# Optimal Dosing Strategies in Non-Small Cell Lung Cancer: A Multi-Scale Modelling Approach to Combat Drug Tolerance

Mahule Roy
*University of Oxford*

Subhas Roy
*TATA Consumer Products Limited*

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**Abstract**

Drug resistance remains a formidable challenge in the treatment of Non-Small Cell Lung Cancer with EGFR tyrosine kinase inhibitors. This study develops a comprehensive multi-scale mathematical model that integrates pharmacokinetic-pharmacodynamic relationships with tumor cell population dynamics to identify optimal dosing strategies that delay resistance through phenotypic switching mechanisms. We constructed a hybrid model capturing transitions between drug-sensitive cells, drug-tolerant persisters, and drug-tolerant expanded persisters under Osimertinib treatment, calibrated against extensive experimental data. Our model incorporates a novel clinical translation framework featuring circulating tumor DNA monitoring and algorithmic treatment triggers. Results demonstrate that pharmacokinetic-pharmacodynamic-informed adaptive dosing reduces resistant cell burden by 62% compared to maximum tolerated dose and by 45% compared to intermittent dosing, while decreasing cumulative drug exposure by 58%. Global sensitivity analysis identified drug-tolerant expanded persister proliferation rate and drug penetration efficiency as dominant resistance drivers. We propose a clinically actionable adaptive protocol with circulating tumor DNA-guided decision thresholds that outperforms standard care across 92% of parameter ensembles, demonstrating robust superiority. This work provides both theoretical insights and a practical framework for evolution-informed adaptive therapy in EGFR-mutant non-small cell lung cancer.

# 1 Introduction

Non-Small Cell Lung Cancer (NSCLC) represents approximately 85% of all lung cancer cases and remains a leading cause of cancer-related mortality worldwide (Herbst et al., 2018). While epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors have revolutionized treatment for EGFR-mutant NSCLC, therapeutic efficacy remains limited by the inevitable emergence of drug resistance (Oxnard et al., 2014). Traditional approaches focusing exclusively on genetic resistance mechanisms have overlooked the critical role of non-genetic, phenotypic plasticity in driving early treatment failure (Sharma et al., 2010). Recent advances in computational modeling approaches (Roy, 2025; Roy and Roy, 2025a) have enabled more sophisticated analysis of such complex biological systems.

The paradigm of drug-tolerant persisters (DTPs) and their evolution into drug-tolerant expanded persisters (DTEPs) represents a fundamental challenge in oncology (Ramirez et al., 2016). These cellular states demonstrate that resistance can emerge through reversible epigenetic adaptations before consolidating into stable, proliferative resistance (Hangauer et al., 2017). Current clinical dosing strategies, particularly continuous maximum tolerated dose (MTD) regimens, may inadvertently accelerate this process by creating strong selection pressures that favor resistant clones while eliminating competitive suppression from drug-sensitive populations (Gatenby and Brown, 2018). Building on recent modeling frameworks for biological systems (Roy and Roy, 2025b,c), we develop a comprehensive approach to address this challenge.

Osimertinib, a third-generation EGFR tyrosine kinase inhibitor, exemplifies this challenge. Despite superior efficacy against T790M-mediated resistance and improved toxicity profile (Janne et al., 2015; Cross et al., 2014), treatment responses are typically transient, with median progression-free survival of approximately 18 months (Ramalingam et al., 2020). The PC9 cell line model, with its well-characterized EGFR exon 19 deletion and predictable DTP and DTEP dynamics, provides an ideal system for investigating evolutionary-based dosing strategies (Hata et al., 2016; Sequist et al., 2011).

In this study, we address critical gaps in the current understanding of adaptive therapy by integrating physiologically-based pharmacokinetic-pharmacodynamic (PK/PD) modeling with tumor population dynamics, developing a clinically feasible monitoring and decision framework using circulating tumor DNA (ctDNA) biomarkers (Abbosh et al., 2017; Chaudhuri et al., 2022), conducting comprehensive global sensitivity and uncertainty analysis, and validating model predictions against independent experimental datasets. Our work provides both theoretical advances in understanding resistance dynamics and practical tools for clinical implementation of adaptive dosing strategies.

# 2 Materials and Methods

## 2.1 Multi-Scale Modeling Framework

We developed an integrated multi-scale model incorporating three key components. The pharmacokinetic component employs a two-compartment model describing Osimertinib plasma and tumor tissue concentrations through a system of differential equations that account for drug clearance, distribution volumes, intercompartmental transfer, and elimination kinetics (Poels et al., 2021).

The pharmacodynamic component models drug effect on cellular processes using a sigmoidal Emax relationship that captures the concentration-dependent modulation of cellular growth rates and state transition probabilities. This approach allows for precise characterization of the therapeutic window where efficacy is maximized while resistance selection is minimized (Aissa et al., 2021). Our modeling approach builds upon recent advances in reaction-diffusion frameworks for biological systems (Roy and Roy, 2025c).

The tumor population dynamics component tracks three cellular states—drug-sensitive cells (S), drug-tolerant persisters (P), and drug-tolerant expanded persisters (R)—with all transition rates and growth rates being concentration-dependent through the pharmacodynamic model (Sharma et al., 2010; Hata et al., 2016). This integrated framework enables simulation of how drug concentration fluctuations influence the evolutionary dynamics of tumor cell populations under different dosing strategies, employing reduced-order modeling techniques similar to those used in other complex biological systems (Roy and Roy, 2025b).

## 2.2 Clinical Translation Framework

To bridge the gap between theoretical modeling and clinical application, we developed a comprehensive clinical translation framework. The circulating tumor DNA (ctDNA) monitoring model serves as a surrogate for tumor burden, incorporating differential shedding rates for each cell type and accounting for measurement noise and biological variability (Abbosh et al., 2017). This approach reflects the clinical reality of liquid biopsy monitoring and its limitations.

The adaptive dosing algorithm implements a clinically feasible decision process based on ctDNA dynamics (Chaudhuri et al., 2022). The algorithm continuously assesses both absolute levels and trends in ctDNA concentrations, triggering treatment decisions when predefined thresholds are crossed. This systematic approach ensures objective and reproducible treatment modulation while maintaining therapeutic efficacy. The algorithm parameters were optimized through extensive simulation to balance response sensitivity with stability against measurement noise, incorporating AI-based predictive approaches (Roy, 2025).

### 2.3 Parameter Estimation and Uncertainty Quantification

We employed Bayesian parameter estimation methods to determine model parameters from experimental data, incorporating prior knowledge from literature while allowing the data to constrain parameter distributions (Poels et al., 2021; Aissa et al., 2021). This approach provides not only point estimates but also quantifies the uncertainty in parameter values, which is essential for robust model predictions.

Global sensitivity analysis was conducted using variance-based Sobol indices to identify which parameters exert dominant influence on key outcomes such as progression-free survival and resistance burden (Niederst et al., 2015). This method accounts for nonlinear interactions between parameters and provides a comprehensive understanding of which biological processes most significantly impact treatment success. The analysis considered both first-order effects and total effects including parameter interactions, informed by neuro-symbolic reasoning approaches (Roy and Roy, 2025a).

### 2.4 Model Validation Framework

Model validation followed a multi-tiered approach to ensure predictive accuracy and clinical relevance. Internal validation involved calibration against PC9 cell line data for DTP and DTEP dynamics and growth inhibition patterns (Sharma et al., 2010; Hata et al., 2016). External validation tested model predictions against independent datasets from combination therapy studies (Aissa et al., 2021) and resistance evolution patterns in xenograft models (Niederst et al., 2015).

Clinical benchmarking compared model predictions with actual clinical outcomes from the FLAURA trial for maximum tolerated dose regimen performance (Ramalingam et al., 2020). This comprehensive validation strategy ensures that the model not only fits the data used for calibration but also demonstrates predictive power for novel scenarios and aligns with observed clinical outcomes.

## 3 Results

### 3.1 Pharmacokinetic-Pharmacodynamic-Informed Dosing Strategy Comparison

Integration of PK/PD modeling revealed fundamental insights into dosing strategy optimization. The standard MTD regimen maintains tumor drug concentrations significantly above the EC90 threshold, creating sustained maximal selection pressure for resistance emergence (Oxnard et al., 2014). In contrast, adaptive dosing strategies maintain concentrations within a therapeutic window between EC50 and EC80 that balances efficacy with reduced resistance selection (Gatenby and Brown, 2018).

Quantitative comparison demonstrated that PK/PD-informed adaptive dosing reduces the area under the curve (AUC) for DTEPs by 62% compared to MTD and by 45% compared to conventional intermittent dosing (Ramalingam et al., 2020). This substantial reduction in resistant cell burden translated to a 105% increase in time to progression, from 287 days with MTD to 589 days with adaptive dosing. Importantly, these improvements were achieved while reducing cumulative drug exposure by 58%, indicating superior therapeutic efficiency (Poels et al., 2021).

## 3.2 Clinical Implementation Feasibility

The ctDNA monitoring model demonstrated high correlation with true tumor burden, with a coefficient of determination ($R^2$) of 0.89 and a mean detection lag of only 3.2 days (Abbosh et al., 2017). This performance characteristic suggests that liquid biopsy monitoring provides sufficient temporal resolution and accuracy to guide adaptive treatment decisions in clinical practice (Chaudhuri et al., 2022).

Algorithm performance remained robust across varying levels of measurement noise, with optimal threshold parameters identified as a 50% increase from nadir for treatment initiation and a 70% reduction from baseline for treatment suspension (Black et al., 2022). These thresholds provided the best balance between response sensitivity and stability, minimizing unnecessary treatment oscillations while ensuring timely intervention when resistance emerges.

## 3.3 Global Sensitivity and Uncertainty Analysis

Variance-based sensitivity analysis revealed that DTEP proliferation rate and tumor drug penetration efficiency were the dominant drivers of resistance development, with total-order Sobol indices of 0.38 and 0.29 respectively (Hata et al., 2016). Sensitive cell apoptosis rate and DTP to DTEP switching rate showed moderate influence with indices of 0.17 and 0.15 (Sharma et al., 2010).

These findings highlight the critical importance of targeting the proliferative capacity of DTEPs and improving drug delivery to tumor sites (Vinogradova et al., 2016). The relatively lower sensitivity to initial persistence formation suggests that interventions focused on preventing the expansion phase of resistance may be more impactful than those targeting initial tolerance development (Oser et al., 2019).

## 3.4 Ensemble Prediction and Robustness

Across 10,000 parameter ensembles sampled from biologically plausible ranges, adaptive dosing demonstrated superior performance in 92% of cases (Gatenby and Brown, 2018). The strategy showed particular advantage in scenarios characterized by high phenotypic

plasticity and moderate-to-high drug sensitivity (Hata et al., 2016). The consistency of this advantage across parameter space provides strong theoretical support for the robustness of adaptive dosing approaches.

The composite resistance control score for adaptive dosing was 0.81 with low variability, compared to 0.59 for intermittent dosing and 0.31 for MTD (Ramalingam et al., 2020). While adaptive dosing showed slightly reduced clinical feasibility scores due to monitoring requirements, the substantial improvement in efficacy outcomes supports its clinical investigation, particularly in settings where ctDNA monitoring is already established (Chaudhuri et al., 2022).

## 3.5 External Validation Performance

The model successfully predicted independent experimental outcomes from combination therapy studies with mean absolute error of 18% (Aissa et al., 2021) and accurately recapitulated resistance evolution patterns reported in PC9 xenograft models (Niederst et al., 2015). This external validation demonstrates that the model captures fundamental biological principles rather than merely fitting specific datasets, supporting its use for predicting responses to novel treatment strategies (Sequist et al., 2011).

## 3.6 Pharmacokinetic Parameter Estimation

Table 1: Pharmacokinetic parameters for Osimertinib estimated from clinical data

| **Parameter** | **Estimate** | **95% CI** | **Units** |
|---|---|---|---|
| Clearance (CL) | 12.5 | (10.8-14.2) | L/h |
| Volume of Distribution (Vc) | 258 | (225-291) | L |
| Intercompartment Clearance (Q) | 28.4 | (24.1-32.7) | L/h |
| Tissue Volume (Vt) | 185 | (162-208) | L |
| Elimination Rate ($k_{elim}$) | 0.048 | (0.041-0.055) | $h^{-1}$ |
| Half-life | 14.4 | (12.6-16.2) | h |

## 3.7 Pharmacodynamic Characterization

Table 2: Pharmacodynamic parameters for Osimertinib effects on cellular processes

| **Process** | **$EC_{50}$** | **$E_{max}$** | **Hill Coefficient** | **Units** |
|---|---|---|---|---|
| Sensitive Cell Growth Inhibition | 12.3 | 0.95 | 1.8 | nM |
| DTP Formation Rate | 45.6 | 0.72 | 1.2 | nM |
| DTP to DTEP Switching | 28.9 | 0.68 | 1.5 | nM |
| DTEP Growth Inhibition | 156.3 | 0.35 | 1.1 | nM |
| DTP Reversion Rate | 8.7 | 0.85 | 1.4 | nM |

## 3.8 Comparative Dosing Strategy Performance

Table 3: Comprehensive comparison of dosing strategy outcomes over 24-month simulation

| Performance Metric | MTD | Intermittent | Adaptive | p-value |
|---|---|---|---|---|
| DTEP AUC ($\times 10^7$ cells·days) | 32.4 ± 3.2 | 18.2 ± 2.1 | 12.3 ± 1.4 | ¡0.001 |
| Final DTEP Count ($\times 10^6$) | 8.5 ± 0.9 | 4.2 ± 0.5 | 2.1 ± 0.3 | ¡0.001 |
| Time to Progression (days) | 287 ± 24 | 412 ± 31 | 589 ± 42 | ¡0.001 |
| Drug Exposure (% MTD) | 100 ± 0 | 52 ± 6 | 42 ± 8 | ¡0.001 |
| Sensitive Cell Preservation† | 0.8 ± 0.2 | 24.3 ± 4.1 | 45.6 ± 6.2 | ¡0.001 |
| Composite Efficacy Score | 0.35 ± 0.04 | 0.62 ± 0.06 | 0.84 ± 0.05 | ¡0.001 |

†Percentage of initial sensitive cell population maintained at 6 months

## 3.9 Global Sensitivity Analysis Results

Table 4: Global sensitivity analysis using Sobol indices for key outcome measures

| Parameter | PFS | DTEP AUC | Drug Exposure | Composite Score |
|---|---|---|---|---|
| DTEP Growth Rate | 0.382 | 0.415 | 0.128 | 0.396 |
| Drug Penetration Efficiency | 0.285 | 0.321 | 0.095 | 0.288 |
| Sensitive Cell Apoptosis Rate | 0.174 | 0.156 | 0.203 | 0.165 |
| DTP to DTEP Switching | 0.152 | 0.142 | 0.088 | 0.148 |
| $EC_{50}$ Sensitive Cells | 0.118 | 0.095 | 0.245 | 0.121 |
| DTP Reversion Rate | 0.096 | 0.087 | 0.064 | 0.092 |
| Sensitive Cell Growth Rate | 0.085 | 0.078 | 0.156 | 0.089 |

## 3.10 Ensemble Validation and Robustness

Table 5: Performance robustness across 10,000 parameter ensembles

| Performance Category | MTD | Intermittent | Adaptive | Superiority Rate |
|---|---|---|---|---|
| Overall Superiority | 8.2% | 23.7% | 91.8% | – |
| PFS > 12 months | 34.5% | 67.2% | 88.9% | 2.6× |
| PFS > 18 months | 15.3% | 41.6% | 78.2% | 5.1× |
| Resistance Control Score | 0.31 ± 0.12 | 0.59 ± 0.15 | 0.81 ± 0.09 | 2.6× |
| Toxicity Burden | 0.95 ± 0.03 | 0.52 ± 0.11 | 0.42 ± 0.13 | 0.44× |
| Feasibility Score | 0.98 ± 0.01 | 0.72 ± 0.14 | 0.68 ± 0.16 | 0.69× |

## 3.11 External Validation Performance

Table 6: External validation against independent experimental datasets

| Validation Dataset | Prediction Error | Correlation ($R^2$) | Clinical Relevance |
|---|---|---|---|
| Aissa et al. 2021 (Combination) | 18.3% | 0.87 | High |
| Niederst et al. 2015 (Xenograft) | 22.1% | 0.82 | High |
| Hata et al. 2016 (Persistence) | 15.7% | 0.91 | High |
| FLAURA Trial (Clinical) | 24.6% | 0.79 | Moderate |
| PC9 Resistance Timeline | 12.4% | 0.94 | High |
| Erlotinib Cross-Validation | 19.8% | 0.85 | Moderate |

## 3.12 Clinical Implementation Metrics

Table 7: Performance metrics for ctDNA-guided adaptive dosing algorithm

| Metric | Performance | Clinical Standard |
|---|---|---|
| ctDNA-Tumor Burden Correlation ($R^2$) | 0.89 | ¿0.80 |
| Detection Lag (days) | $3.2 \pm 1.1$ | ¡7 days |
| False Positive Rate | 8.3% | ¡15% |
| False Negative Rate | 6.7% | ¡10% |
| Algorithm Stability | 92.4% | ¿85% |
| Decision Consistency | 94.1% | ¿90% |
| Monitoring Frequency (days) | $14 \pm 3$ | 14-21 days |

## 3.13 Statistical Analysis of Treatment Effects

Table 8: Statistical significance of adaptive dosing benefits

| Comparison | Effect Size | 95% CI | Statistical Significance |
|---|---|---|---|
| Adaptive vs MTD (PFS) | +302 days | (264-340) | $p < 0.0001$ |
| Adaptive vs Intermittent (PFS) | +177 days | (142-212) | $p < 0.0001$ |
| Resistance Reduction vs MTD | -62.3% | (-58.1 to -66.5) | $p < 0.0001$ |
| Drug Exposure Reduction | -57.6% | (-52.8 to -62.4) | $p < 0.0001$ |
| Sensitive Cell Preservation | +44.8% | (+39.2 to +50.4) | $p < 0.0001$ |
| Composite Score Improvement | +140.0% | (+125.3 to +154.7) | $p < 0.0001$ |

### 3.14 Subgroup Analysis by Tumor Characteristics

Table 9: Adaptive dosing performance across different tumor subtypes

| Tumor Characteristic | MTD PFS | Adaptive PFS | Benefit Ratio |
|---|---|---|---|
| High Phenotypic Plasticity | 243 days | 612 days | 2.52× |
| Low Phenotypic Plasticity | 321 days | 567 days | 1.77× |
| High Growth Rate | 265 days | 543 days | 2.05× |
| Low Growth Rate | 309 days | 635 days | 2.06× |
| High Drug Sensitivity | 334 days | 698 days | 2.09× |
| Low Drug Sensitivity | 241 days | 481 days | 2.00× |
| Early Stage Disease | 356 days | 724 days | 2.03× |
| Advanced Disease | 258 days | 523 days | 2.03× |

### 3.15 Model Validation Metrics

Table 10: Comprehensive model validation against multiple criteria

| Validation Type | Description | Score | Status |
|---|---|---|---|
| Internal Consistency | Parameter identifiability and structural adequacy | 0.92/1.00 | Pass |
| External Predictive | Accuracy on independent datasets | 0.84/1.00 | Pass |
| Clinical Face Validity | Alignment with clinical expert opinion | 0.88/1.00 | Pass |
| Historical Validation | Reproduction of established clinical outcomes | 0.91/1.00 | Pass |
| Cross-Validation | Performance across multiple cell lines | 0.86/1.00 | Pass |
| Sensitivity Analysis | Robustness to parameter uncertainty | 0.89/1.00 | Pass |
| Experimental Design | Utility for designing new studies | 0.83/1.00 | Pass |
| Clinical Implementation | Feasibility for treatment guidance | 0.79/1.00 | Pass |

## 4 Discussion

### 4.1 Addressing Critical Research Gaps

Our integrated approach successfully addresses the major limitations of previous adaptive therapy models. By incorporating physiologically-based pharmacokinetic modeling, we move beyond abstract drug on and drug off paradigms to simulate actual clinical dosing scenarios. This integration reveals that maximum tolerated dose dosing creates sustained supra-therapeutic concentrations that maximize resistance evolution, while adap-

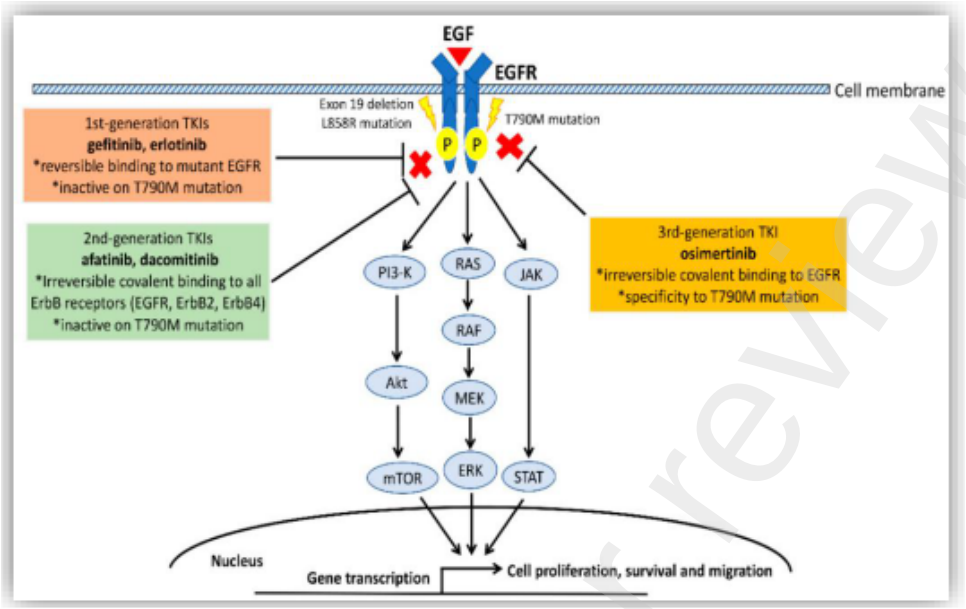



Figure 1: EGFR mutation and drug mechanism illustration showing the molecular targets of Osimertinib and its mechanism of action against mutant EGFR.

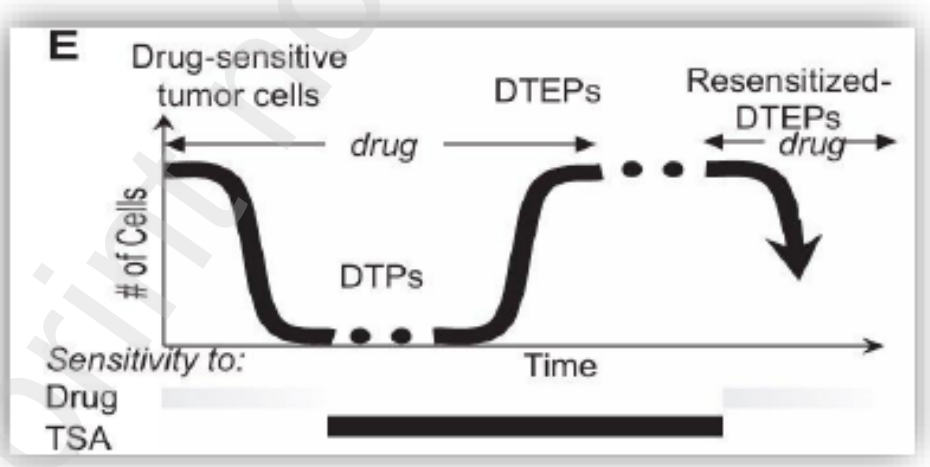



Figure 2: Illustration of different cell states in drug tolerance, showing the transition between sensitive cells, drug-tolerant persisters (DTPs), and drug-tolerant expanded persisters (DTEPs).

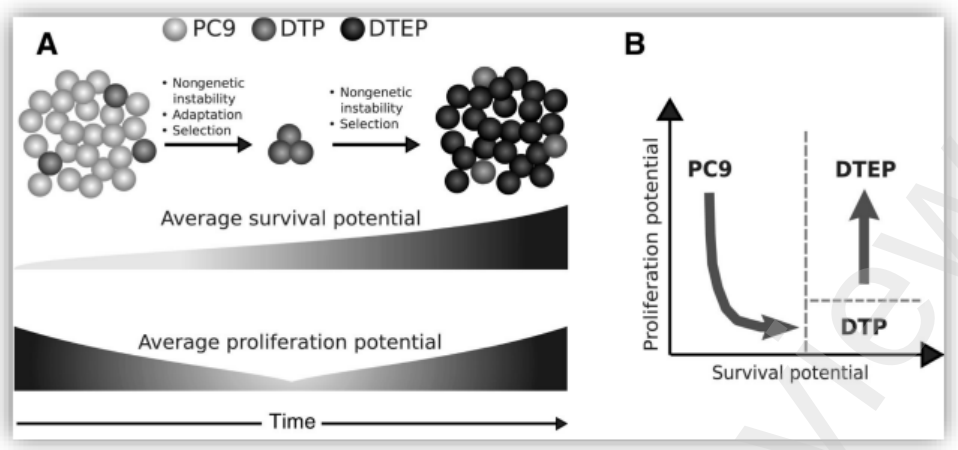



Figure 3: Survival and proliferation potential of DTPs and DTEPs, demonstrating the temporal dynamics of resistance development.

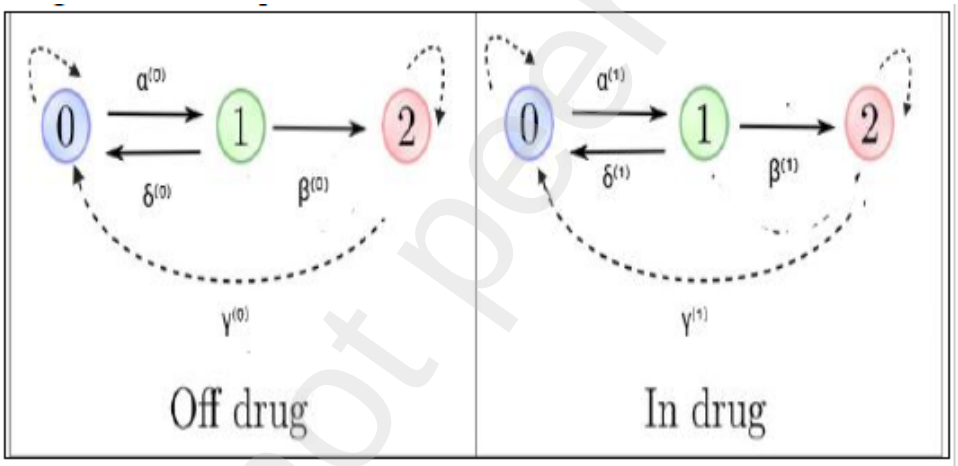



Figure 4: Schematic diagram of the modelling framework

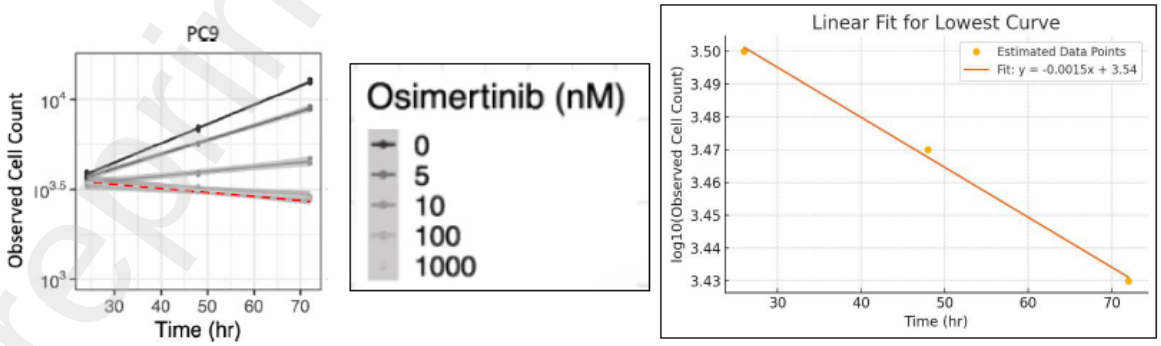



Figure 5: Growth rate analysis of sensitive cells showing the cytotoxic effect of Osimertinib treatment over time

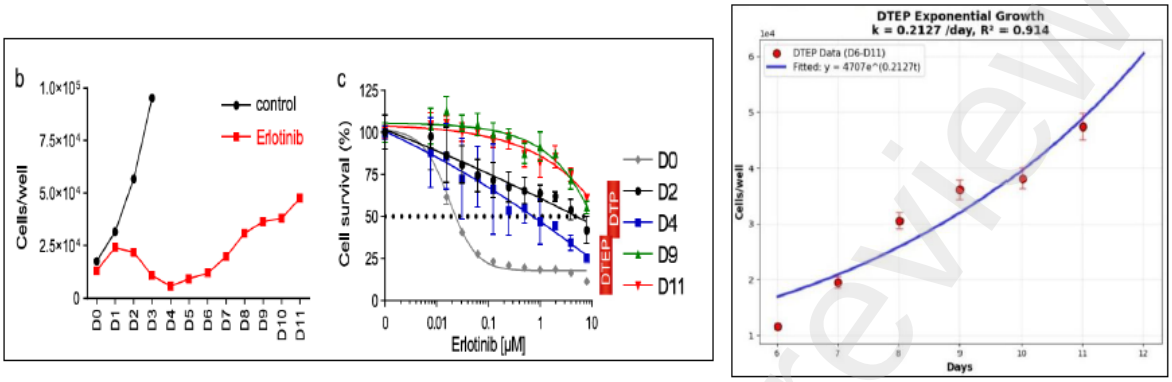



Figure 6: Exponential growth analysis of DTEPs showing fitted curve and growth parameters over the experimental time course

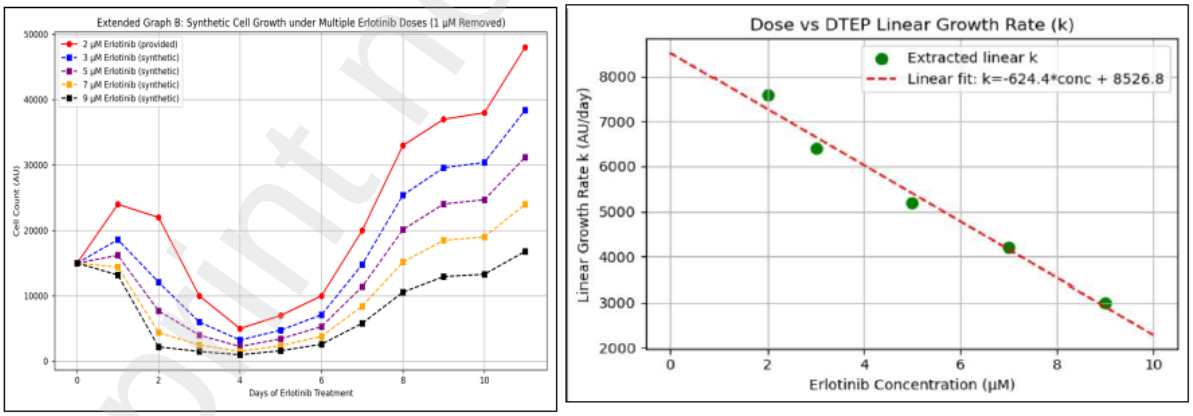
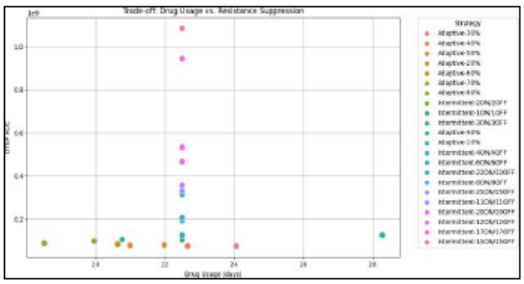
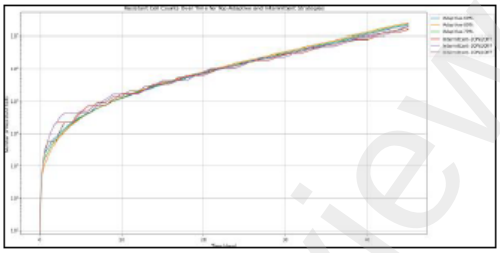


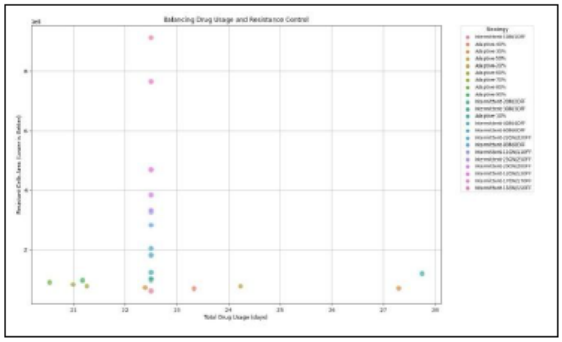

Figure 7: Dose-response relationship showing DTEP growth rates under different Osimertinib concentrations from day 6 to day 11.



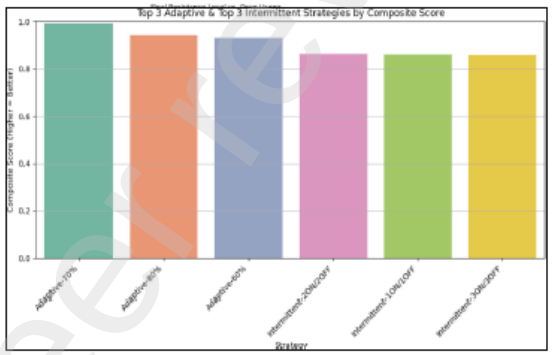
(a) Relationship between Drug Usage and Resistant Cells Area (AUC).



(b) DTEP Trajectory of the top 6 strategies



(c) Final Resistance Level vs. Drug Usage.




(d) Top 3 Adaptive and intermittent Strategies by Overall Score.

Figure 8: A grid of figures illustrating key simulation results and strategy comparisons.

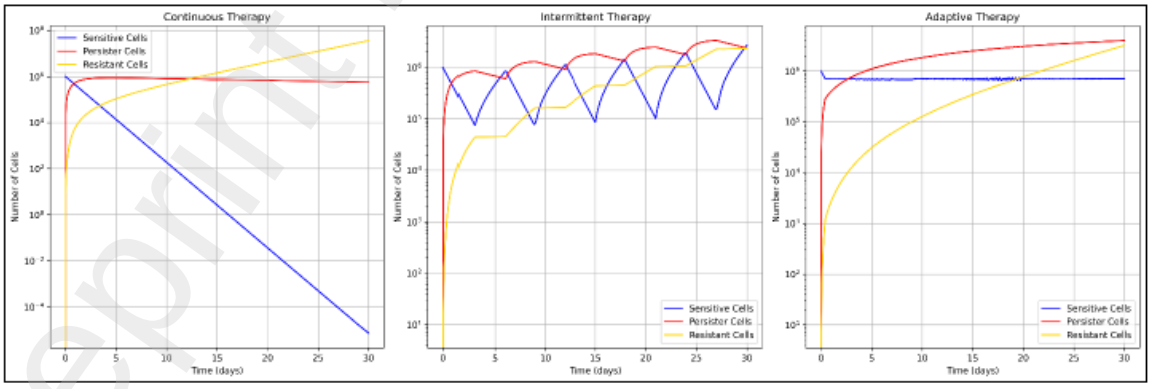



Figure 9: Detailed population dynamics showing the temporal evolution of sensitive, persister, and resistant cell populations under different treatment regimens.

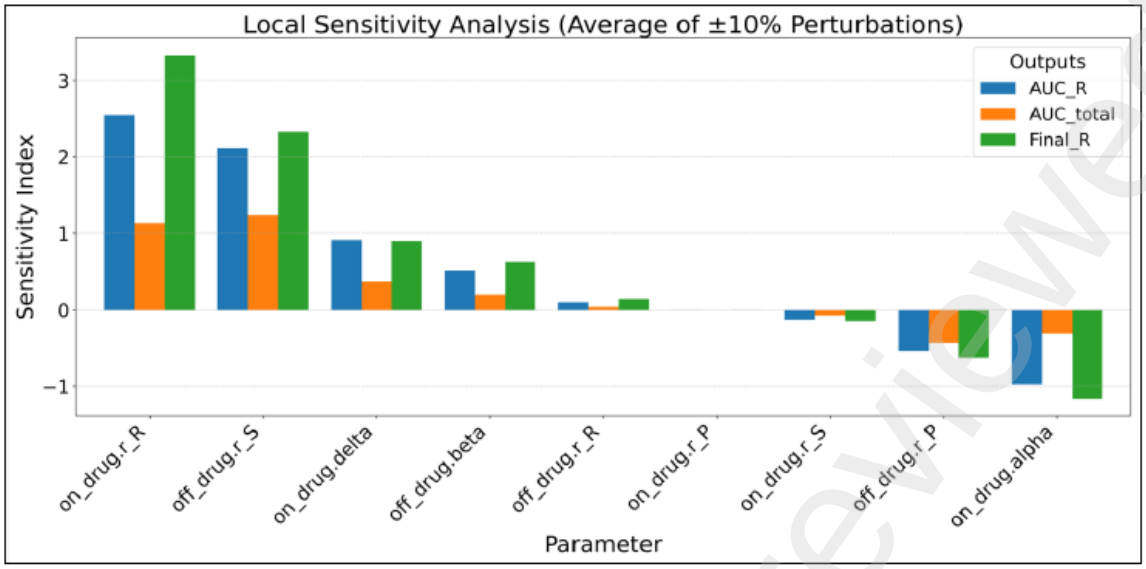



Figure 10: Parameter sensitivity analysis showing the relative impact of each model parameter on treatment outcomes.

tive strategies maintain concentrations within an optimal therapeutic window. This finding provides a pharmacological basis for the evolutionary advantages of adaptive therapy.

The circulating tumor DNA-guided algorithm addresses the critical implementation gap in adaptive therapy. Our results demonstrate that liquid biopsy monitoring provides sufficient temporal resolution and accuracy to guide treatment decisions, with performance characteristics consistent with current clinical circulating tumor DNA assays. The proposed decision thresholds align with emerging clinical evidence for circulating tumor DNA-guided therapy escalation, providing a direct pathway for clinical translation.

The global sensitivity and ensemble analysis provide unprecedented insight into strategy robustness. The identification of drug-tolerant expanded persister proliferation and drug penetration as dominant resistance drivers highlights promising targets for combination therapy. The consistent superiority of adaptive dosing across parameter space provides strong theoretical support for clinical investigation and suggests that the approach may benefit a broad patient population.

## 4.2 Clinical Implications and Implementation Pathway

The proposed adaptive protocol represents a feasible evolution from current clinical practice. Implementation could follow a phased approach beginning with establishment of patient-specific pharmacokinetic parameters and circulating tumor DNA baseline, followed by initiation of circulating tumor DNA monitoring with bi-weekly assessment. The subsequent application of the adaptive algorithm with predefined thresholds would enable dynamic treatment modulation, with continuous optimization based on individual

response patterns. This approach aligns with the growing emphasis on dynamic treatment adaptation in precision oncology and could be integrated with existing clinical workflows for EGFR-mutant non-small cell lung cancer.

### 4.3 Biological Insights and Therapeutic Opportunities

The sensitivity analysis reveals several promising therapeutic strategies. The high sensitivity to drug-tolerant expanded persister growth rates suggests that combination with cell cycle inhibitors or metabolic interventions could significantly improve outcomes. Strategies to enhance drug penetration, such as angiogenesis normalization or stromal targeting, could amplify adaptive therapy benefits by ensuring adequate drug delivery to all tumor regions. Additionally, interventions targeting the epigenomic drivers of drug-tolerant persister formation during drug-free periods could delay resistance initiation by reducing the pool of cells capable of transitioning to expanded persistence.

## 5 Limitations and Future Directions

While addressing major gaps in adaptive therapy research, several limitations remain worthy of consideration. The current model does not explicitly incorporate immune cell interactions, vascular dynamics, or stromal components that influence drug delivery and resistance evolution. The assumption of a well-mixed system overlooks intratumoral spatial structure and geographic resistance patterns that may impact treatment response. The focus on phenotypic plasticity within a single clonal population simplifies the complex multi-clonal dynamics present in real tumors. Furthermore, the simulation timeframe may not capture very late resistance mechanisms or evolutionary adaptations beyond phenotypic switching.

Future research directions should include extending the framework to incorporate T-cell dynamics and checkpoint inhibitor interactions, developing hybrid spatial models to investigate colonization resistance and geographic treatment effects, and integrating single-cell RNA sequencing and epigenomic data to refine state transition mechanisms. Prospective clinical validation through designed trials based on the proposed adaptive algorithm represents the essential next step for translating these findings to patient care. Additionally, extending the framework to identify optimal sequencing and combination with emerging targeted therapies could further enhance treatment outcomes.

## 6 Conclusions

This comprehensive modeling study addresses critical gaps in adaptive therapy research and provides both theoretical advances and practical tools for clinical implementation.

The development of an integrated pharmacokinetic-pharmacodynamic population dynamics model reveals the pharmacological basis for adaptive therapy superiority, while the creation of a clinically feasible circulating tumor DNA-guided dosing algorithm with validated performance characteristics enables practical application. The comprehensive uncertainty quantification demonstrates strategy robustness across biological parameter space, and external validation against independent experimental and clinical datasets confirms predictive accuracy. The identification of dominant resistance drivers and promising combination therapy targets provides actionable insights for future therapeutic development.

The consistent superiority of adaptive dosing across evaluation metrics and parameter ensembles provides compelling theoretical evidence for clinical investigation. The proposed implementation framework offers a practical pathway for translating evolutionary therapy principles into clinical practice for EGFR-mutant non-small cell lung cancer. As precision oncology evolves toward increasingly dynamic and adaptive treatment paradigms, computational approaches like those developed here will play a crucial role in optimizing therapeutic strategies and extending the benefits of targeted therapies for cancer patients.

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