Identifying Novel Drivers of Drug Sensitivity using an AI-Enabled Multi-Modal Biomarker – Osimertinib sensitivity beyond EGFR

ZEPHYR AI

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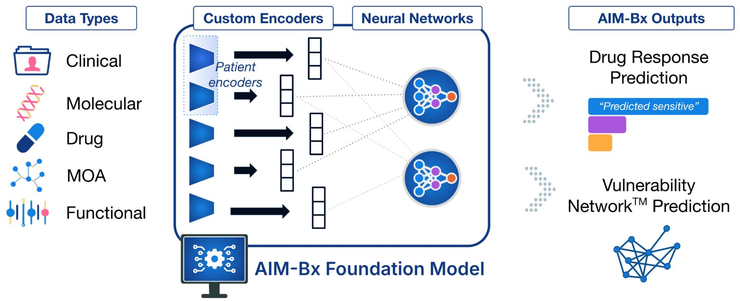
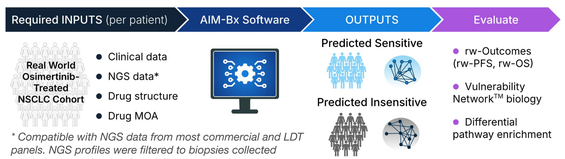
Bridging the Predictive Biomarker Gap: AI-Powered Drug Response Prediction Using Clinicogenomics Data Available in Real-World Settings

- Precision oncology remains limited by the lack of effective biomarkers. Few tumors harbor actionable alterations, and even when present, many patients fail to benefit. Conversely, some patients without recognized biomarkers respond to therapies—highlighting the need for more robust, biologically informed approaches.
- Traditional biomarkers, based on single mutations or genomic signatures, often miss critical drivers of drug response—especially in late-line, heterogeneous populations.
- AIM-Bx, Zephyr AI's multi-modal, AI-enabled software-based platform, addresses this gap by integrating clinical, molecular, pharmacological, and phenotypic data to generate real-world validated drug response predictions.
- The platform uses data routinely available in clinical settings—including standard features and genomic inputs from most commercial NGS and LDT panels—supporting both retrospective validation and prospective deployment.
- As a use case, AIM-Bx predicted osimertinib sensitivity in NSCLC using tissue and liquid biopsy data, identifying EGFR+ non-responders and EGFR– responders. These results highlight AIM-Bx's ability to uncover hidden biological drivers, expand targeted therapy utility, and enable longitudinal prediction in real-world contexts.

Fig 1 | AI-Enabled Multi-Modal Biomarkers (AIM-Bx) Architecture Overview.



The AIM-Bx Foundation Model encodes complex data modalities—including patient-level clinicogenomic features and drug structure—into rich, ML-ready representations. These are processed by neural networks trained to predict drug response and generate Vulnerability Networks™ that reveal predicted tumor dependencies relevant to response.



** Compatible with NGS data from most commercial and LDT panels. NGS profiles were filtered to biopsies collected within 2 years prior to osimertinib treatment start.*

Fig 2 | Evaluation Framework.

Clinical & NGS data to run AIM-Bx predictions, along with real-world treatment outcomes for post-hoc evaluation, were sourced from public (AACR Project GENIE) and non-public data (CancerLinQ, Aster Insights™ Optum® Market Clarity, Guardant Health™).

Sensitive and non-sensitive groups were biologically characterized post hoc using Vulnerability Networks™ and gene set enrichment analysis of reconstructed gene expression from the AIM-Bx patient encoder (Fig 1).

AIM-Bx Stratifies NSCLC Patients by Osimertinib Sensitivity with Clinically Meaningful Outcomes Across Diverse Real-World Cohorts

Fig 3 | AIM-Bx Identifies Osimertinib Responders Independent of EGFR Status.

NSCLC clinicogenomic and outcome data were sourced from AACR Project GENIE (N=97), CancerLinQ (N=32), and Aster Insights (N=21). **[A]** AIM-Bx–predicted osimertinib-sensitive NSCLC patients had significantly improved rw-OS compared to predicted insensitive patients (median 10 months; HR = 0.54 indexed from treatment start). **[B]** Most patients were on-label (EGFR+) and AIM-Bx predictions (ZephyrAI) were significantly associated with survival in a univariable Cox PH analysis adjusting for available confounders. **[C]** EGFR variants were not significantly enriched in AIM-Bx–predicted sensitive vs insensitive groups.

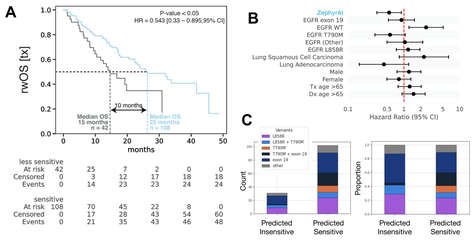


Fig 4 | AIM-Bx Predicts Improved Real-World Outcomes in an Expanded rw-NSCLC Cohort.

An expanded NSCLC cohort (N=308) from Optum® Market Clarity† was analyzed in a secure ODDW environment. AIM-Bx–predicted sensitive patients had significantly improved outcomes compared to non-sensitive patients: **[A]** rw-PFS: +16 months median survival (HR = 0.51, p < 0.001) and **[B]** rw-OS: +17 months median survival (HR = 0.50, p < 0.001). Real-world outcomes were indexed to osimertinib treatment start. AIM-Bx predictions (ZephyrAI) were the only factor significantly associated with improved survival in univariable Cox PH models adjusting for available confounders. Results support AIM-Bx performance across diverse real-world settings and heterogeneous NGS inputs.

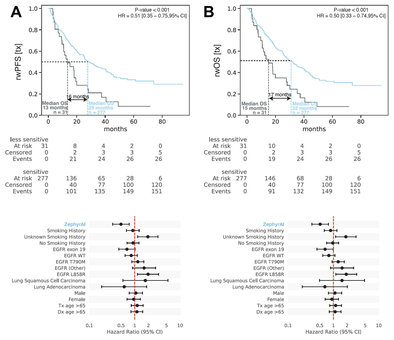
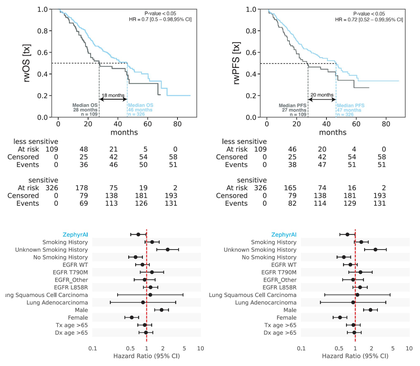


Fig 5 | AIM-Bx Validates Osimertinib Predictions Using Liquid Biopsy–Derived NGS Data.

A NSCLC cohort (N=435) treated with osimertinib and profiled via ctDNA (Guardant Health™) was used to evaluate AIM-Bx on liquid biopsy inputs. AIM-Bx–predicted sensitive patients had significantly improved outcomes: **[A]** rw-OS: +18 months; HR = 0.70, p < 0.05 and **[B]** rw-PFS: +20 months; HR = 0.72, p < 0.05, indexed to osimertinib treatment start dates. AIM-Bx predictions are significantly associated with improved survival in univariable Cox models, alongside patient sex (female) as an independent factor. Results support AIM-Bx performance across diverse NGS inputs, including ctDNA, positioning AIM-Bx for broader clinical integration and longitudinal modeling.



Uncovering Tumor Dependencies and Transcriptomic Programs Driving Osimertinib Response via VNs and Reconstructed mRNA

Fig 6 | Vulnerability Networks Reveal Distinct Tumor Dependencies Associated with Osimertinib Response Not Captured by EGFR Genomic Status.

VNs were generated for NSCLC tumors from Fig. 3, with two networks significantly enriched in each AIM-Bx–predicted sensitive and insensitive groups. VNs reveal predicted patient-specific mechanisms underlying AIM-Bx response predictions.

[A] Responder VNs were characterized by dependencies on EGFR, EGFR signaling and key survival and metabolic pathways, suggesting that network-level activity—beyond EGFR DNA level alterations— drive sensitivity to osimertinib.

[B] Non-responding NSCLC VNs were characterized by dependencies in cell cycle, transcriptional, and integrin signaling pathways, consistent with EGFR independence and known osimertinib resistance mechanisms.

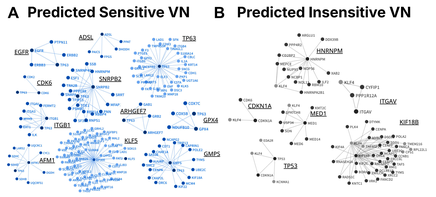
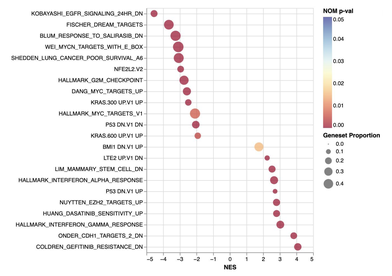


Fig 7 | GSEA of Reconstructed mRNA Profiles Reveals Distinct Biological Programs Across AIM-Bx Predicted Response Groups.

Reconstructed mRNA profiles for tumors in Fig. 3 were generated using the AIM-Bx Patient Encoder (Fig. 1) from clinical and genomic inputs, and analyzed by GSEA.

Less-sensitive tumors were enriched for oncogenic programs linked to proliferation and poor outcomes in NSCLC, including DREAM, E2F, MYC, KRAS, and NRF2—pathways previously associated with TKI resistance, including resistance to osimertinib.

In contrast, predicted osimertinib-sensitive tumors were enriched for EGFR signaling, kinase inhibitor response signatures (e.g., gefitinib, dasatinib) and deactivation of stem-like programs suggesting a less proliferative, TKI-responsive phenotype.



Normalized enrichment scores (NES, x-axis) reflect gene set enrichment (y-axis) from MSigDB collections (c2, hallmark, oncogenic). Positive NES values indicate enrichment in AIM-Bx–predicted sensitive tumors; negative NES in non-sensitive tumors. Circle size reflects gene set size; color indicates statistical significance (p-value). Differential expression was performed with Limma and filtered for p-value < 0.05.

Platform Summary & Future Directions

- AIM-Bx predicts drug response using routinely available clinical and genomic data from tissue or liquid biopsy, revealing tumor vulnerabilities and biological programs beyond traditional DNA biomarkers.
- Validated using osimertinib as a proof-of-concept, AIM-Bx is adaptable to novel drugs, mechanisms, and indications through scalable, transfer learning–based model development.
- Our software seamlessly integrates into clinical workflows and supports rapid deployment in trials or retrospective studies using standard NGS and LDT panel data.
- Zephyr AI welcomes partnerships to co-develop AI-enabled CDx strategies for precision oncology.

†Optum's de-identified Market Clarity Data (Optum® Market Clarity) is an integrated, multi-source medical claims, pharmacy claims, and electronic health records data set. Optum® Market Clarity links electronic health record data - including lab results, vital signs and measurements, diagnoses, procedures and information derived from unstructured clinical notes using natural language processing - with historical, linked administrative claim data - including pharmacy claims, physician claims, clinical information facility claims and medications prescribed and administered. Optum® Market Clarity is statistically de-identified under the HIPAA Privacy Rule's Expert Determination method and managed according to Optum® customer data use agreements.

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