Novel Method for Predicting Sensitivity to Lantern Pharma's Pipeline Drug Candidate Using the Response Algorithm for Drug Positioning and Rescue (RADR™)

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Leveraging AI to Transform Cancer Therapy

Abstract

Lantern Pharma has developed a technology platform termed RADR™ that can be used to predict true responders before conducting a clinical trial in order to achieve higher success rates. RADR™ is an Artificial Intelligence (AI)-based machine learning approach for biomarker identification and patient stratification. RADR™ is a combination of three automated modules working sequentially to generate drug- and tumor-specific gene signatures predictive of response. RADR™ emphasizes the integration of biological knowledge, data-driven feature selection, and robust AI algorithms to derive hypothesis-free biomarker identification. In analytic demonstrations, RADR™ was able to achieve more than 85% accuracy in validation tests using preclinical datasets associated with selected solid tumor indications and approved drugs. As part of RADR™ drug model building and development, we used a dataset showing preclinical efficacy of our pipeline oncology candidate LP-184. Perceived cancer indications for LP-184 include solid tumors such as prostate, ovarian, renal, neurological, lung and colorectal. We obtained cell line gene expression profiles covering >18,000 transcripts per cell line and proprietary LP-184 sensitivity records from the NCI-60 screening database. Upon entering more than a million data points into the RADR™ program, we derived a panel of 10 genes whose expression levels are predictive of overall response at an accuracy of 100%. Thus, RADR™ was able to identify the top 10 genes for prediction of either drug sensitivity or insensitivity, demonstrating the hypothesis-free identification of biomarkers with biological relevance and statistical rigor with highest possible prediction accuracy. Genes from the final 10 predictive list were found to be functionally involved in LP-184-specific induction of bioactivation and are in agreement with the known mechanism of action of LP-184. These preliminary biomarker analyses will be further validated using LP-184 sensitivity and gene expression data derived from fresh tumor biopsy specimens.

Challenges

Despite recent developments in diagnostic and therapeutic strategies for patients with solid tumors especially prostate, ovarian and kidney cancers, there are a number of critical knowledge gaps in relation to their screening and treatment. There is insufficient knowledge of patient characteristics, including genetic profiles, for optimal stratification of patients into response groups at the time of diagnosis. There is also insufficient knowledge of the risk factors for developing or dying from these cancers and a lack of effective implementation of real-world evidence into clinical practice. This lack of knowledge means that predicting which patients will have the best outcomes with specific treatments is suboptimal. In addition, current predictions of which patients may be harmed by unnecessary or inappropriate treatment or managed safely without treatment remain poor. Our research aims to improve the gaps in screening and treatment of cancer patients by developing predictive biomarker-based screening tests that will enable tailoring precision medicine-based therapies to patients. To this end, Lantern's RADR™ platform is being used to correlate LP-184 sensitivity with molecular profiles and to develop a gene signature that can predict response and lead to a companion diagnostic.

Objectives

1) Derive a robust, validated and biologically meaningful genomic signature to predict the potential for a patient to respond to a specific cancer drug
2) Stratify patients prospectively using RADR™-derived genomic and biomarker analyses for greater success, and lower cost in clinical trials
3) Develop genetic feature selection methodologies that can be game changing in the development of Companion Diagnostics (CDx) for oncology patient management
4) Identify biomarkers to assist clinicians in selecting the most effective treatment

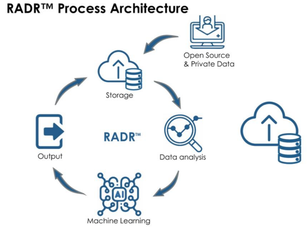
LP-184 Overview

Unmet need in solid tumor indications	**LP-184 preclinical profile**
Few approved non-hormone, non-chemotherapy treatment options specifically for the growing indications of hormone-resistant metastatic prostate and ovarian cancers, and also for late-stage renal, lung and colorectal cancers	Enhanced efficacy and potency with anticancer activity equaling or exceeding Irofulven
	Improved therapeutic index relative to Irofulven
	Remarkable tumor regression in xenograft model of multi-drug resistant lung adenocarcinoma without dose-limiting toxicities (Staake et al., 2016)
LP-184 properties • Second generation analog of Irofulven • DNA damage repair (DDR) inhibitor synergistic with many classes of anticancer agents • Multiple cytotoxic effects on tumor cell biology beyond chemical modification of DNA • Broad anti-tumor inhibitor that counteracts multi-drug resistance	Favorable *in vivo* pharmacokinetics (bioavailability/ clearance) and safety
	Knowledge of potential biomarkers implicated in (i) induction of bioactivation (ii) synthetic lethal interactions (iii) response prediction

Methodology

RADR™ Technology

RADR™ Process Architecture



RADR™ Modules

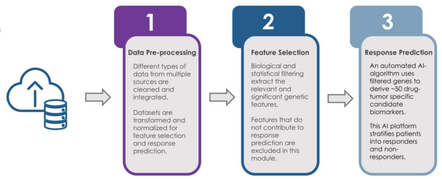


Figure 1. Process architecture and modules of RADR™

RADR™'s AI-based machine learning approach for hypothesis-free biomarker identification and patient stratification is a combination of three sequential automated modules. These modules displayed in **Figure 1**, include data pre-processing, feature selection, and response prediction.

(1) Data pre-processing includes data cleaning, transformation and normalization without compromising data quality and integrity.

(2) RADR™'s proprietary process performs gene filtering via biological, statistical and machine learning-based methods. Feature selection ensures that genes that do not contribute to response prediction are excluded from output data.

(3) The prediction component applies an AI-driven reduction algorithm to the previously filtered genes (approximately 500), generating a targeted set of typically less than 50 predictive candidate biomarkers.

Preclinical datasets of NCI-60 cell lines from solid tumor origins have been used in building and testing an LP-184 specific RADR™ model. The model provides a set of robust candidate biomarkers predictive of LP-184 response.

Results

LP-184 / Solid tumors

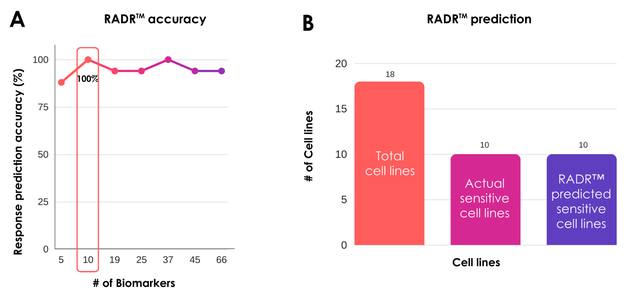


Figure 2. RADR™ validation for LP-184 sensitivity in preclinical experiments

RADR™ was used to analyze Lantern's proprietary dataset on preclinical LP-184 sensitivity to and baseline gene expression profiles of 57 cell lines from the NCI-60 panel. **Figure 2A** highlights the comparison of LP-184 sensitivity prediction accuracy across a range of biomarker numbers. Starting from >18,000 genes, RADR™ identified the 10 most significant genes as predictive of response to LP-184 treatment with an overall sensitivity or insensitivity prediction accuracy of 100%. As depicted in **Figure 2B**, out of 18 cell lines included in the blinded test set, RADR™ correctly predicted all 10 out of the actual 10 sensitive cell lines (100% true positive rate).

Results

LP-184 / Solid tumors

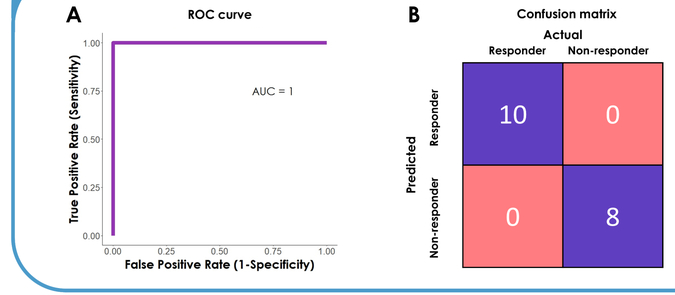


Figure 3. RADR™ performance metrics for LP-184 sensitivity prediction in preclinical experiments

Figures 3A and **3B** show model performance metrics such as area under curve (AUC) and confusion matrix representation, respectively.

Key Findings & Future Perspectives

Drug candidate	Cancer indication	RADR™-derived # of drug- and cancer-specific candidate biomarkers	RADR™-derived predictive genes reported to be correlated with enhanced drug sensitivity
LP-184	Solid tumors (prostate, ovarian, lung, renal, CNS, colorectal)	10	PTGR1 (Yu et al., 2012)

- Based on preclinical data analysis, RADR™ derived a ten-gene signature of candidate biomarkers predictive of response to LP-184.
- Genes from this set have been shown to be functionally involved in LP-184-specific mechanism of action, thereby reaffirming the utility and value of the RADR™ platform. As an illustrative example, the enone reductase enzyme PTGR1 is known to be critical for the metabolic activation of Irofulven, the parent compound of LP-184. The presence of PTGR1 in the top 10 RADR™-derived predictive genes improves confidence in the algorithm's output.
- Lantern intends to further extend and validate these cell line-derived preliminary biomarker analyses using LP-184 sensitivity and gene expression data derived from fresh tumor biopsy samples. The goal is to determine the molecular profiles of patient tumors that predict drug responses and to derive a diagnostic assay for stratifying patients.
- Precision biomarker approaches increase the likelihood that a treatment will be found to be effective in a relatively small Phase 2 cohort by eliminating the most likely non-responders and selecting the most likely responders. RADR™-driven determination of molecular profiles of tumor tissues that are sensitive to LP-184 will enable stratification of patients in a future phase II clinical trial.

References

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