Predicting sensitivity to Lantern Pharma's pipeline drug candidate LP-184 using the Response Algorithm for Drug positioning and Rescue (RADR™)

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Abstract

LP-184 or hydroxyurea methylacylfulvene is a DNA Damage Repair inhibitor being developed by Lantern Pharma primarily as a non-hormone, non-chemotherapy option for the growing indication of taxane- and hormone-resistant metastatic prostate cancer. LP-184 is a next-generation analog of Irofulven with broad anti-tumor activity that counteracts multi-drug resistance pathways and is potentially synergistic with many classes of anticancer agents. LP-184 has a favorable therapeutic index and pharmacokinetic profile. Knowledge about its shared mechanism of action with Irofulven and potential biomarkers implicated in induction of bioactivation and synthetic lethal interactions is available. To advance LP-184 into clinical stages and achieve accelerated approval, Lantern Pharma is employing its proprietary Artificial Intelligence (AI)-driven technology. Lantern Pharma has developed a technology platform termed RADR that can be used to construct responder/ non-responder profiles based on gene expression signatures and predict true responders before conducting a clinical trial in order to achieve higher success rates. RADR is an AI-based machine learning approach for candidate 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 biomarkers in a hypothesis-free manner. In analytic demonstrations, RADR was able to achieve an average accuracy of 85% 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. We obtained baseline cell line gene expression profiles covering more than 18,000 transcripts per cell line and corresponding LP-184 sensitivity records from the NCI60 cancer cell line panel. Using RADR, 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 and having 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 its mechanism of action. These preliminary biomarker analyses will be further validated using LP-184 sensitivity and pre-treatment gene expression data derived from ex vivo models of fresh prostate tumor biopsy samples.

Challenges

Despite recent developments in diagnostic and therapeutic strategies for patients with solid tumors, there are a number of critical knowledge gaps in relation to their screening and treatment:

- Incomplete knowledge of patient characteristics including genetic profiles for optimal stratification of patients into response groups at the time of diagnosis
- Insufficient understanding of the risk factors for developing or dying from cancer and a lack of effective implementation of real-world evidence into clinical practice.
- Suboptimal predictive value of biomarkers in decision making around which patients will have the best outcomes with specific treatments

Our aim is 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

- Develop genetic feature selection methodologies that can be game changing in the development of Companion Diagnostics (CDx) for oncology patient management
- Derive a robust, validated and biologically meaningful genomic signature to predict the potential for a patient to respond to a specific cancer drug
- Stratify patients prospectively using RADR™-derived genomic and biomarker analysis for greater success, and lower cost in clinical trials

RADR™ Technology Overview

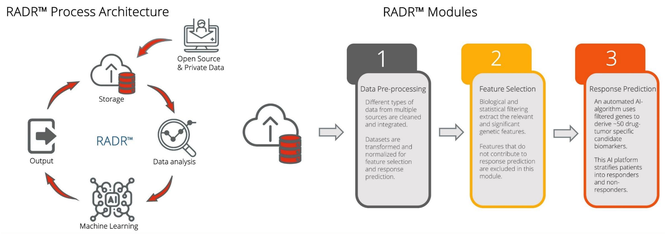
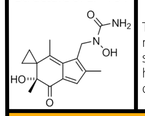


Figure 1. Process architecture and modules of RADR™

LP-184 Overview

Structure of LP-184



Unmet needs in solid tumor indications

There are few approved non-hormone, non-chemotherapy treatment options specifically for the growing indications of hormone-resistant metastatic prostate cancer.

LP-184 properties

- Next-generation analog of Irofulven, currently in phase II biomarker-driven clinical trial in Europe
- DNA damage repair (DDR) inhibitor
- Multiple cytotoxic effects on tumor cell biology beyond chemical modification of DNA
- Broad anti-tumor inhibitor that counteracts multi-drug resistance

LP-184 preclinical profile

- 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 [1]
- 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

RADR™-driven analysis of LP-184-specific biomarkers

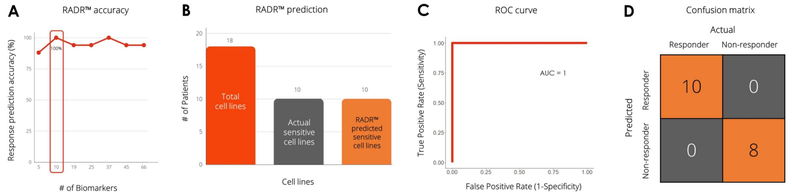


Figure 2. RADR™ validation for LP-184 sensitivity in preclinical experiments

RADR™ was used to analyze Lantern's proprietary preclinical dataset on 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 a 10-gene signature in solid tumors predictive of response to LP-184 treatment with an overall 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). Figures 2C and 2D show model performance metrics such as area under curve (AUC) and confusion matrix representation, respectively. Model training was performed using an initial set of 66 genes derived from 39 cell lines in NCI-60 panel data. Model testing was conducted on 18 cell line records isolated as the blinded hold-out set.

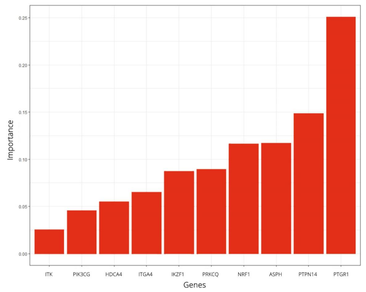


Figure 3. Relative importance of LP-184 signature genes

In this relative variable importance plot, gene weightage analysis was performed using Garson's function to analyze the relative ranking of 10 genes in the LP-184 signature in solid tumors. PTGR1 (Prostaglandin Reductase 1) stands out as the gene with highest relative importance.

LP-184 gene signature analysis

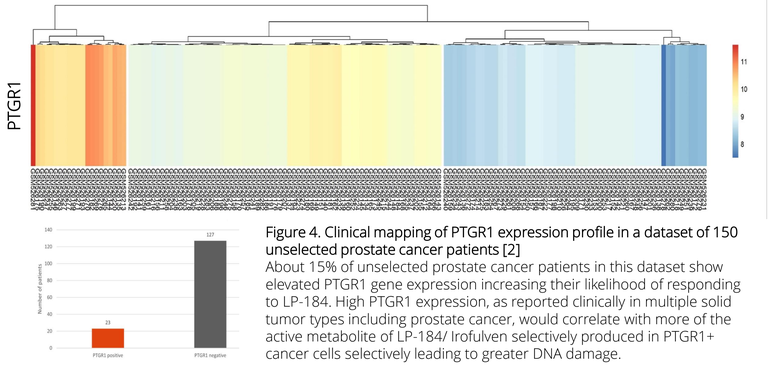


Figure 4. Clinical mapping of PTGR1 expression profile in a dataset of 150 unselected prostate cancer patients [2]

About 15% of unselected prostate cancer patients in this dataset show elevated PTGR1 gene expression increasing their likelihood of responding to LP-184. High PTGR1 expression, as reported clinically in multiple solid tumor types including prostate cancer, would correlate with more of the active metabolite of LP-184/ Irofulven selectively produced in PTGR1+ cancer cells selectively leading to greater DNA damage.

Analysis of Lantern Pharma's asset LP-184 using the RADR™ platform yielded a 10-gene pan-cancer signature of biomarkers associated with LP-184 sensitivity.

Key findings and future perspectives

Drug candidate	Potential cancer indications	RADR™-derived # of drug- and cancer-specific candidate biomarkers	RADR™-derived predictive genes correlated with enhanced drug sensitivity
LP-184	Solid tumors (prostate, ovarian, lung, renal, colorectal cancers)	10	PTGR1 [3]

- Based on preclinical data analysis, RADR™ derived a 10-gene signature of candidate biomarkers predictive of response to LP-184.
- Genes from this set have been shown to be functionally involved in the postulated mechanism of action of LP-184, 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 II 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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[2] Taylor BS, Schultz N, Hieronymus H, Gopalan A et al. Integrative genomic profiling of human prostate cancer. Cancer Cell 2010 Jul 13;18(1):11-22. PMID: 20579941

[3] Yu, X., Erzinger, M. M., Pietsch, K. E., Cervoni-Curet, F. N., Whang, J., Niederhuber, J., & Sturla, S. J. (2012). Up-Regulation of Human Prostaglandin Reductase 1 Improves the Efficacy of Hydroxymethylacylfulvene, an Antitumor Chemotherapeutic Agent. Journal of Pharmacology and Experimental Therapeutics. https://doi.org/10.1124/jpet.112.195768

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