CERTIS™ ONCOLOGY INTELLIGENCE

5th Annual RAS-Targeted Drug Development
Personalizing Medicine Via Targeting Oncogenic RAS for Cancer

LEVERAGING ADVANCED RAS-MUTANT CANCER MODELS AND PREDICTIVE AI TO REALIZE THE PROMISE OF PRECISION ONCOLOGY

Long H Do, PhD[1]; Raffaella Pippa, PhD[1]; Warren Andrews, PhD[1]; Yuan-Hung Chien, PhD[1]; Rowan Prendergast [1], Jantzen Sperry, PhD[1]; Michael Boice, PhD[1]; Jonathan Nakashima, PhD[1]

ABSTRACT

RAS is the most frequently mutated oncogene in human cancer – approximately 19% of cancer patients harbor RAS mutations, the equivalent of 3.4 million new cancer cases each year, globally.[2] The three cancers in which KRAS mutations are the predominant RAS mutations are pancreatic cancer (88%), colorectal adenocarcinoma (50%) and lung adenocarcinoma (32%).[3] RAS was for the longest time considered 'undruggable".[3] However, with the approval of Lumakras (sotorasib/AMG-510) and KRAZATI (adagrasib) for the treatment of locally advanced or metastatic KRAS G12C NSCLC, preclinical and clinical efforts have been intensified to develop novel therapies and treatment strategies targeting this problematic oncogene. With this renewed enthusiasm comes a need for appropriate preclinical models that closely recapitulate clinical response, including therapeutic resistance and efficacy of rational combination therapies. Certis utilizes MRI-confirmed, AI-enabled functional precision oncology using orthotopic PDX models as a validation platform and takes a similar approach to validate drug developers' novel RAS-targeting strategies.

METHODS

In October 2022, 24 cancer patients completed enrollment in personalized, observational, clinical research studies.

CertisAI™ Methodology: Each study design provides for a control arm, four physician-directed therapeutic options, and two options predicted as efficacious by CertisAI. The proprietary technology utilizes over one million drug screening results from *in vitro* and clinical data to train our in-house machine learning (ML) models to predict effective treatments specific to an individual's cancer. CertisAI has shown over 90% accuracy in predicting monotherapy sensitivities, and over 90% accuracy in predicting synergistic drug combinations. The ML models find genetic biomarker features along with drug features predictive of therapy response for many cancer types. Patient tumors grown from the PDX model are fully sequenced and genetic results are fed to CertisAI to predict outcomes of various investigational and approved therapies. For these clinical research studies, Certis limited AI-directed therapies to FDA-approved drugs.

PDX Pharmacology: Patient biopsies were surgically implanted into subcutaneous and orthotopic sites of female NOG mice. Animals were imaged with the M3™ compact MRI from Aspect Imaging to monitor tumor growth. In the following highlighted study (XM67), a colorectal orthotopic PDX was dosed with various inhibitors formulated and administered per the manufacturer's instructions or past publications.

RESULTS

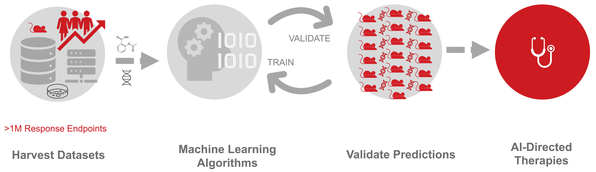


Figure 1. Developing CertisAI-Directed Therapies. Three of the five clinical research studies completed to date (including XM67) were for the benefit of patients diagnosed with advanced colorectal cancer. While running algorithms used to make AI-based predictions, the Certis Bioinformatics team discovered intriguing biomarker patterns predictive of positive response to certain therapies not currently indicated for these "untreatable" forms of cancer. Hypotheses were validated *in vivo* and confirmed by MRI as part of conducting the three clinical research studies. These results compelled a deeper interrogation of public *in vitro* and clinical outcomes datasets. All findings point to an opportunity to repurpose existing, FDA-approved drugs to improve clinical outcomes for individuals diagnosed with colorectal and other forms of cancer with KRAS mutations.

Colorectal Cancer Patient	
CRS	XM67
Age/Gender	79 M
Cancer Subtype	Colon Adenocarcinoma
Biopsy Site	Liver
Primary/Metastatic	Metastatic to Liver
KRAS Status	KRAS G12D (49.8%)
Other Notable Biomarkers	AURKA amp, BCL2L1 amp, PIK3CA G118D, APC E1309fs*4, TP53 R248Q

Figure 2. Clinical Research Study Highlight (Patient XM67). Patients with KRAS mutations are associated with poor prognosis and resistance to therapy, with limited to no treatment options. The patient's PDX model was established at Certis and engrafted into the caecum of animals to model the disease of the patient.

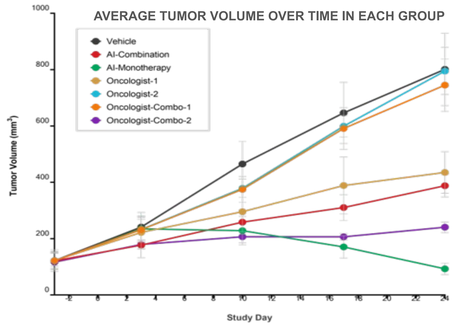


Figure 3. (XM67) Using CertisAI to Predict Responses in Metastatic Colorectal KRAS G12D-Mutant Orthotopic Models. Six different therapies were tested for efficacy. Four of the arms (two monotherapy and 2 combinations) were chosen based on oncologist recommendations due to tumor type and predicted response. Two arms (one monotherapy and one combinations) were deduced based on the genetic signature of the model and structure of the compounds. The two AI-directed therapies performed the best, with tumor growth inhibition (TGI) at ~600% for the AI-monotherapy and ~350% for the AI-combination therapy. The AURKA inhibitor chosen by the oncologist performed reasonably well, with a TGI of 300%.

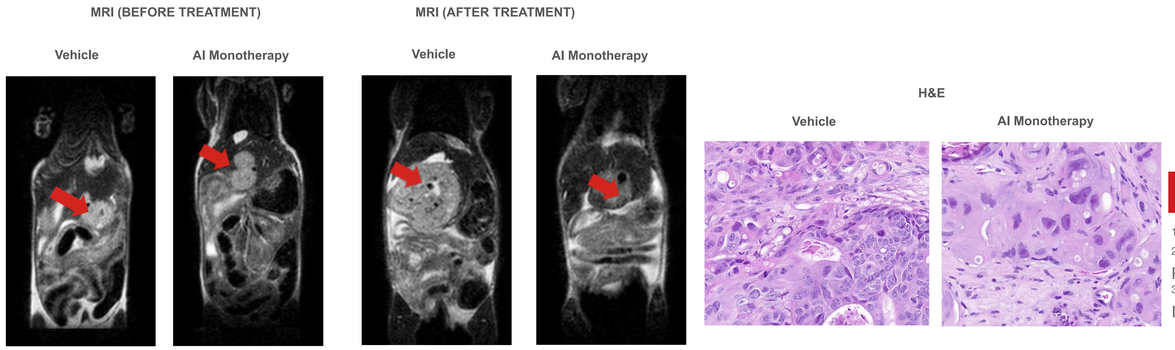
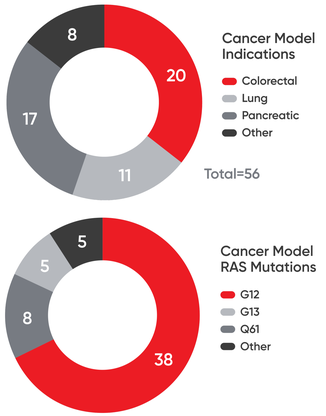


Figure 4. Representative MRI and Confirmatory Histology. Results of pre-and post-treated animals for clinical research study patient XM67. The #1 ranked AI-directed monotherapy had a -23.15% change in tumor volume. The red arrow indicates the tumor. Tumor volumes are quantified using the MRI and Vivoquant software. H&E images of Vehicle treated animals show highly cellular tumors with pleomorphic viable nuclei. In contrast, the AI Monotherapy treated tumors show degenerating nuclei and a focal area of necrosis/fibrosis.

CONCLUSIONS

Functional precision oncology using personalized orthotopic patient-derived xenografts (O-PDX) combined with MRI closely recapitulates human disease response, and can improve clinical outcomes by informing treatment decisions for individual patients. AI-enabled precision medicine holds great promise as a clinical decision support tool that can exponentially multiply the number of patients Certis can serve with personalized treatment decisions. Having a clinically relevant test system (O-PDX models) and a quantitative imaging platform (MRI) in which to validate AI-based predictions and train machine learning algorithms represents an opportunity to accelerate AI predictive medicine within the field of oncology. Furthermore, this two-pronged approach also translates to drug developers: 1) Using a proprietary predictive medicine platform to evaluate and predict response, and 2) Developing clinically relevant, advanced patient-derived xenograft (PDX) models from patients with KRAS mutations in the most common tumor subtypes. These two distinctive, advanced tools can help further preclinical development of RAS targeted therapies.



Figures 5. A Growing Number of Certis PDX Models Available. (Top) 56 PDX models that represent the three most common type of cancers with RAS mutations: pancreatic, colorectal, and lung. These PDX models are all deeply characterized from patients that are both naïve or pretreated from primary or metastatic tumors. **(Bottom)** The mutations represented in these 56 PDX models offer a representation of those mutations seen in the clinic. Most of these mutations are G12 mutations followed by G13 and Q61 mutations.

REQUEST ACCESS NOW

BARNEYOI™
CANCER MODEL DATABASE

CITATIONS & ACKNOWLEDGEMENTS

[1]Certis Oncology Solutions, San Diego, CA.
[2] Trott M, PhD. The Ras Pathway and Cancer: Regulation, Challenges and Therapeutic Progress. Technology Networks: *Cell Science*. May 4, 2021.
[3] Kwan AK et al. The Path to the Clinic: A Comprehensive Review on Direct KRASG12C Inhibitors. *J Exp Clin Cancer Res*. 2022;41(27).

aspectimaging

TACONIC Models For Life.