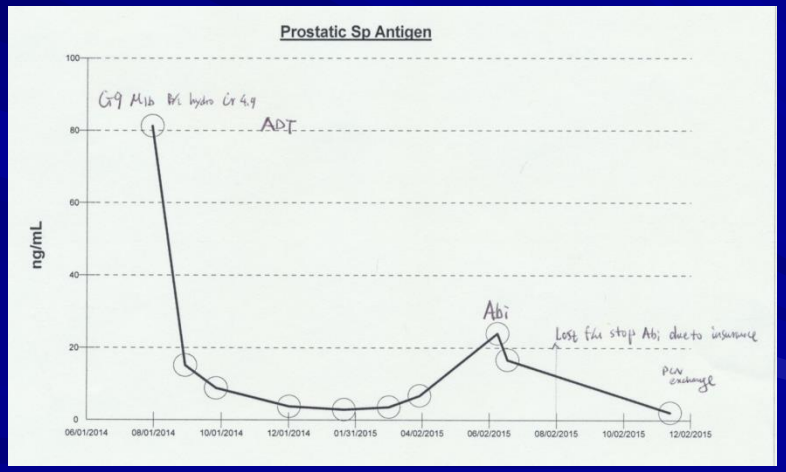
- Initial administration of abiraterone
- When PSA is <50% of pretreatment value, discontinue abiraterone
- Tumor grows but treatment sensitive cells (TP and cheater T+) suppress growth of the resistant T- cells in the absence of treatment
- Resume abiraterone when PSA returns to the pretreatment level and start the cycle over
- Simulations predict control for 2 to 20 cycles

Accrual goals met: Cycle length 4 to 14 months. Earliest recurrence at 2 cycles. Some patients still on treatment at 14 cycles





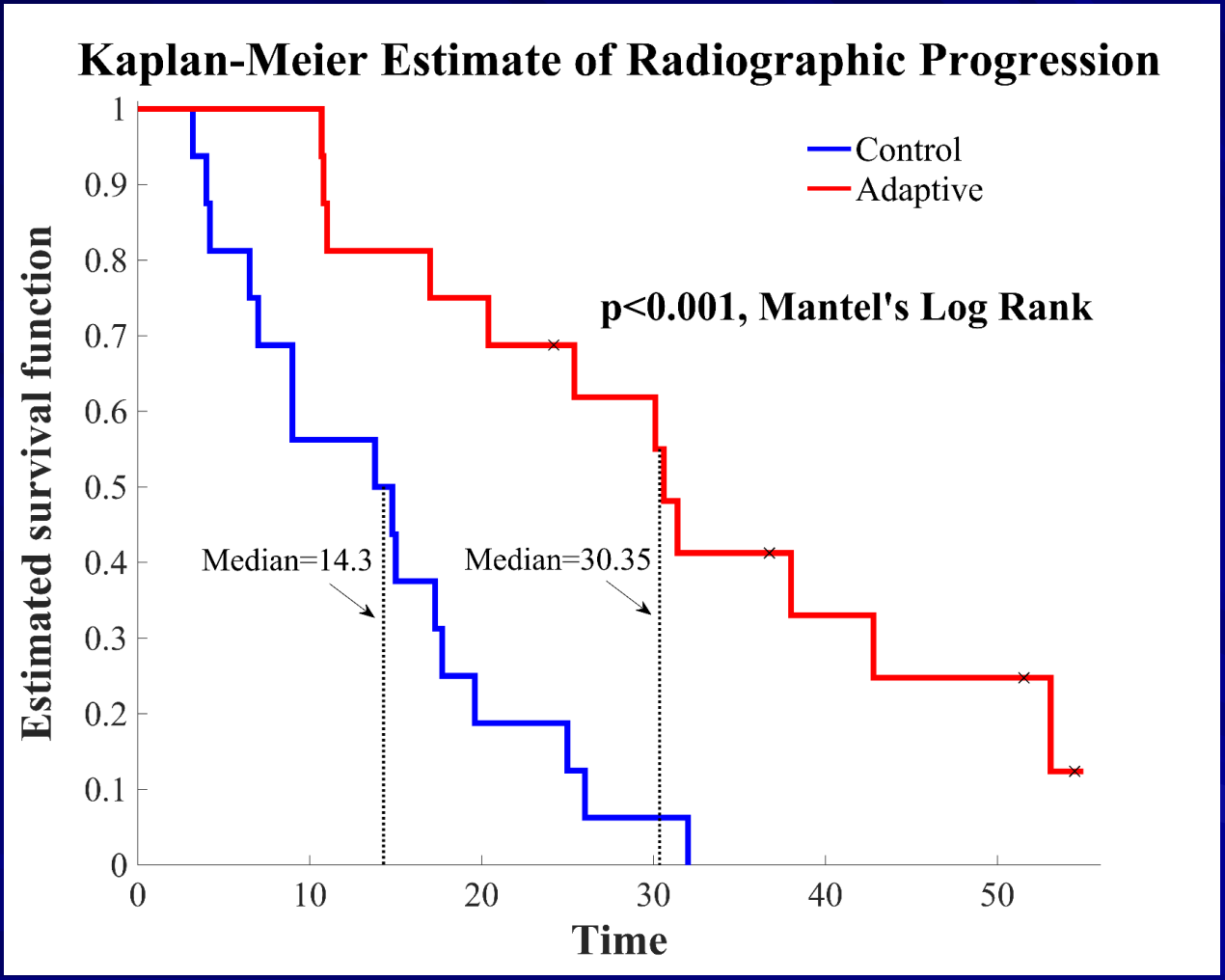




About 1 in 4 patients had long delay in upcycle after decline suggesting achievement of new steady state

The novel eco-evolutionary dynamics of small populations

Current status



Adaptive therapy patients received 41% (22-66%) of SOC

Average cost reduction: $50,00 per patient per year

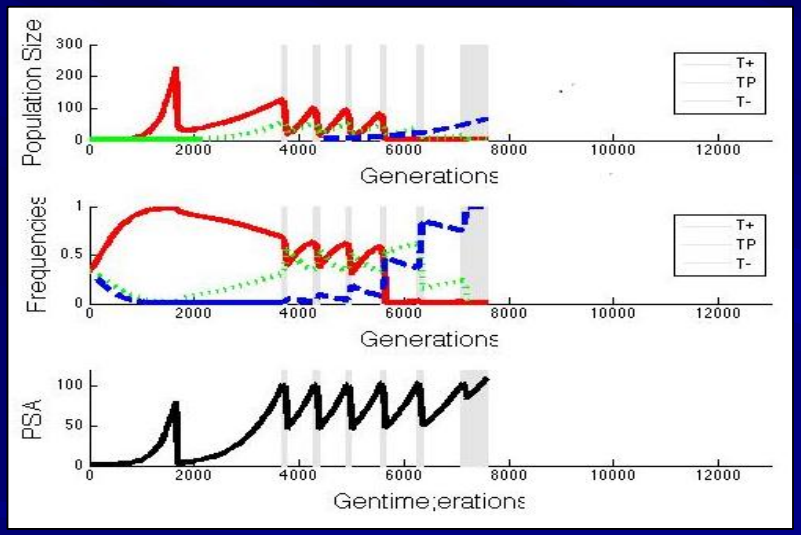
Treatment sensitive cells have a positive (and probably >1) competition coefficient (α_{SR}) for resistant cells in the absence of treatment

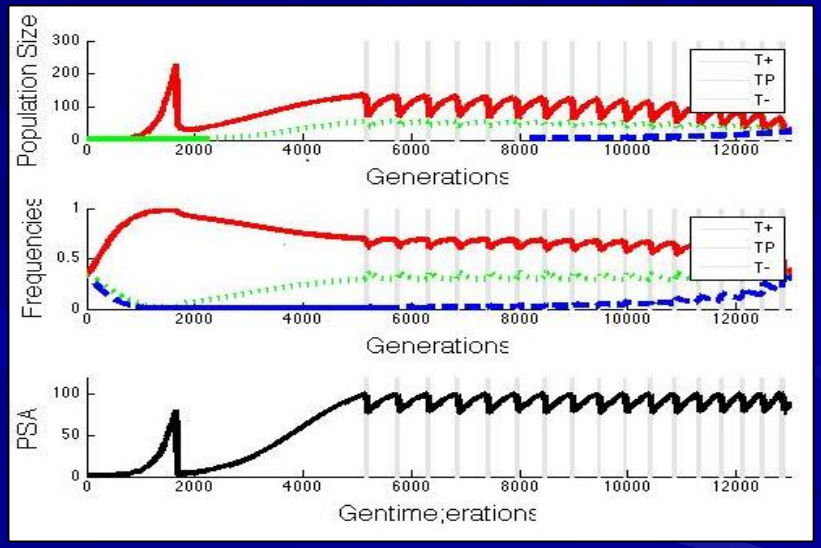
Total suppression is function of $\alpha_{SR}N_S$, where N_S is the number of resistant cells.

Beyond cohort analysis: Investigating each patient using the trial mathematical model

Inverse problem approach: Run the model backward from outcome to initial conditions followed by computational exploration of treatment parameter space to improve outcomes (West et al. Clin. Cancer Res. 2019).

Subject 1010 progressed after 6 cycles (30 months)





Modeling recommendation: Stop abiraterone at 80% of pre-treatment value. Cycle time shorter but control maintained for 58 cycles ~ 63 months

Mathematical analysis of evolution dynamics suggests future trial strategies and can investigate outcomes when other agents are added.

Pediatric oncologists: “Adaptive therapy is ok, but we only want cures”

Adult oncologists: “This is bullshit, just give me better drugs … ”

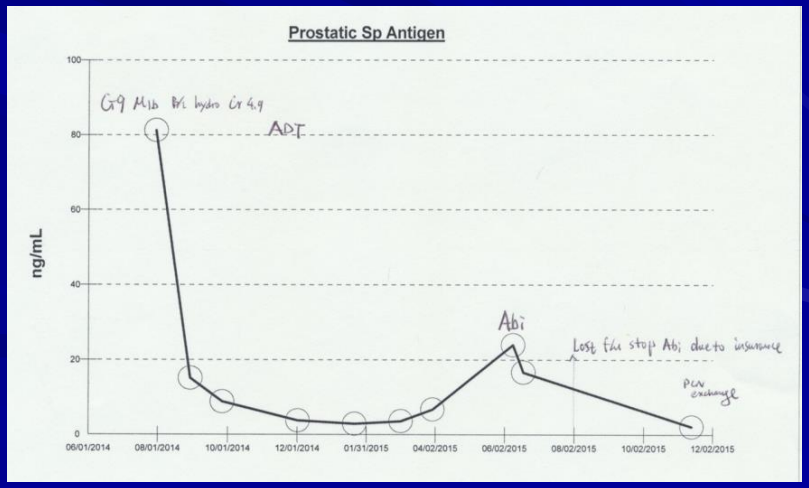
Back to the drawing board: Cancer Cure as Extinction of large, diverse, spatially-dispersed, asexually-reproducing clades

Brute force as an extinction strategy is limited by indiscriminate effects

Current MTD treatment arguably mimics the dinosaur extinction – curing cancer by application of maximum force. But limited by toxicity to normal cells

In the popular imagination extinction = KT impact caused extinction of the mighty dinosaurs

Extinction caused by application of massive evolutionary force also destroyed 60% of other land animal species



Is there an alternative?

In the Anthropocene era, extinction dynamics have been revisited

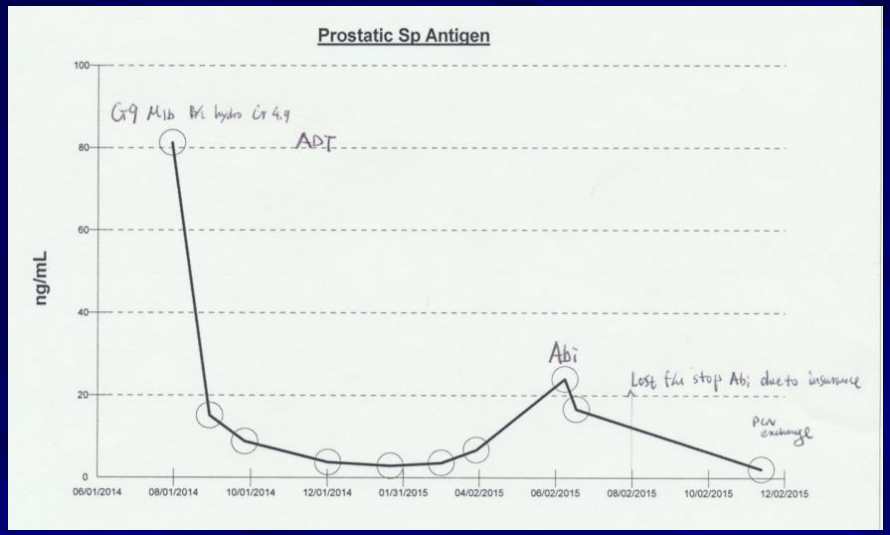
Intentional Anthropogenic extinction: The Galapagos Goat

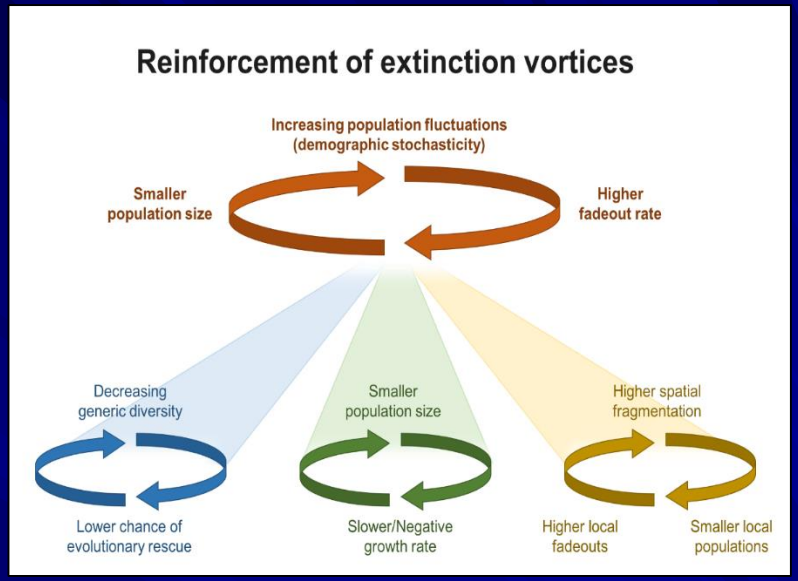
First Strike
Reducing population size and heterogeneity

Second Strike
Dynamics of small populations

Key principle: Background and anthropogenic extinctions are multi-step, multi-cause. *None of perturbations that cause the extinctions can, as a single agent, eradicate the species.*

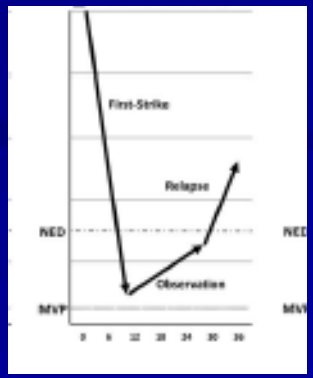
“The extinction vortex”

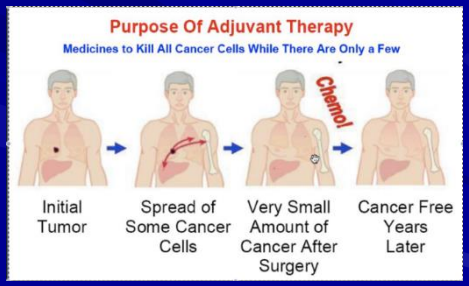




Once a population begins to decline, it is vulnerable to stochastic and Allee effects, which become synergistic and self-reinforcing

Hypothesis: Small population dynamics in cancer treatment are relevant to eradication of microscopic metastases (adjuvant/neoadjuvant therapy) and following initial response in non-curative treatment

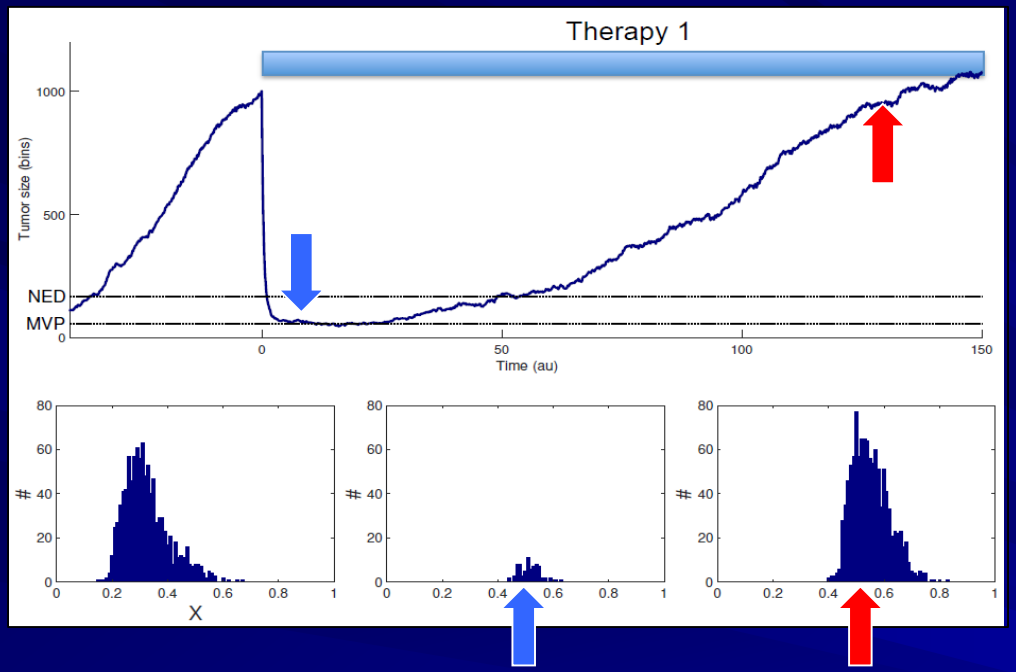




Metastatic Pediatric Rhabdomyosarcoma

Reed et. al. Caner, 2020

Highly effective therapies that reduce metastatic cancers to NED (e.g. ADT in mCSPC, platinum in pediatric sarcomas) are excellent first strikes but usually result in evolutionary rescue



Extinction vulnerability is maximum when the surviving populations is smallest and homogeneous.

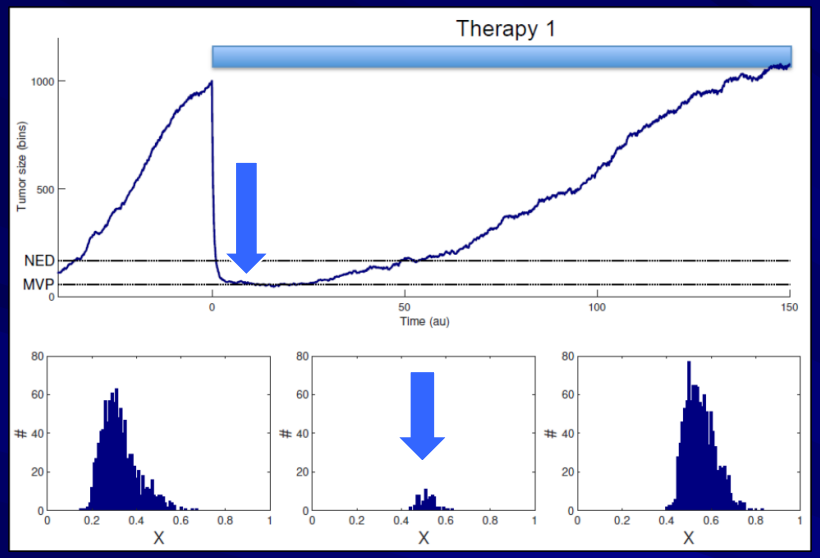
Key Principle

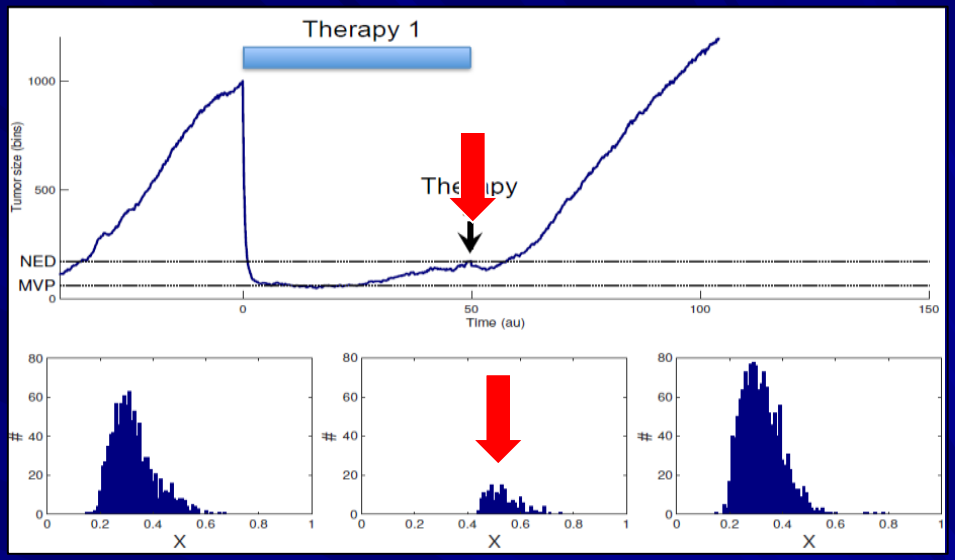
Time is of the essence

Continued application of first strike therapy allows the surviving population to proliferate, occupy additional niches, and increase diversity.

The opportunity to cause extinction is lost!

Cancer therapy at MTD until progression





"Measurable" tumor >2 cm probably >1 billion cells.

Lessons from simulations

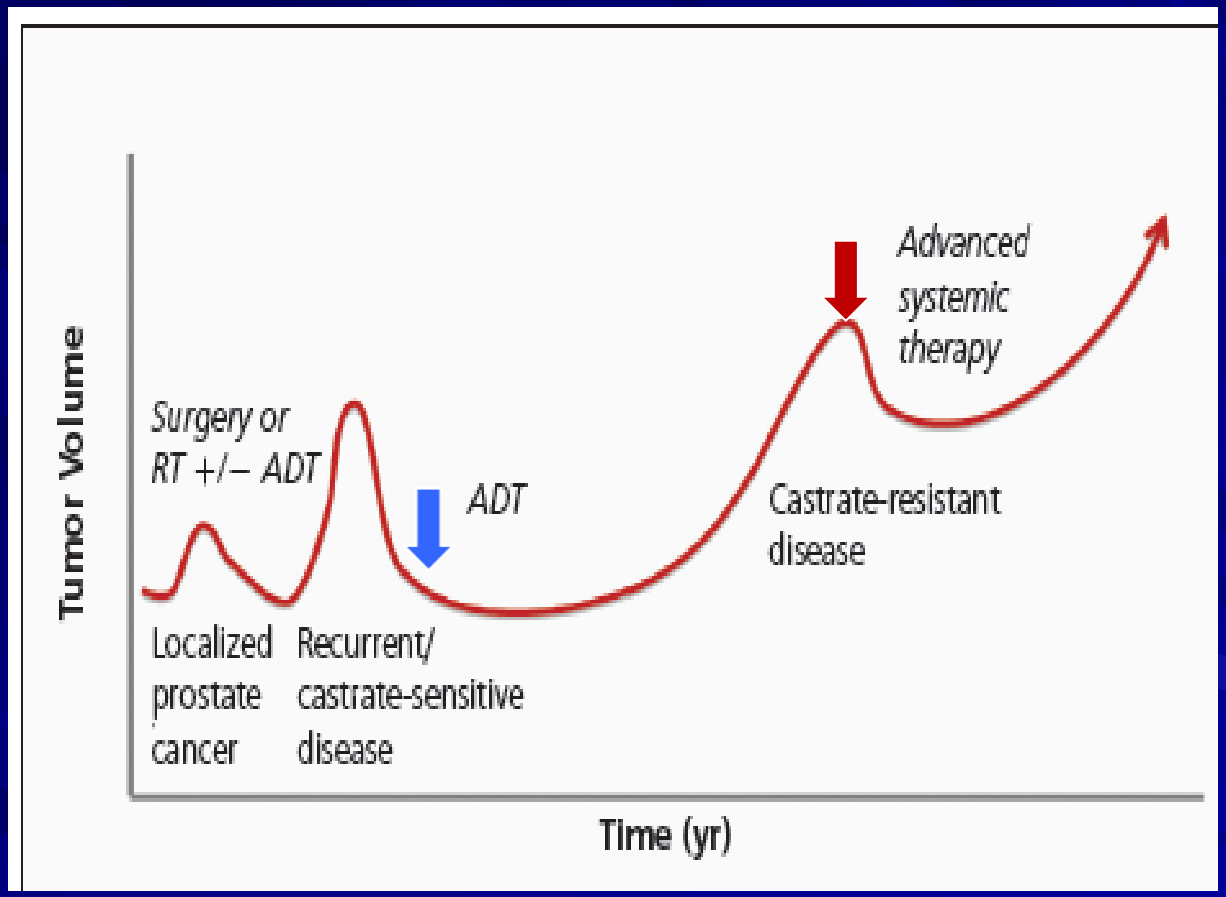
Waiting for measurable disease after first strike is too late

The ideal second strike is a *sequence* of *different* demographic and ecological perturbations. Continuous application of second-strike agent(s) until progression is evolutionarily unwise

Lessons from Anthropogenic extinctions

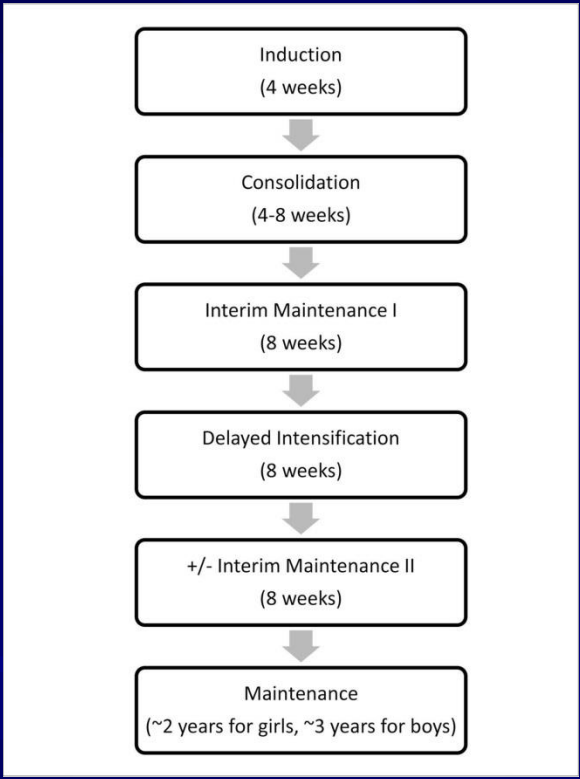
1. Kick them when they are down!

2. The final nail in the extinction decline is virtually never the first strike agent



Androgen Deprivation Therapy (ADT) is an effective first strike but never curative. When do you add second line therapies?

This theoretical strategy is virtually identical to treatment for curative treatment pediatric developed through decades of trial and error



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Controversy and Consensus

Cancer Research

First Strike–Second Strike Strategies in Metastatic Cancer: Lessons from the Evolutionary Dynamics of Extinction

Robert A. Gatenby[1,2,3], Jingsong Zhang[4], and Joel S. Brown[1,3]

CANCER RESEARCH | CONVERGENCE AND TECHNOLOGIES

Eradicating Metastatic Cancer and the Eco-Evolutionary Dynamics of Anthropocene Extinctions

Robert A. Gatenby[1,2], Yael Artzy-Randrup[3], Tamir Epstein[1], Damon R. Reed[4], and Joel S. Brown[1]

Lacking *magic bullets*, cure may be achievable through strategic combinations of regular bullets

Integrating evolution and mathematics into routine clinical oncology

The Moffitt Evolution Tumor Board

Thank you

Moffitt

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