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Embracing Project Optimus: Can we leverage evolutionary theory to optimize dosing in oncology?

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Abstract

Project Optimus is a US Food and Drug Administration (FDA) initiative to reform dose selection in oncology drug development. Here, we focus on tumor evolution, a broadly observed phenomenon that invariably leads to therapeutic failure and disease relapse, and its effect on the exposure-response (E-R) relationships of oncology drugs. We propose a greater emphasis on tumor evolution during clinical development to facilitate the selection of optimal doses for molecularly targeted therapies and immunotherapies in oncology.

Keywords

Oncology; precision medicine; tumor evolution

Dose finding in light of tumor evolution

Demonstration of superior clinical efficacy is a major barrier to the approval of investigational oncology drugs. For indications with limited treatment options, sponsors frequently conduct efficacy trials under expedited timelines in hopes of making their therapy available to patients in need as quickly as possible. These factors lead sponsors to use high drug doses in hopes of maximizing drug exposure, eliciting strong signals of efficacy, and supporting expeditious regulatory approval. This “more is better” dogma is rooted in the use of cytotoxic chemotherapies at their maximum tolerated dose (MTD) to treat hematological malignancies [1]. Physicians may prefer to use the MTD despite increased toxicity out of

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Competing interests

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Supplemental materials

Supplemental Item 1: MATLAB R2020b code used for simulations and figure generation.

fear that lower doses, while more tolerable, could lead to subtherapeutic drug exposure and therapeutic failure.

Recently, the MTD paradigm has been challenged by nonlinear and even flat E-R relationships observed during the clinical development of molecularly targeted therapies and immunotherapies [2]. For these modalities, higher doses, especially when administered chronically, can incur significant additional toxicity. One recent high-profile example of this was the approval of sotorasib, which exhibited an unclear relationship between drug exposure and response metrics including overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) (Table 1). If lower doses are found to be non-inferior to the approved 960 mg dose, which comprises eight 120 mg tablets, patients may benefit from reduced pill burden as well as potentially lower rates of gastrointestinal side effects. To address these shortcomings, FDA launched Project Optimus to reform dose optimization and selection strategies used in oncology drug development [3].

This work contributes an evolutionary perspective to the misconception that higher doses invariably confer greater efficacy. Tumor evolution may contribute to the E-R relationships associated with targeted therapies and immunotherapies. We apply basic tumor evolutionary models composed of heterogenous cell populations and a hypothetical targeted therapy to illustrate how tumor evolution can contribute to saturable drug pharmacodynamics and comparable or superior long-term efficacy at doses below the MTD [4].

Tumor heterogeneity is a key factor contributing to therapeutic failure, drug resistance, and mortality. Optimizing clinical outcomes requires consideration for how evolutionary forces affect tumor growth and heterogeneity over time. By design, targeted therapies are highly specific to cell populations harboring particular genetic alterations. For tumors composed of cell populations with diverse genetic backgrounds, sensitivity to targeted therapy is variable and outgrowth of resistant populations is inevitable. One clear example is BRAF V600E-targeting therapies for melanoma, which trigger quick, transient responses followed by rapid relapse [5]. This unfortunate reality limits the benefit of many targeted therapies to short-term tumor control and significantly confounds their E-R relationships, as dose selection based on early responses may not yield optimal long-term tumor control. In addition, the relative expression of a target between tumor and healthy tissue may limit the upper range of doses able to be explored while maintaining acceptable levels of toxicity. It is regrettable that our ever-growing knowledge of tumor heterogeneity and clonal evolution is not yet routinely considered during clinical trial design and dose selection, as it may provide key insights to the optimization of targeted therapies [6].

Evolutionary origins of diverse E-R relationships

Tumor heterogeneity, which both drives and results from tumor evolution, refers to the co-existence of cell populations with distinct genotypes and phenotypes within a primary tumor and its metastases. Consider a simple tumor of two subpopulations: one with genetic alterations that confer susceptibility to a targeted therapy, and one without. Cells in the second population are intrinsically resistant to treatment and compete with sensitive cells for limited resources [7], [8]. High drug exposure causes swift and extensive

elimination of sensitive cell populations, reducing the competition faced by resistant populations ("competitive release") and facilitating their outgrowth. The competitive release phenomenon has motivated clinical trials that employ novel dosing schedules designed to maintain a residual population of sensitive cells that compete with resistant cells [9]. The speed at which resistant cells regrow after the treatment-mediated elimination of sensitive cells correlates, predictably, with treatment outcomes [10]. We view these efforts as paradigm-shifting for oncology because they challenge conventional thought and recharacterize cancer as a long-term disease to be managed through evolutionarily-motivated treatment strategies.

Here, we propose that competition and inter-population interactions profoundly influence the E-R relationships of oncology drugs (Fig 1). To illustrate this point, we first model tumors with a homogeneous population of sensitive cells to serve as a reference. Next, we adapt a tumor model comprising one subpopulation fully sensitized to treatment and one subpopulation with primary resistance. Given the competition for limited resources among cancer cells, particularly in late-stage metastatic disease where tumor burden is high, we also investigate a scenario where both populations share a carrying capacity that slows growth logistically as tumor size increases. We use the Hill function to model treatment action against the sensitive population and assume either 100% or 95% of cells are sensitive. Finally, we explore an additional scenario with treatment-mediated phenotype switching of sensitive cells into resistant cells. Model equations and parameter values are provided in the code accompanying this article.

- Scenario 1: homogenous population. The level of tumor heterogeneity largely depends on the types and stages of tumors. At the early stage of many hematological malignancies, clonal heterogeneity is generally believed to be low and maximally tolerated doses may result in the highest likelihood of tumor eradication. However, for solid tumors, diverse subclones can co-exist, making it challenging to achieve complete tumor eradication. Scenario 1 is presented mainly to serve as a comparator.
- Scenario 2: independent clones. Many tumor growth models considered distinct tumor clones but not all incorporate clonal interactions. With such a model assumption, the potential relationship between tumor early response and long-term tumor control cannot be appropriately evaluated.
- Scenario 3: clonal competition. Strong evidence for clonal competition during therapeutic treatment has been observed in prostate cancer [9].
- Scenario 4: clonal interconversion. It is possible that tumor clones can switch their phenotypic status in response to treatment. Tumor phenotypic conversion has been observed in colorectal cancer patients during anti-EGFR therapies [11]-[13].

In homogenous tumors, higher drug exposure resulted in greater tumor killing (Fig 1A), similar to intensive chemotherapy for hematologic malignancies. In tumors with mixed sensitivity to targeted therapy, however, E-R relationships were more shallow, flat, or even inverse (Fig 1B-D), depending on the manner and extent to which the subpopulations

interacted. These response patterns were observed regardless of whether populations were assumed to grow independently or in competition and were exacerbated by modest treatment-mediated phenotype switching of cells from sensitive to resistant. Clinically observed examples of flat, inverse, and unclear E-R relationships are noted in Table 1.

We also simulated 5-patient cohorts and incorporated heterogeneity by modeling patients with varying levels of resistant cell regrowth rates. There was no meaningful E-R relationship across 3 exposure levels when comparing the average tumor size reduction at a 12-week landmark timepoint (Fig 1E). Given this scenario, it is possible that heterogeneity in patient tumor biology (e.g., regrowth rates) has significantly confounded E-R relationships. Though the regrowth rate of resistant cells is not estimable prior to enrollment, our simulations provide a proof of concept that greater focus should be placed on characterizing intratumoral heterogeneity and the clonal fraction of therapy-sensitizing alterations during patient enrollment. Further efforts to design oncology trials with tumor heterogeneity and evolution in mind may be warranted by stratifying patients not only on by the presence of a genetic alteration, but also by its clonal fraction.

Insights for dose-finding studies

Patient populations.

The clinical efficacy of targeted therapies depends not only on tumor evolution, but the complex interplay between tumor evolution and the ecological system where the tumor resides. This includes biophysical and immunological factors within the tumor microenvironment as well as patient physiological conditions. Sponsors investigating novel targeted therapies may be motivated to enroll all patients with the genetic alteration of interest despite considerable variability in disease histology and treatment history. Enrolling sufficient numbers of patients with similar tumor biology and treatment history is critical to characterizing E-R relationships within subpopulations but can be unrealistic given these biologically diverse and often heavily pretreated populations. The resulting heterogeneity in tumor composition, anatomical distribution of lesion sites, and baseline patient characteristics could confound outcomes and the observed E-R relationship (Table 1, Figure 1) [14]. Other factors, such as stromal cells within the tumor microenvironment or systemic immune status, may influence tumor evolutionary trajectories. Given these differences, there is likely no truly optimal dose for an unselected patient population. Additional effort should be made in dose-finding studies to identify optimal dose regimens for specific patient populations characterized by key disease features such as the presence of a given genetic alteration and its clonal fraction.

Longitudinal biomarkers.

Early changes in tumor size metrics serve as a signal for drug efficacy but can be insufficient to fully elucidate E-R relationships. As shown in Figure 1, given a certain proportion of resistant cells prior to treatment, higher drug exposure invariably leads to deeper and faster responses. However, a swift, initial decline may be associated with stronger selective pressure for resistant lineages that survive and repopulate the tumor. The durability of response (DOR) elicited by higher drug exposure can be comparable or inferior to those

elicited by lower exposure, as noted elsewhere [4]; this is particularly apparent in tumors with high regrowth rates. In clinical terms, lower drug exposure in high-regrowth tumors might result in longer DOR and PFS. Mechanistically, longer DOR could be conferred through sufficient removal of sensitive cells to achieve an objective response while sparing enough to "crowd out" or thwart resistant cell growth. This suggests later-stage dose finding studies may benefit from emphasizing long-term outcomes (e.g., DOR, PFS, and OS) and deprioritizing short-term response metrics such as ORR; dose selection based on ORR from early trials alone might lead to supratherapeutic drug exposure, greater toxicity, and worse long-term outcomes. Longitudinal measures of response and tumor evolutionary dynamics, including radiomics and blood-based biomarkers, could prove valuable in evaluating E-R relationships in conjunction with standard pharmacokinetic (PK) and pharmacodynamic (PD) metrics. Rates of ctDNA shedding have been correlated with early cancer detection and could be useful for monitoring residual disease [15]-[17]. Further refinement of these methodologies may help identify distinct cancer cell lineages and quantify their relative proportions throughout the course of treatment [18], [19].

In conclusion, while substantial evidence exists to support alternative dosing strategies for targeted therapies, robust characterization of E-R relationships has been a low priority during clinical development. Evolutionary theory, coupled with conventional PK/PD modeling approaches, could be valuable to elucidating E-R relationships for targeted therapies and supporting the selection of doses and regimens that provide optimal long-term clinical benefit. Discovering and validating biomarkers of tumor evolution should be prioritized to serve this aim.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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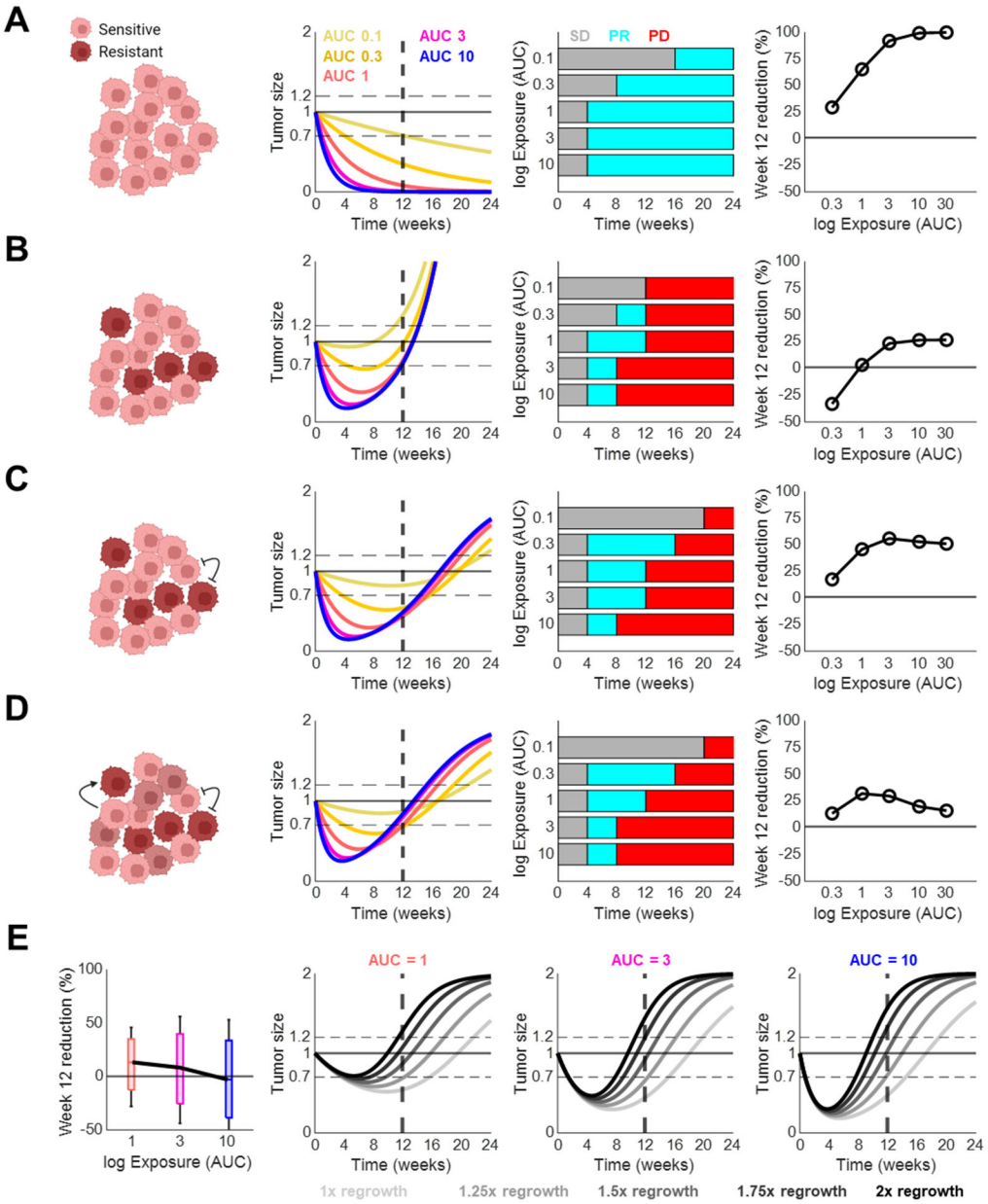

Figure 1. Impact of intratumoral heterogeneity on exposure-response relationships

A. Anti-tumor activity at 5 exposure levels in a homogenous population of sensitive cells. Left: Normalized tumor growth over 24 weeks of therapy with 4-week intervals between radiographic assessment of tumor volume. AUC, area under the curve. Horizontal dashed lines indicate thresholds for stable disease and progressive disease per RECIST v1.1 criteria. Center: Patient RECIST v1.1 classification over 6 months of treatment. SD, stable disease; PR, partial response; PD, progressive disease. Right: responses at the 12-week landmark time across 3 exposure levels.

B. (A) for a heterogenous population of sensitive (95%) and resistant (5%) cells with independent growth rates.

C. (A) for a heterogenous population of sensitive (95%) and resistant (5%) cells with a shared carrying capacity.

D. (A) for a heterogenous population of sensitive (95%) and resistant (5%) cells with a shared carrying capacity and treatment-mediated conversion of sensitive cells to resistant cells.

E. Impact of inter-patient variability in resistant cell growth rates on rebound kinetics and landmark-based exposure response relationships. Simulations were performed as in (C), spanning 3 levels of drug exposure and 5 levels of resistant cell regrowth. Responses at each exposure level were averaged at the 12-week landmark time (left).

Table 1:

Examples of FDA-approved drugs with flat, inverse, or unclear observed E-R relationships.

Drug	Indicated population	Exposure metric	Response metric	Description
atezolizumab	UC	Cycle 1 $C_{trough,}$ Steady-state AUC	ORR	No evaluated exposure metrics were significant predictors of ORR
capmatinib	metastatic NSCLC with *MET* exon 14 skipping mutation	Average C_{trough}	ORR	No E-R relationship for ORR
ceritinib	*ALK*+ metastatic NSCLC	Steady-state C_{trough}	ORR/PFS	No E-R relationship for ORR or PFS
enfortumab vedotin-ejfv	metastatic UC	Cycle 1 AUC, C_{max}, C_{trough}	BOR	Positive E-R relationship with intact drug; inverse relationship with free monomethyl auristatin E
entrectinib	*ROS1*+ metastatic NSCLC	C_{avg}/ C_{trough}	ORR	No relationship between entrectinib exposure and ORR. Response rates were comparable across exposure quartiles
erdafitinib	Metastatic UC with susceptible *FGFR2/3* mutations	Average daily AUC_{0-24}, C_{trough}, C_{max}	ORR	No significant differences in ORR between terciles of average daily AUC_{free} up to Day 14 or week 6 of treatment
fam-trastuzumab deruxtecan	*HER2*+ metastatic BC	Cycle 1/steady-state C_{avg}, C_{max}, C_{trough}, AUC	ORR	Trend toward increased ORR with increased intact DS-8201a exposure but not with increased released drug exposure. ORR increased with greater C_{avg}
idelalisib	Refractory/relapsed indolent NHL/CLL	Steady-state C_{tau}	ORR/PFS	No relationship between ORR and C_{tau} in patients with indolent NHL. Idelalisib C_{tau} quartile groups uniformly beneficial relative to placebo
nivolumab	MSI-H or dMMR metastatic CRC	Cycle 1-2 C_{avg}, C_{troug}	ORR	No E-R relationship observed, similar to other E-R analyses for efficacy in previous reviews (Reference ID: 4229532) demonstrating lower C_{trough} achieved with 480 mg Q4W compared to 3 mg/kg is unlikely to compromise efficacy
osimertinib	*T790M*+ metastatic NSCLC	Steady-state AUC	ORR	Response rate concluded to be relatively flat across a wide exposure range
pembrolizumab	metastatic melanoma	Steady-state AUC	ORR	Flat E-R relationship used to support approval of 2 mg/kg dosing
pemigatinib	Metastatic cholangiocarcinoma with *FGF2* fusion or rearrangement	Steady-state C_{max}, AUC	ORR/PFS	Lowest ORR in highest C_{max} quartile. Non-significant difference in PFS in the highest AUC_{ss} quartile
ponatinib	CML or Philadelphia chromosome ALL	Dose intensity (average daily dose)	MaHR	Significant E-R relationship in CP-CML patients, but not in AP-CML/BP-CML/Ph+ ALL patients
pralsetinib	*RET*+ metastatic NSCLC	Steady-state C_{avg}	BOR/PFS/DOR	No E-R analysis relationship in the primary efficacy population
sacituzumab govitecan-hziy	metastatic TNBC	Cycle 1 AUC	ORR/PFS/OS	No correlation between response and AUC of any of the drug's constitutive elements
sotorasib	*KRAS G21C*-mutated NSCLC	Steady-state C_{avg}, C_{trough}	OS/PFS/ORR	Higher exposure associated with worse efficacy. Apparent inverse E-R relationship likely confounded by baseline disease burden on PK and efficacy outcomes
zanubrutinib	MCL	Steady-state AUC, C_{trough}	ORR	Positive E-R trends, but no statistically significant relationship identified

All data are publicly available from FDA summary and clinical pharmacology review documents.

ALL, acute lymphoblastic leukemia; ALK, anaplastic lymphoma kinase; AUC, area under concentration-time curve; BC, breast cancer; BOR, best objective response; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CRC, colorectal cancer; dMMR, deficient mismatch repair; FGFR2/3, fibroblast growth factor receptor 2 or 3; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus; MaHR, major hematologic response; MCyR, major cytogenetic response; MCL, mantle cell lymphoma; MET, mesenchymal epithelial transition factor receptor; MM, multiple myeloma; MSI-H, microsatellite instability-high; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RET, ret proto-oncogene; ROS1, ROS Proto-Oncogene 1 Receptor Tyrosine Kinase; TNBC, triple-negative breast cancer; UC, urothelial carcinoma