COMMENTARIES

Designing In and Around Tolerability Considerations for Immunotherapy Combinations

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Over a century ago, paths diverged in the treatment of cancer: the well-traveled path employed cytotoxic chemotherapy drugs, while one of the roads less traveled included immunotherapies. Cancer immunotherapy is now a path to durable responses, however not all patients benefit. Immunotherapy combinations promise responses for a larger proportion of patients, but tolerability can prove to be a barrier. Providing deep, durable responses to more patients requires us to successfully navigate emerging combination tolerability issues.

With the recent clinical and commercial success of checkpoint inhibitors, especially those targeting CTLA4 and PD-L1/PD-1, has come a seemingly disproportionate increase in clinical investigations in immuno-oncology (IO), now numbering over 1,000 trials.[1] Immunotherapy combination trials comprise a substantial proportion of this unprecedented investment, suggesting that immunotherapies could become backbone therapies across a wide array of malignancies. The so-called "cancer immunity cycle" partitions IO action into several conceptual steps and provides a concise rationale for IO combinations.[2] The cancer immunity cycle commences first with release of cancer cell antigens and proceeds through a series of steps that are critical to generating immunity to cancer and ultimately killing cancer cells. These individual steps represent possible points of therapeutic intervention, and are affected not only by IO agents, but by a myriad of other classes of anticancer drugs, spanning cytotoxic chemotherapies to targeted agents. For example, cytotoxic agents act directly on cancer cell killing (the final step of the cancer immunity cycle), while anti-vascular endothelial growth factor (VEGF) can affect T-cell extravasation occurring in the middle of the cycle. Accordingly, IO–IO agent combinations represent only a small fraction of the possibilities. Exploration of this expansive IO combination landscape will continue to act as a driver for large numbers of clinical investigations well into the future.

The available clinical database across the possible combination partners for IO agents can prove to be inadequate to fully inform IO combination studies. On the one extreme, chemotherapy has a considerable history of use in oncology, now with an accompanying rich database to mine regarding the effect of dose and scheduling on tolerability. In contrast, the clinical database for IO agents is growing only just now for an increasing list of indications. The robustness of model-based predictions for IO combinations can be limited by the lack of available data, although systems pharmacology approaches are beginning to show promise even with this limitation.[3] Clinical investigation of an IO combination, often with one combination partner held at the approved dose and dose escalation for the investigational agent, can reveal information about the maximally tolerated dose (MTD) for that combination. However, especially in the early phase I setting, we explore only a fraction of the possible dosing and scheduling possibilities for a given combination, and are left with only a partial understanding of the underlying exposure–tolerability relationship for the combination (**Figure 1**). A further complicating factor arises from the fact that immune-related adverse events (irAE) can emerge following the first cycle of treatment with IO agents, and that management of these AEs may involve holding subsequent doses and, consequently, reduced overall dose intensity; especially given the unique kinetics of irAE onset and resolution, careful selection of safety endpoints is important to meaningfully inform the exposure–tolerability analysis for IO.[4] In instances where the IO combination is poorly tolerated, we are faced with the prospect of designing a combination treatment regimen around the peaks and valleys of this underlying relationship with only a limited understanding of the topography, while maintaining sufficient levels required for efficacy.

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doi:10.1002/cpt.945

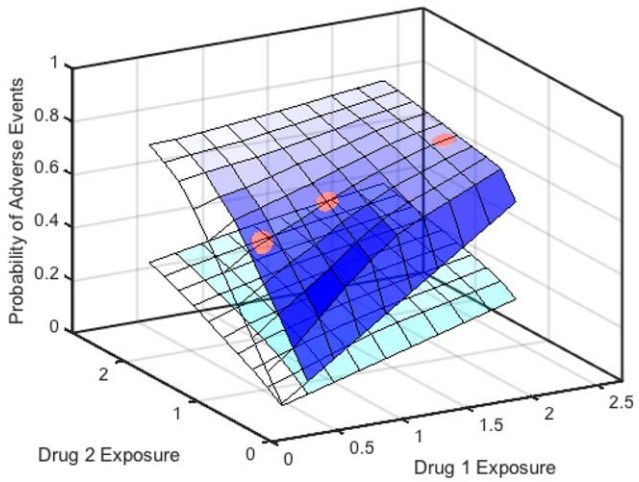

Figure 1 Hypothetical tolerability of a given immuno-oncology (IO) combination as a function of exposure (e.g., area under the curve, maximum concentration, etc.) of combination partners Drug 1 and Drug 2 (upper blue surface). Red shaded areas represent sampling of this underlying relationship in a phase I combination study. Since this underlying relationship is not necessarily known from monotherapy development of the combination partners, identification of a tolerated dose and schedule can require an extended exploration of this underlying relationship across multiple trials. Restricting the action of IO combination agents to the tumor holds promise to flatten this relationship to resemble the cyan surface, resulting in improved tolerability of IO combination by design.

Development of the ipilimumab (IPI) + nivolumab (NIVO) combination provides an important case example of enhancing tolerability through exploration of scheduling and dosing of drugs in the combination. In the phase III investigation CheckMate 067, melanoma patients received IPI 3 mg/kg and NIVO 1 mg/kg every 3 weeks for 4 doses (q3wx4) followed by NIVO alone 3 mg/kg q2w; patients were further randomized to receive NIVO alone 3 mg/kg q2w and IPI alone 3 mg/kg q3wx4. Patients receiving IPI+NIVO had improved survival benefit relative to IPI alone; however, the frequency of Grade 3-4 AEs was 59% for the combination vs. 21% and 28% for NIVO and IPI alone, respectively, with gastrointestinal events as the most common Grade 3-4 select adverse event. Further, 39% of patients receiving IPI+NIVO experienced adverse events of any grade leading to discontinuation.[5] Safety guidelines were followed to manage immune-mediated AEs in part through the use of immune-modulating agents. Multiple dose levels and schedules of IPI and NIVO have been explored in addition to the IPI+NIVO regimen of CheckMate 067 as summarized elsewhere.[6] Starting first with the initial phase Ib investigation where IPI was initially fixed to the approved 3 mg/kg q3wx4 dose and schedule and NIVO was administered q2w and dose escalated in a 3+3 design, the current clinical database now includes both the 1 mg/kg and 3 mg/kg dose levels for both IPI and NIVO and a collection of schedules for IPI spanning q3wx4 to every 12 week (q12w) administration. A subset of this clinical database has been pooled to inform exposure–response (E-R) analyses and support the dosing regimen for this combination in melanoma.[7]

In the example of the IPI+NIVO combination, we note the substantial effort that can be required to design around possible safety considerations with IO combinations. Leveraging historical monotherapy data may not fully inform dosing in combination, and sampling the underlying dose-schedule-tolerability relationship for IO combinations in the clinic can involve multiple trials to yield sufficient cross-sections of this underlying relationship. This begs the question of how we can design better tolerability into combinations.

Restricting the action of the IO and/or combination agent to the tumor provides one route for greater tolerability by design, since poor tolerability can arise from unnecessary systemic exposure to a drug. Perhaps the most conceptually simple means to this end comes from direct administration to the diseased site. An early example of direct administration of IO agents comes from the first use of intravesical Bacillus Calmette–Guérin (BCG) immunotherapy in bladder cancer patients in 1976.[8] Intravesical BCG immunotherapy is now indicated for carcinoma in situ of the bladder, and is under investigation in combination with other agents, including the PD-L1 inhibitor atezolizumab (ClinicalTrials.gov Identifier: NCT02792192) which is administered intravenously. Additional recent investigations of intratumoral IO combinations also include IPI administered with interleukin-2 (IL-2) in advanced melanoma.[9] However, unlike these previous examples, not all tumors are as accessible for direct administration, and local administration to tumors does not preclude at least some leakage back to the systemic circulation.

Given the strengths and limitations that come with direct administration, a complementary approach is to consider safer systemic IO combinations. Several approaches are under development to better restrict IO combination action to the tumor following systemic administration. One example comes from combination of IO with a nanoparticle paclitaxel (PTX) formulation. As mentioned previously, chemotherapy represents a promising combination partner with checkpoint inhibitors by generating antigens following cancer cell killing. However, working against this possible synergy is the hallmark immunosuppression that comes with high-dose chemotherapy. Albumin-conjugated paclitaxel (nab-PTX) provides a possible avenue for reducing this risk. Preclinical data suggest the distribution of PTX is altered following nab-PTX administration relative to following administration of PTX (as Taxol), with elevated PTX levels in the tumor for nab-PTX. Population pharmacokinetic analysis of nab-PTX suggests faster distribution and slower elimination, respectively, of PTX following nab-PTX vs. PTX administration in cancer patients, and that albumin levels are a significant covariate on PTX clearance; it is unclear if this effect would impact relative levels of intratumoral PTX in patients with hypoalbuminemia.[10] Clinical data further demonstrate reduced rates of neutropenia for nab-PTX, and nab-PTX does not require steroid pretreatment due to PTX-associated hypersensitivity. In

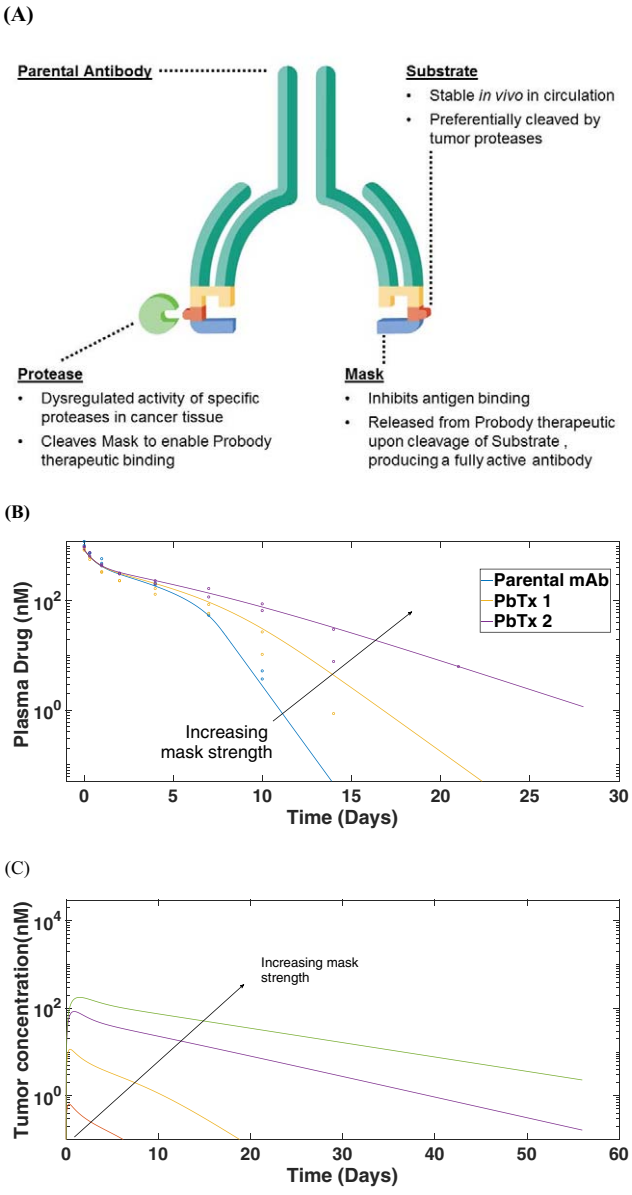

Figure 2 (**a**) A Probody therapeutic (Pb-Tx) is a prodrug form of a monoclonal antibody (mAb), and is comprised of a parental mAb and a prodomain. The prodomain is comprised of a mask that inhibits binding to antigen, and a protease-cleavable substrate between the mask and the light chain of the mAb. The mask inhibits antigen binding in the periphery, and can be removed by tumor-associated proteases. (**b**) A quantitative systems pharmacology (QSP) model was developed and calibrated against monkey pharmacokinetic (PK) data using Pb-Txs directed against CD166, which is broadly expressed in the tumor and periphery. The model predictions (solid lines) adequately described observed monkey PK data (points) following a single dose of Pb-Txs having increasing mask strengths, and captured decreasing Pb-Tx systemic clearance with increasing mask strength, which is consistent with avoiding peripheral target. (**c**) Human projections suggested successively higher levels of Pb-Tx in tumor following a single dose of Pb-Txs having increasing mask strengths at the same dose level.

this way, tolerability is designed into the regimen, with possibly enhanced ability to solicit cancer cell kill at a reduced risk of immunosuppression.[11] Early clinical data of nab-PTX in combination with atezolizumab are limited but encouraging.

Just as with the nab-PTX example, where we attempt to design in tolerability by controlling distribution of the combination partner, emerging technologies enable us to modulate the distribution and action of the IO agent(s) as well. One example comes from Probody therapeutics (Pb-Txs): monoclonal antibody prodrugs that are designed to activate preferentially in the tumor. A mask, which inhibits binding of the Pb-Tx in the healthy peripheral tissues, can be removed by tumor-associated proteases to release an active antibody. Nonclinical data and quantitative systems pharmacology models alike suggest the distribution of Pb-Tx in the tumor and the systemic compartment is tunable with mask strength (**Figure 2**), leading to an enhanced therapeutic index.[12] A Pb-Tx directed against PD-L1 is now in phase I investigation (ClinicalTrials.gov Identifier NCT03013491) both in monotherapy and combination, with several other IO Pb-Txs under development. *Ex vivo* results in selected human tumor samples suggest no correlation of protease activity with stage or grade of disease[12] and that protease activity can be detected in most patients (unpublished data). The emerging clinical dataset will permit identification of patient populations for further investigation, as well as evaluation of any significant covariates on Pb-Tx pharmacokinetics and E-R.

In summary, as the era of IO monotherapy passes an inflection point in cancer treatment, we enter a new era of IO combinations in our campaign to provide durable responses to more patients. This era of IO combinations represents the intersection of multiple paths, some well-traveled and some new, toward the ultimate goal of a cure. As responses become more durable for increasing numbers of patients, the tolerability of IO combinations becomes ever more important as we increasingly manage cancer as a chronic disease. Through a comprehensive characterization of the dose and schedule dependency of combination tolerability, we can inform regimens for IO combination that minimize toxicity; by restricting the action of IO combination agents to the tumor, we can possibly improve tolerability by design.

ACKNOWLEDGMENTS

We thank Applied BioMath for their scientific and technical contributions to the Pb-Tx QSP model which was supported by CytomX Therapeutics Inc. We also thank Sean A. McCarthy, DPhil, Carol Verser, PhD, Rachel Humphrey, MD, Jason Sagert, PhD, and Michael Kavanaugh, MD for helpful contributions and discussion.

AUTHOR CONTRIBUTIONS
M.S. wrote the article.

CONFLICT OF INTEREST
M.S. is an employee of CytomX Therapeutics, Inc., and owns CytomX stock.

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Psychedelic Drugs as Therapeutics: No Illusions About the Challenges

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Interest in the potential therapeutic benefits of psychedelic agents has recently increased. In addition to psilocybin, a wide variety of agents with psychedelic properties have been proposed and partially tested. However, the challenges of obtaining approval to market a restricted psychotomimetic agent are formidable.

Recent clinical trials with psilocybin for intractable anxiety and depression in patients with life-threatening cancer, a Review article and Commentary in this journal, have renewed interest in the potential therapeutic usefulness of psychedelic agents.[1–5] Medically, in addition to psilocybin, other substances with psychedelic properties, e.g., ketamine, 3,4methylenedioxymethamphetamine (MDMA), microdoses of lysergic acid diethylamide (LSD), and N, N-dimethyltryptamine (DMT), have been proposed to treat psychiatric and other diseases. While most past hallucinogen research was entirely descriptive, attempts at improved exploratory studies (e.g., obsessive-compulsive disorder, major depression, substance use disorders) have occurred in the past 20 years. While introducing elements of randomization, blinding, and a control arm, these are generally not placebo-controlled studies. Research to understand the mechanism of action of psychedelic agents as neurochemical probes is of scientific interest. The possibility of resetting even part of the brain's default network would have wide scientific, medical, ethical, and social implications.[4] The obstacles to drug approval remain daunting. This Commentary addresses some of the regulatory considerations and potential precedents.

PRACTICAL BARRIERS

Pragmatic barriers include: lack of intellectual property protection for composition of matter for old drugs; developments costs in the hundreds of millions of dollars; difficulty of designing and conducting double-blind trials with drugs that have easily detected effects; unique clinical trial constraints (e.g., limited appropriate treatment settings, small number of experienced investigators); need for a site license to possess a controlled substance; and the perceived risk of such a product from a pharmaceutical company perspective. In addition, since for most potential therapeutic applications a variety of effective drugs exist, it is not obvious where drugs with a risk of behavioral toxicity would fit.

PHARMACOLOGY AND MECHANISM OF ACTION

Psychedelic drugs are not identical in their mechanisms of action. Their basic pharmacology is diverse and pleomorphic, including complex agonist and partial agonist/antagonist actions on 5HT2A, 5HT2C, 5HT1A, dopamine D2, trace amine associate receptors 1, various transporters (e.g., serotonergic, dopaminergic), intracellular

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doi:10.1002/cpt.776