Journal for ImmunoTherapy of Cancer

Rethinking the immunotherapy numbers game

Rebecca A Bekker ,[1,2] Mohammad U Zahid ,[1] Jennifer M Binning ,[3] Bryan Q Spring ,[4,5,6] Patrick Hwu ,[7] Shari Pilon-Thomas ,[8] Heiko Enderling [1,9]

To cite: Bekker RA, Zahid MU, Binning JM, *et al*. Rethinking the immunotherapy numbers game. *Journal for ImmunoTherapy of Cancer* 2022;**10**:e005107. doi:10.1136/jitc-2022-005107

RAB and MUZ contributed equally.

Accepted 21 June 2022

For numbered affiliations see end of article.

Correspondence to
Dr Heiko Enderling;
heiko.enderling@moffitt.org

ABSTRACT

Immunotherapies are a major breakthrough in oncology, yielding unprecedented response rates for some cancers. Especially in combination with conventional treatments or targeted agents, immunotherapeutics offer invaluable tools to improve outcomes for many patients. However, why not all patients have a favorable response remains unclear. There is an increasing appreciation of the contributions of the complex tumor microenvironment, and the tumor-immune ecosystem in particular, to treatment outcome. To date, however, there exists no immune biomarker to explain why two patients with similar clinical stage and molecular profile would have different treatment outcomes. We hypothesize that it is critical to understand both the immune and tumor states to understand how the complex system will respond to treatment. Here, we present how integrated mathematical oncology approaches can help conceptualize the effect of various immunotherapies on a patient's tumor and local immune environment, and how combinations of immunotherapy and cytotoxic therapy may be used to improve tumor response and control and limit toxicity on a per patient basis.

SIMPLE MODEL OF TUMOR–IMMUNE DYNAMICS

To effectively use cancer immunotherapies, either alone or in combination with other treatment approaches, it is necessary to understand the dynamics of tumor–immune interactions and how the different treatment approaches perturb these dynamics. This involves the consideration of the immune state of a given patient. Just like early-stage cancers are treated differently than late-stage disease, tumors with different degrees of immune involvement may need very different therapeutic approaches.[1 2] The tools of mathematical oncology provide a logical, abstract framework to decipher the immunotherapy numbers game, wherein the response to immunotherapy, and therefore patient outcomes, critically depends not only on the number of tumor cells, and/or the presence of appropriate immune markers (eg, PD-L1, etc), but rather on the relative numbers of the tumor and relevant immune populations.

In its most abstract simplification, we could assume a homogeneous tumor cell population that expresses a tumor-specific antigen and is susceptible to recognition and elimination by cancer-specific immune effector cells.[3] Without infiltrating immune cells, tumor cells will grow unchecked. Conversely, without cancer cells, cancer-specific immune cells will decline in numbers. It is conceivable that when a million tumor cells are confronted by a single immune effector cell, the tumor will escape immune surveillance. The inverse scenario, when a single tumor cell is surveilled by a million immune effector cells, results in immune-mediated tumor elimination. Between these two extremes, there are many combinations of population numbers that lead either to immune exhaustion and tumor growth or tumor eradication—two of the three *E*'s of immunoediting.[4] At intermediate numbers, there may be complex dynamics that lead to prolonged coexistence of both populations, which provides coexistence or tumor–immune equilibria, the third immunoediting *E*.

All possible combinations of tumor and immune population numbers and their non-linear interactions can be described with a mathematical model that simulates the number of tumor cells and the number of immune cells over time (figure 1A). We assume that the tumor cells follow logistic growth and can be eliminated at a certain rate via interaction with immune effector cells. Additionally, immune effector cells enter the system through recruitment by tumor cells and through a constant background influx, while they are eliminated through immune exhaustion through interaction with tumor cells and background clearance proportional to the number of effector cells in the system.[3] In this system, any combination of initial tumor and immune cell numbers leads to one of two distinct outcomes (figure 1B):

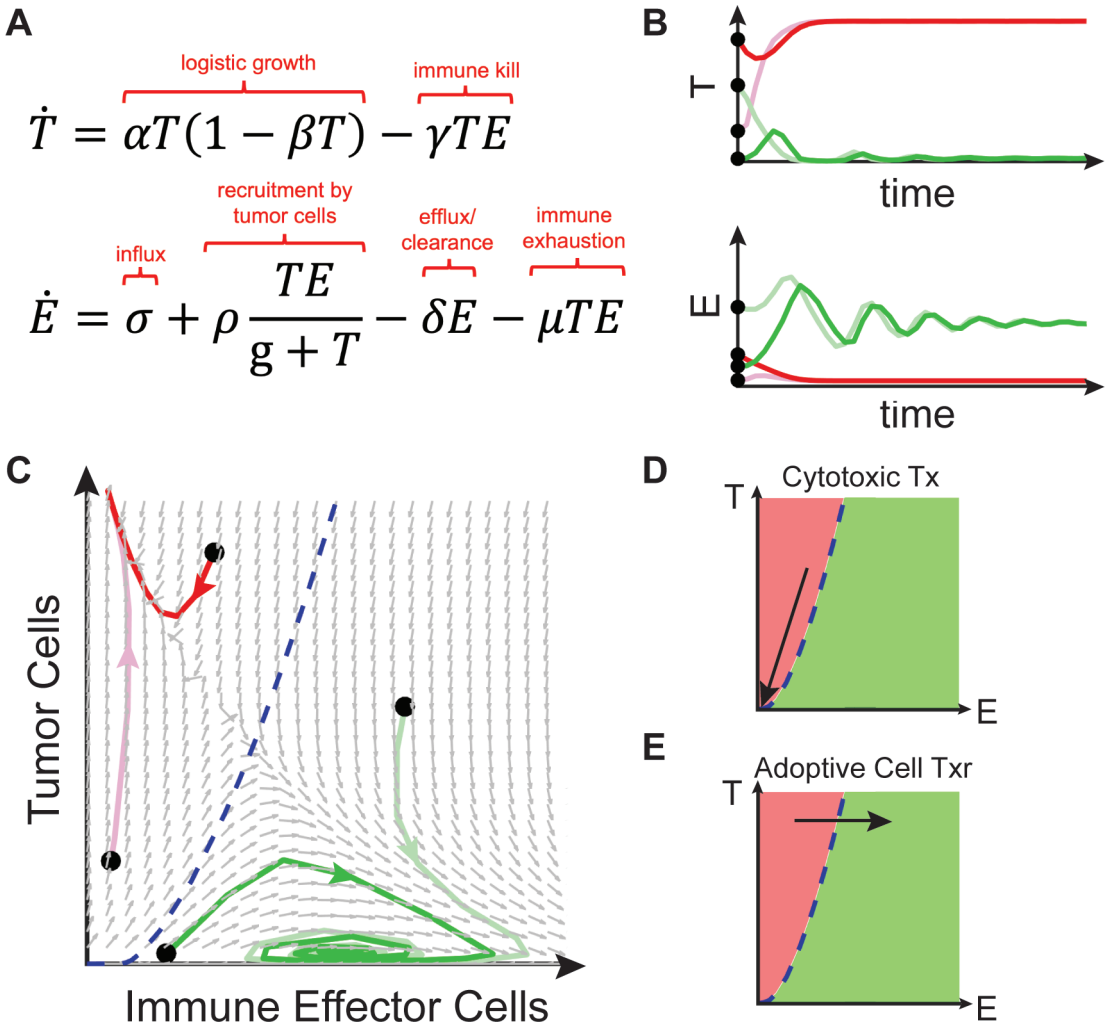

Figure 1 Tumor–immune interactions in a simplified system. (A) Ordinary differential equation representation of a simple model of tumor–immune effector cell interactions, which represents the change in number of tumor cells (*T*) and immune effector cells (*E*) over time. (B) Plots of tumor cells and immune effector cells over time for two initial conditions where the tumor evades the immune cells (red and pink) and two where the tumor is controlled by the immune population (green and light green). (C) Phase plane representation of the system with trajectories shown for the same four initial conditions from panel B. The gray vector field in the background depicts the instantaneous direction of the dynamical system for the respective tumor-immune states; the blue dashed curve is the separatrix between the two basins of attraction (immune evasion and immune escape). (D and E) Conceptual schematic of the disparate effects of cytotoxic therapies (D) and adoptive cell transfer (E) on the tumor–immune system.

immune escape, where the tumor cells grow to the carrying capacity, while the effector cells decay to a negligible number (red and pink trajectories), or immune-mediated tumor control, where the tumor and effector cells follow oscillatory dynamics, similar to predator–prey dynamics,[5] that result in low tumor cell numbers (green trajectories). These dynamics can also be visualized on a phase plane, that is, the temporal evolution of tumor and immune cell numbers plotted against each other (figure 1C). This visualizes the separation of the two outcomes, tumor escape and tumor elimination, based on the numbers of the respective populations and the rate constants of their interactions. The boundary between the two outcome regions is called a separatrix. A population of any combination of tumor cells and immune effector cells on the left-hand side of the separatrix supports tumor growth, whereas tumor–immune population combinations on the right-hand side of the separatrix yield transient oscillatory dynamics and ultimately immune-mediated elimination of tumor cells over time.

EFFECTS OF TREATMENT ON THE TUMOR–IMMUNE DYNAMICS

Cytotoxic treatments

Most patients will present in the clinic with a tumor–immune ecosystem composition on the left-hand side of the separatrix with a growing tumor that outcompetes the immune system. Many cancer therapies alter the absolute number of both tumor cells and immune effector cells, and the post-treatment location of a patient within this phase plane may

determine the ultimate response and outcome to the particular therapy. Surgery and cytotoxic therapeutics like chemotherapy and radiotherapy have historically focused on complete tumor burden reduction, which would translate to a vertical downwards shift in the phase plane. However, most chemotherapies indiscriminately kill both cancer and immune effector cells, although at different rates,[6] which translates to a downward-left shift towards the (0,0) origin of the cancer–immune phase plane (figure 1D). In contrast, the effect of radiotherapy is more nuanced. Despite being used traditionally as a local cytotoxic therapeutic, there is an increasing appreciation of the local and systemic immunological consequences of radiation. Due to high inherent radiosensitivity, immune effector cells within the irradiated area die at high numbers.[7] Thus, in the short term, radiation would induce a downward-left shift. Immunostimulatory radiation schemas would yield a subsequent shift to the right towards larger immune numbers. However, immunostimulatory and immunosuppressive radiation properties are likely dose and dose fractionation as well as tumor site specific.[8]

Cell-based immunotherapies

Adoptive cell transfer (ACT) increases the absolute immune effector population, shifting patients to the right horizontally within the phase plane (figure 1E). This may, for some patients, induce a shift towards the phase plane region of immune-mediated tumor control and thus boost the number of immune effector cells to overwhelm and control the tumor. Despite challenges inherent to ACT production and significant treatment-associated toxicities, response rates are approximately 50% for some cancers.[9] This indicates that some patients successfully cross to the right-hand side of the separatrix with ACT treatment, while the induced shift may be insufficient to achieve tumor control for others.

Immune-checkpoint inhibitors

In contrast to both cytotoxic therapeutics and ACT, immune checkpoint inhibitors (ICIs) would affect the system by changing the nature of the population interactions, rather than directly changing the size of either population. In the language of our dynamical system, this changes the 'landscape' of the interaction due to an increase in the killing efficiency of the immune effector cells.[10] Anti-PD-1 therapies enhance the antitumor effect of the immune effector response, which would result in fewer immune cells being able to kill larger numbers of cancer cells, while anti-CTLA-4 therapies increase the proliferation rate of the effector cells. In the context of our dynamical system, we may imagine that there are many possible starting tumor–immune states that would result in clinical presentation of a tumor (figure 2A) and that both anti-PD-1 and anti-CTLA-4 change the underlying system dynamics, which moves the phase plane separatrix leftwards, thereby increasing the set of tumor–immune number combinations that lead to tumor control (figure 2B). This suggests that among patients with clinically presenting tumors, only the subset of patients within this 'reclaimed' region of the phase plane prior to therapy would be controlled by ICIs alone—a visualization consistent with the modest effect of ICIs on increasing the antitumor function of immune effector cells and the relatively low response rates seen in trials of ICIs.[11] In a similar fashion, the effects of other immunotherapies such as oncolytic virotherapy, dendritic cell vaccines, or immune system modulators such as interleukins would either shift patients horizontally to the right, or shift the

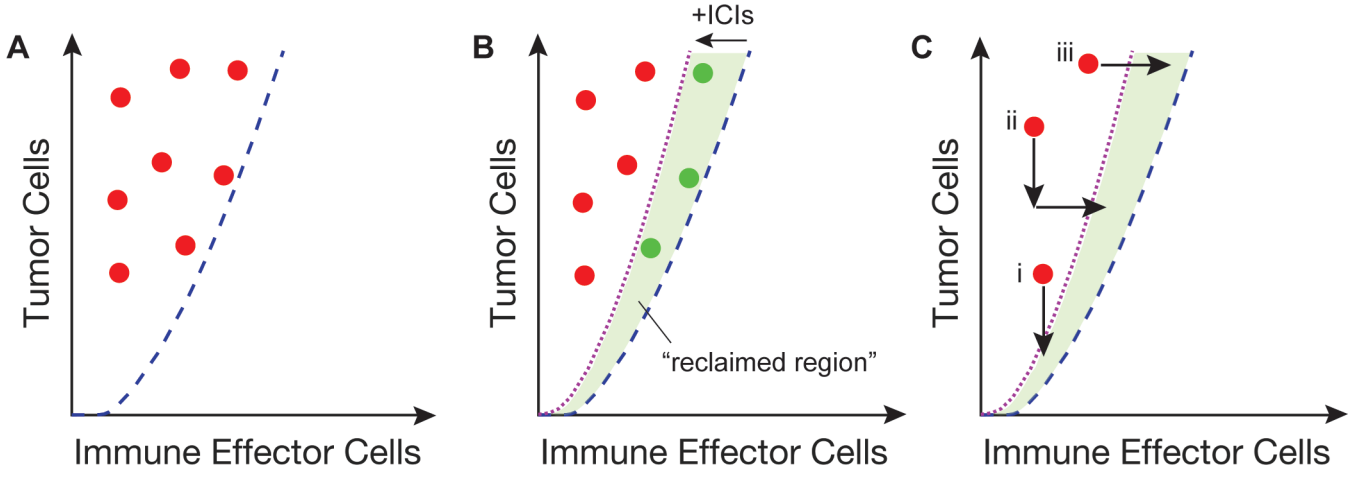

Figure 2 Model realizations of immune checkpoint inhibitor (ICI) therapy. (A) Examples of potential tumor–immune states resulting in immune-escaped tumors, where each circle represents different possible pretreatment states for individual patients. (B) Depiction of the effect of ICI therapy shifting the separatrix between the regions of tumor control and escape. Patients who would benefit from ICI therapy (green circles) due to their tumor–immune state in the 'reclaimed region' and those that would not (red circles). The ICIs induced 'reclaimed region' of tumor control is indicated in light green shading. (C) Potential combination therapy routes for patients that would not experience tumor control from ICI therapy alone.

separatrix to the left, increasing the set of tumor-immune combinations that may lead to tumor control.

Combination therapies

This abstraction allows us to conceptualize how cytotoxic and immune-modulating therapies may be rationally combined to leverage an individual patient's tumor–immune state towards immune-mediated tumor control (figure 2C). For example, a patient for whom ICI therapy alone is insufficient to achieve tumor control may benefit from the addition of an ACT and/or neoadjuvant chemotherapy or radiation. For patients with multiple viable treatment options, the (combination) therapy that yields the shortest path across the separatrix may be the optimal, least toxic approach. For example, rather than a large cytotoxic dose of chemotherapy or radiation, a smaller cytotoxic dose combined with an ICI treatment may be used to push the tumor–immune state over the separatrix, where the antitumor immune cells can take over and drive cancer to extinction. Additionally, emerging therapy options that have both cytoreductive and immunostimulatory properties, such as stereotactic body radiotherapy or photodynamic therapy, may enable such moves in the phase space. Thus, understanding the tumor–immune dynamics may allow us to increase response and reduce treatment-associated toxicities for individual patients and improve outcomes for the patient population as a whole.

Of course, tumor–immune dynamics are much more complex than the simple model presented here. A more complex model could account for the effect of regulatory immune cells among other factors[12] that will then span a three-dimensional space with the separatrix becoming a curved surface separating tumor control and escape. Further complicating matters are the evolutionary dynamics of tumor adaptations to treatments and immune predation, yielding a time-varying separatrix and an ever-moving target. Additional dimensions and nuances will likely need to be incorporated moving forward. Even though chemotherapies and radiotherapy have traditionally been considered mainly cytotoxic, their impact on the immune system—both immune kill and immune stimulation—is well known and needs to be considered in modeling and harnessing tumor–immune dynamics.[13]

Additionally, the nature of the parameters underlying such mathematical models need to be considered carefully. For instance, the underlying assumptions that all immune effector cells within the tumor immune microenvironment are cancer specific and can recognize cancer cells due to sufficient major histocompatibility class 1 expression levels are not always true. However, the relaxing of these assumptions can be allowed for via the adjustment of the cytotoxicity and efficacy parameters within the model, or via the addition of additional parameters describing heterogeneous tumor and immune populations. In addition, the expansion of T cells following the recognition of tumor-associated mutations can easily be incorporated into the existing model. The exact shape and location of the separatrix are highly dependent on the model parameters, which may themselves be specific to a particular cancer site, cancer type or even unique for every patient.

CLINICAL TRANSLATABILITY

For this type of quantitative modeling to be translated into the clinic and applied to predict response to treatment and recommend optimal, patient-specific therapies, there must be systematic characterization and measurement of the model parameters. Additionally, a method to measure a patient's tumor–immune state must be developed before a model of tumor–immune dynamics can be applied. The tumor state may be approximated by measurements of tumor stage or size, while new metrics may be needed to determine the immune state. There are already some promising metrics using sequencing[12 14 15] or imaging[16] that could be leveraged for this purpose. If it is possible to assess a patient's tumor–immune state over time, either through serial radiology imaging or solid/liquid biopsies, we may begin to understand how a patient moves in the tumor–immune phase space in response to a particular therapy. This could ultimately lead to a dynamic staging of the disease and pave the way for an era of response-informed adaptive therapies.

Many of the biological and clinical factors are yet to be fully studied and characterized in order to appropriately calibrate and validate this or any model of tumor–immune dynamics.[17] It may even be possible to calibrate model parameters for individual patients to strengthen the connection to individual patient outcome, if appropriate mapping of clinical measurements to parameter values can be established. For instance, it may be possible to incorporate measures of T cell function using measurements of PD-L1 levels to inform the effector cell efficacy parameter. A detailed roadmap for model translation has been laid out in previous work.[13] Despite all the critical theoretical and experimental work that remains to be done before any such model can be deployed in the clinic, mathematical oncology abstraction provides a novel and promising way to conceptualize the effect of various cancer treatments on a patient's tumor and the local immune environment and gives us an opportunity to rethink the immunotherapy numbers game.

Author affiliations
[1]Department of Integrated Mathematical Oncology, H Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA
[2]Cancer Biology Ph.D. Program, University of South Florida, Tampa, Florida, USA
[3]Department of Molecular Oncology, H Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA
[4]Translational Biophotonics Cluster, Northeastern University, Boston, Massachusetts, USA
[5]Department of Physics, Northeastern University, Boston, Massachusetts, USA
[6]Department of Bioengineering, Northeastern University, Boston, Massachusetts, USA
[7]Moffitt Cancer Center, Tampa, Florida, USA
[8]Department of Immunology, H Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA

[9]Department of Radiation Oncology, H Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA

Twitter Rebecca A Bekker @rebecca_bekker, Mohammad U Zahid @MohammadUZahid, Jennifer M Binning @JenBinning, Patrick Hwu @PatrickHwuMD, Shari Pilon-Thomas @spt_lab and Heiko Enderling @HeikoEnderling

Contributors RAB, MUZ, SP-T, and HE conceived the study. All authors wrote and edited the manuscript.

Funding This work was supported in part by National Institutes of Health/National Cancer Institute U01CA244100 (HE and SPT), R21CA263911(HE), and the Ocala Royal Dames for Cancer Research (HE and BQS).

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Rebecca A Bekker http://orcid.org/0000-0002-3002-2724
Mohammad U Zahid http://orcid.org/0000-0003-4893-4462
Jennifer M Binning http://orcid.org/0000-0001-5871-686X
Bryan Q Spring http://orcid.org/0000-0001-7332-7707
Patrick Hwu http://orcid.org/0000-0002-8293-1313
Shari Pilon-Thomas http://orcid.org/0000-0001-7785-3034
Heiko Enderling http://orcid.org/0000-0002-9696-6410

REFERENCES

1 Bonaventura P, Shekarian T, Alcazer V, *et al*. Cold tumors: a therapeutic challenge for immunotherapy. *Front Immunol* 2019;10:168.
2 Fridman WH, Pagès F, Sautès-Fridman C, *et al*. The immune contexture in human tumours: impact on clinical outcome. *Nat Rev Cancer* 2012;12:298–306.
3 Kuznetsov VA, Makalkin IA, Taylor MA, *et al*. Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. *Bull Math Biol* 1994;56:295–321.
4 Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol* 2004;22:329–60.
5 Wangersky PJ. Lotka-Volterra population models. *Annu Rev Ecol Syst* 1978;9:189–218.
6 Shurin MR, Naiditch H, Gutkin DW, *et al*. ChemoImmunoModulation: immune regulation by the antineoplastic chemotherapeutic agents. *Curr Med Chem* 2012;19:1792–803.
7 Trowell OA. The sensitivity of lymphocytes to ionising radiation. *J Pathol Bacteriol* 1952;64:687–704.
8 Arnold KM, Flynn NJ, Raben A, *et al*. The impact of radiation on the tumor microenvironment: effect of dose and fractionation schedules. *Cancer Growth Metastasis* 2018;11:1179064418761639.
9 Baruch EN, Berg AL, Besser MJ, *et al*. Adoptive T cell therapy: an overview of obstacles and opportunities. *Cancer* 2017;123:2154–62.
10 Sullivan MR, Ugolini GS, Sarkar S, *et al*. Quantifying the efficacy of checkpoint inhibitors on $CD8^+$ cytotoxic T cells for immunotherapeutic applications via single-cell interaction. *Cell Death Dis* 2020;11:979.
11 Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. *Int Immunopharmacol* 2018;62:29–39.
12 Alfonso JCL, Grass GD, Welsh E, *et al*. Tumor-immune ecosystem dynamics define an individual radiation immune score to predict pan-cancer radiocurability. *Neoplasia* 2021;23:1110–22.
13 Brandmaier A, Formenti SC. The impact of radiation therapy on innate and adaptive tumor immunity. *Semin Radiat Oncol* 2020;30:139–44.
14 Angell HK, Bruni D, Barrett JC, *et al*. The immunoscore: colon cancer and beyond. *Clin Cancer Res* 2020;26:332–9.
15 Zahid MU, Mohsin N, Mohamed ASR, *et al*. Forecasting individual patient response to radiation therapy in head and neck cancer with a dynamic carrying capacity model. *Int J Radiat Oncol Biol Phys* 2021;111:693–704.
16 Wang JH, Wahid KA, van Dijk LV, *et al*. Radiomic biomarkers of tumor immune biology and immunotherapy response. *Clin Transl Radiat Oncol* 2021;28:97–115.
17 Brady R, Enderling H. Mathematical models of cancer: when to predict novel therapies, and when not to. *Bull Math Biol* 2019;81:3722–31.