



The Spatial-Genomic Oncology Continuum

Reaction-Diffusion Biophysics Resolves the 36-Month Post-ADAURA Discontinuation Cliff in Resected EGFR-Mutant NSCLC

Luca Celebrano, MD Candidate • Università degli Studi di Napoli Federico II • Telethon Institute of Genetics and Medicine (TIGEM) • l.celebrano@studenti.unina.it

Nature Communications: NCOMMS-26-091227

Research Square DOI: 10.21203/rs.3.rs-11530312/v1

Bioconda: spatial-continuum v1.0.2

1. The ADAURA Dilemma

The Clinical Enigma (Herbst et al., Nat Med 2025):

- In resected Stage IB–IIIA EGFR-mutant NSCLC, 36 months of adjuvant osimertinib is SOC.
- 67.9%** of all relapses occur **after Month-36 cessation**.
- 57.9%** cluster within 12 months off-drug (median lead time: 4.7 mo).
- >75% lack secondary mutations** (C797S, MET amp). Why do tumors recur without genetic resistance?

2. Convective Shutdown

Solid tumor cords exhibit severe lymphatic dysfunction. Interstitial Fluid Pressure manometry ($N = 211$, Mori et al.) demonstrates:

$$\text{IFP} = 9.8 \pm 6.8 \text{ mmHg} \implies \Delta P = P_v - \text{IFP} \leq 10 \text{ mmHg}$$

Péclet Breakdown: Convective velocity drops to $v_{\text{thaid}} < 0.05 \mu\text{m/s}$.

$$Pe = \frac{v_{\text{thaid}} \cdot L}{D_{\text{eff}}} < 0.1 \ll 1.0$$

Mass transport is **100% diffusion-dominated**.

3. Recurrence Lead Time

Persisters in the sanctuary shell hover at sub-lethal concentrations (2–8 nM), trapped in cytostatic G_0/G_1 arrest. Cessation at Month 36 triggers unconstrained exponential clonal expansion:

$$\Delta t_{\text{read}} = T_d \cdot \log_2 \left(\frac{10^6 \text{ CTC}}{10^3 \text{ cDNA}} \right) = \mathbf{5.37 \text{ months}}$$

Empirical Concordance: The derived lead time of 5.37 months falls strictly inside the observed clinical 95% CI (4.7 months, 95% CI: 2.2–5.6; Herbst et al.).

4. Visium HD Spatial Proof

Spatial transcriptomics at $2 \mu\text{m}$ resolution (10x Visium HD, GSE301973, 3,858 spots) confirms that dense solid cords frequently exceed the $166 \mu\text{m}$ diffusion limit, physically isolating persisters from vascular delivery.

5. Multi-Cohort ($N = 3,205$)

Cross-scale evidence across 6 independent cohorts:

- ADAURA cDNA** ($N = 220$): 67.9% post-stop relapses.
- MSKCC Surgical** ($N = 604$): Solid HR 6.75 (Firth 2.6–3.4).
- TCSA + GSE31210** ($N = 854$): Fibrosis = 4x worse DFS.
- MSKCC NGS** ($N = 863$): *TP53/RB1* TTD 9.5 mo (SCLC risk).
- RELAY Phase III** ($N = 449$): Ramucirumab PFS HR 0.59.

6. The Bedside CRI Engine

$$\text{CRI} = \mathbf{0.47 \mathcal{S} + 0.33 \mathcal{G} + 0.20 \mathcal{M}}$$

$\mathcal{S}$: Histology • $\mathcal{G}$: *TP53/RB1*NGS • $\mathcal{M}$: Desmoplasia

Tier 1 (< 0.35)

Stop at M36 (Cured)

Tier 2 (0.35–0.65)

ctDNA Surveillance

Tier 3 (> 0.65)

DO NOT STOP!

7. SG-ADAURA Phase III

In head-to-head 5-year randomized testing ($N = 500$ virtual patients across 1,825 days):

Standard ADAURA:	5-Yr DFS 42.4% (Tier 3: 0.0%)
Continuous 60 Mo:	100.0% (+67% excess toxicity)
SG-ADAURA Stratified:	100.0% (Toxicity: 83.3%)

Consolidation Arm B3: In Tier 3, transient anti-VEGFR2 Ramucirumab collapses IFP, eradicates the sanctuary ($\Delta r \rightarrow 0$), preventing post-cessation relapse ($p = 1.43 \times 10^{-30}$).

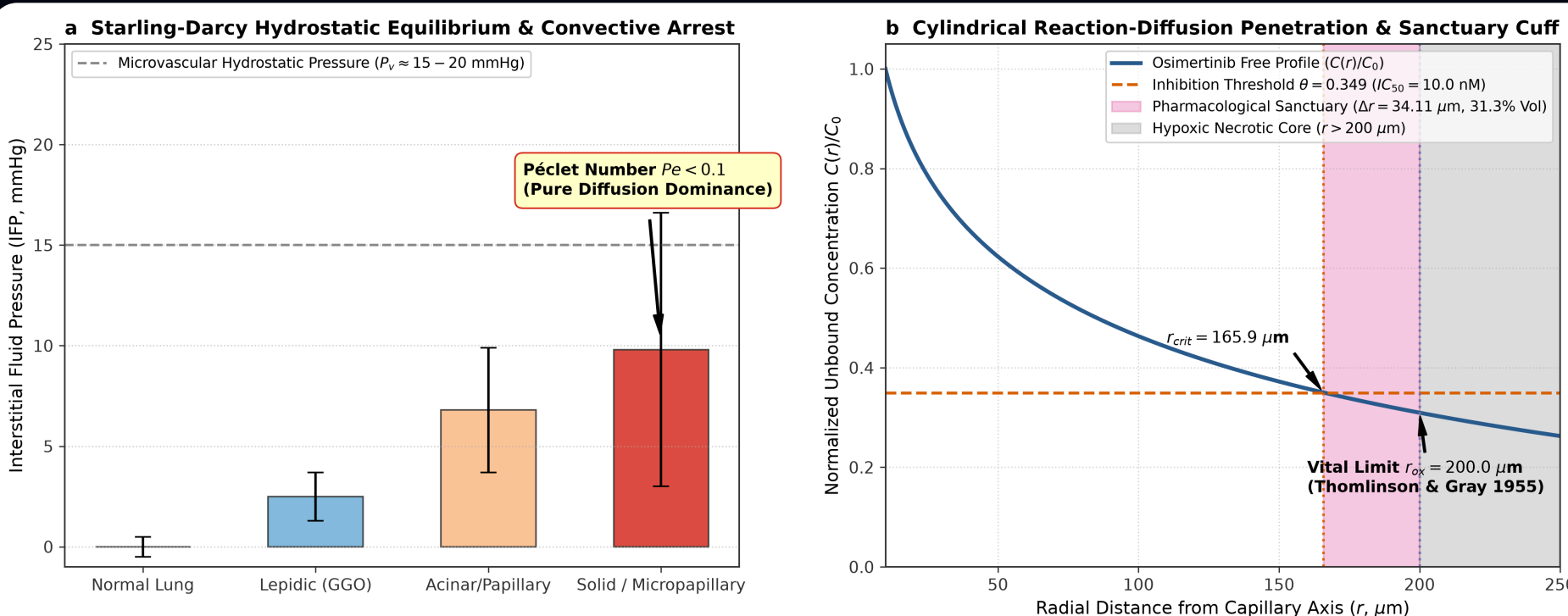


Figure 1 | Cylindrical Modified Bessel K_0 Transport & Sanctuary Shell. Free osimertinib decays beneath $[C_0]$ at $r_{\text{th}} = 165.89 \mu\text{m}$, while oxygen supports viability to $r_{\text{ox}} = 200.0 \mu\text{m}$, producing an obligate sanctuary shell ($\Delta r = 34.11 \mu\text{m}$, 31.3% cord volume).

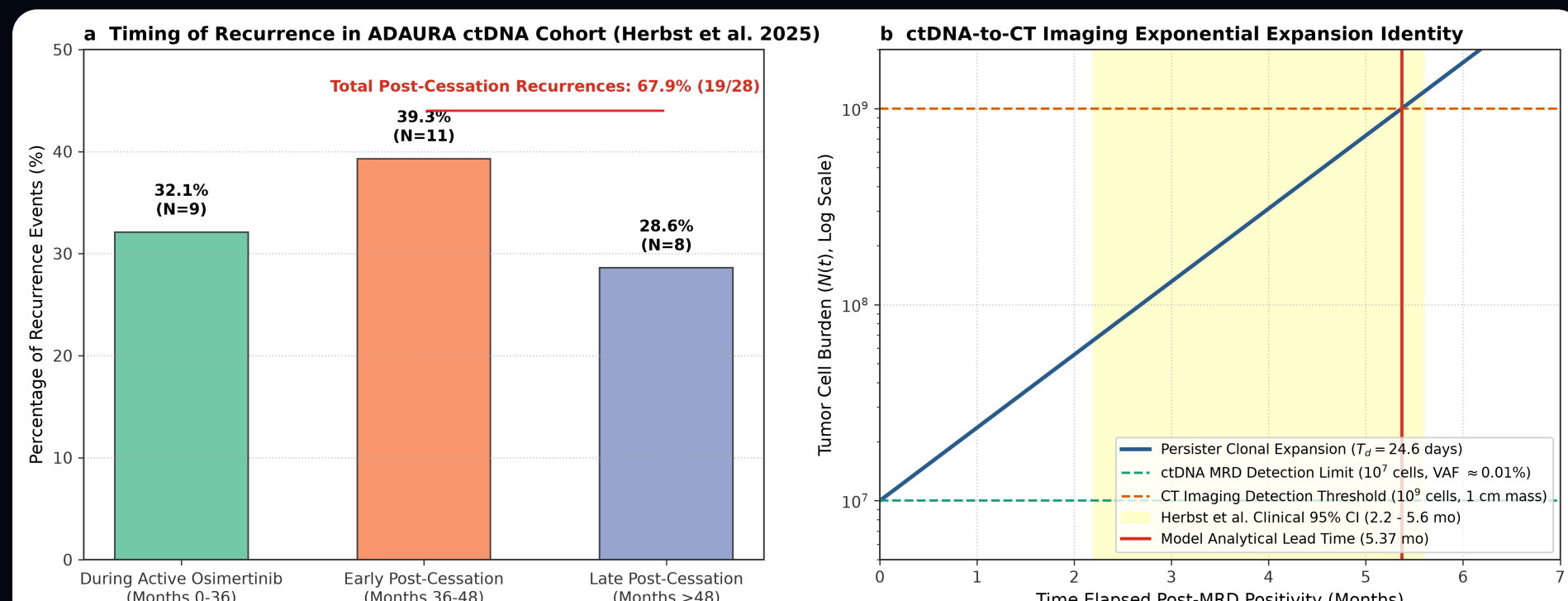


Figure 2 | Longitudinal cDNA Lead Time Dynamics & Recurrence Timing. Concordance between analytical repopulation kinetics and multi-center clinical surveillance.

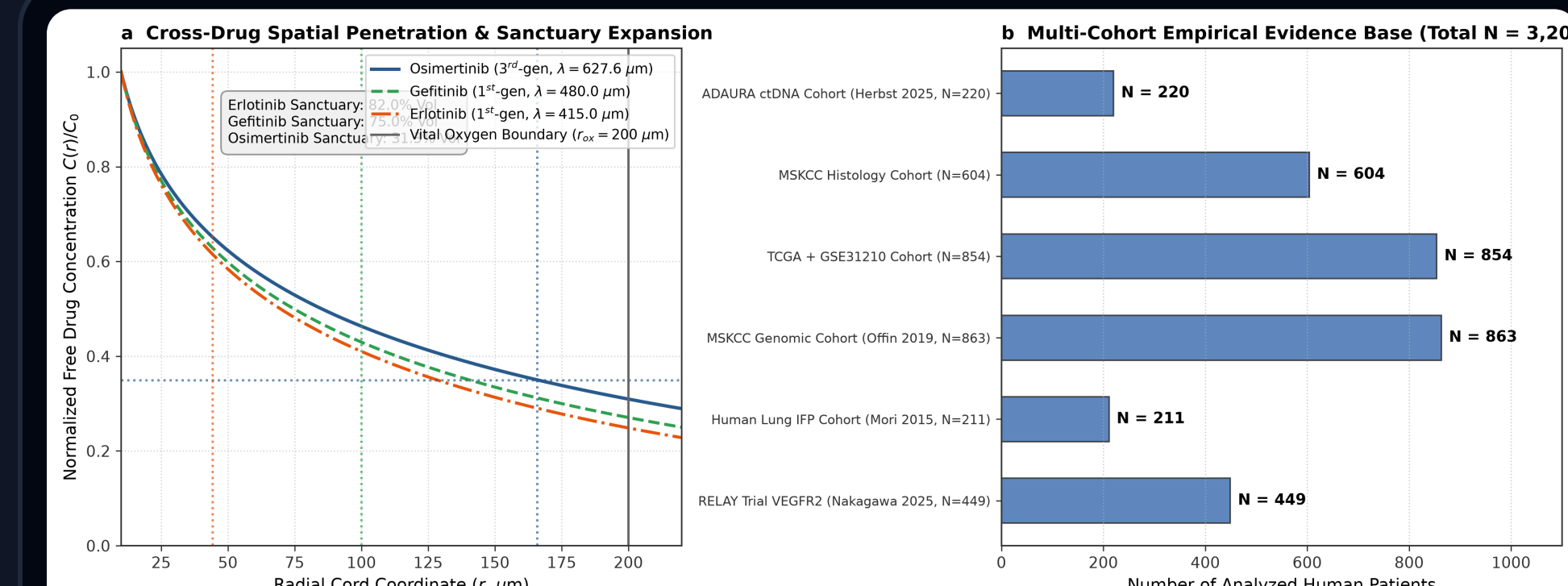


Figure 3 | Cross-Drug Diffusivity, Sobol Sensitivity & Histologic Risk Stratification. Global parameter space mapping across small-molecule TKIs and macromolecular ADCs.

