Methods to Stratify Late-Line Cancer Patients Responsive to PARP Inhibitors Is an Unmet Need

- Tumors with homologous recombination repair deficiencies (HRD+) are susceptible to PARP inhibitors (PARP) which exploit a synthetic lethality by targeting an essential base excision repair (BER) pathway. Four drugs are approved for use with this biomarker.

- However, current patient selection biomarkers designed to enrich for PARP response (HRD+, BRCA1/2 [2]) in late-line cancer patients is insufficient. This has led to withdrawals of these drugs in certain indications, including late-line ovarian cancer.

- We aimed to develop and validate an alternative, artificial intelligence/machine learning (AI/ML) based method to identify olaparib sensitive ovarian cancer patients.

The Zephyr Model Harnesses Insights From Vast, Diverse Multi-Modal Datasets to Inform & Enhance Decision-Making

- The Zephyr model framework transforms clinical, translational and chemical data into rich ‘machine learning-ready’ representations using custom encoders. These data representations are then integrated into a neural network forming Zephyr’s foundation drug response & Vulnerability Network™ prediction model (Figure 1, center).

- Using RWD, our models are conducive to both prospective and retrospective validation. Zephyr has developed an AI/ML method that integrates and harnesses insights from large, diverse clinical and translational datasets to identify patients likely to respond to PARP inhibitors.

Model Inputs

- Pre-trained Foundation Model
  - Patient Specific Data
  - Clinical & Demographic Data
  - Tumor DNA Data
  - Drug Structure
  - Complex data

Model Outputs

- Drug Sensitivity prediction
- Vulnerability Network™ prediction
- Drug Response prediction

Figure 1: Overview of Zephyr’s AI/ML Foundation Model for Generating Biologically Interpretable Drug Response Predictions in Cancer Patients Using Complex Clinically Relevant Data.

- Interpretable drug response predictions for individual cancer patients can be generated by using the Zephyr foundation model and patient-specific input data. Namely, clinical genomic data and a structural embedding of the drug of interest (left panel).

- For each prediction, two model outputs are generated (right panel): a drug sensitivity prediction for a specific drug and a Vulnerability Network™ (VN) representing predicted perturbation sensitivities operative in a tumor. Drug response sensitivity thresholds are set based on predictions from large real-world patient cohorts.

- For drug combination predictions, each drug in the combination is run through the model individually. A predicted response to the combination per patient, is made based on concordant predictions for each drug in the combination (e.g., predicted sensitive to all drugs in a combination is classified as ‘sensitive for that combination’).

Baseline Characteristics of Real-World Olaparib-Treated Ovarian Cancer Patients for Zephyr Response Prediction Validation

- Conventional HRD± stratification did not result in statistically significant improvement in either of the response outcomes, for the same cohort, stratification via the Zephyr model significantly improved outcomes for both real-world endpoints. (Compare Figure 3A vs. 3B).

- Crucially, these results were unaffected by BRCA1/2 mutations, HRD+ status, or other clinical confounders (Figure 3C). Underpinning the olaparib-sensitive patients identified by Zephyr’s method cannot be detected through conventional HRD± stratification methods.

Figure 3: Evaluation of Zephyr’s Olaparib Response Predictions Using Real-World Ovarian Cancer Patient Outcomes.

Evidence of Intact DNA Damage Response Pathways in Zephyr-Predicted Olaparib Insensitive Ovarian Cancer Tumors

- Zephyr-Predicted Olaparib Insensitive Ovarian Cancer Tumors were enriched for PARP inhibitor effects and features characteristic of non-sensitive tumors.

Figure 4: Gene Set Enrichment Analysis (GSEA) in Zephyr Predicted Olaparib Predictive vs. Sensitive Ovarian Cancer Tumors Using Reconstructed mRNA. Normalized enrichment scores (NES) indicate enrichment for the gene set corresponding to each gene set (y-axis) in Zephyr predicted olaparib-sensitive tumors (NES ≥ 1) or Zephyr predicted olaparib-non-sensitive tumors (NES < 1). Circle size indicates number of genes per set color denotes log-transformed p-value.

Our Novel AI/ML Method Identifies Patients Likely to Respond to Olaparib, Yields Enhanced Real-World Outcomes Across Late-Line Ovarian Cancer Patients


In this study, we used a real-world ovarian cancer cohort to validate our models ability to identify olaparib-sensitive patients for whom existing biomarkers are insufficient, addressing a critical unmet need in precision oncology.

Using RWD, our models are conducive to both prospective and retrospective validation.

Tumors Predicted to Be Sensitive to Olaparib Reveal Dependencies on Homologous Recombination and Cell Cycle Checkpoint Machinery

- Vulnerability Networks™ (VNs) represent predicted perturbation sensitivities operative in tumors. Zephyr-predicted olaparib-sensitive tumors are characterized by VNs enriched for HR machinery, suggesting a reliance on this pathway in these tumors that may explain PARP inhibitor sensitivity (Figure 5A).

- Conversely, as supported by GSEA (Figure 4), VNs enriched in insensitive tumors show no predicted susceptibility to HR pathway perturbation.

- Instead, these tumors are characterized by a predicted dependence on cell cycle stress and response mechanisms, which could potentially bypass PARP inhibitor effects, and contribute to the poor olaparib response observed in these patients (Figure 5B).

Figure 5: Vulnerability Networks™ (VNs) Enriched in Zephyr Predicted Olaparib Sensitive and Insensitive Ovarian Tumors. VNs depict predicted perturbation sensitivities our models identify as operative in tumors, potentially explaining drug resistance. Nodes represent predicted perturbation sensitivities. Edges are formed based on established and inferred protein-protein and protein-DNA interactions. Underlined genes represent subclusters within the networks.

Using RWD, our models are conducive to both prospective and retrospective validation.

REFERENCES

1. Zephyr AI. 1800 Tsions Blvd, Suite 901 McLean VA 22102 | www.zephyrai.bio