ATR inhibitor RP-3500 demonstrates safety and early clinical benefit

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In a first-in-human, Phase I trial, researchers at The University of Texas MD Anderson Cancer Center discovered that ATR inhibitor RP-3500 was safe and well tolerated with promising clinical benefit. Principal investigator Timothy A. Yap, Ph.D., associate professor of Investigational Cancer Therapeutics, today presented initial data from the trial at the AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics.

The trial is the largest biomarker-selected study to test an ATR inhibitor as a single agent in cancers harboring synthetic lethal genomic alterations in DNA damage repair (DDR) pathways. Yap and his team observed preliminary antitumor efficacy in patients with advanced solid tumors—including ovarian, prostate and breast cancers—that were resistant, refractory or intolerant to standard therapy, including BRCA1 and BRCA2 mutated cancer patients who had previously received PARP inhibitor treatment. The potent and highly selective RP-3500 achieved meaningful clinical benefit across a variety of gene alterations in 34 of 69 evaluable patients (49%), including 12 patients with objective tumor responses, 14 patients with RECIST-defined stable disease for at least 16 weeks, and eight patients with early significant decreases in tumor markers and tumor shrinkage.

"Not only did RP-3500 demonstrate a favorable and differentiated safety profile, but our initial data also showed promising and distinct early efficacy," Yap said. "Although this Phase I study has only had approximately nine months of dosing at efficacious doses of 100mg or more of RP-3500, we are encouraged by what we have observed so far in this hard-to-treat advanced cancer patient population."

Various conditions of DNA damage, specifically breaks in the DNA double strand and replication stress, activate a complex network of DDR mechanisms. One of the key mediators of the DDR signaling pathway is the protein kinase ATR, which is activated in response to DNA replication stress—making it a promising therapeutic target in cancers with a range of DDR defects.

Based on a genome-wide CRISPR-based screening platform, 17 biomarkers for sensitivity to RP-3500—including ATM, BRCA1/2 and other alterations—were identified for prospective patient selection for this trial.

"We were keen to give every patient the best chance of responding by only enrolling those who had at least one of these pre-identified actionable predictive biomarkers of response to RP-3500," Yap said.

The study enrolled a total of 101 patients with heavily pre-treated advanced solid tumors carrying synthetic lethal genomic alterations that researchers predicted for ATR inhibitor sensitivity. The primary endpoints of the study were safety and tolerability, as well as recommended phase 2 dose (RP2D) and optimal schedule. Other endpoints included pharmacokinetics, pharmacodynamics and preliminary antitumor activity.

Patients were treated on different doses and schedules of RP-3500. Treatment emergent adverse events of all grades most commonly included grade 1-2 anemia, fatigue and decreased appetite. Grade 3 anemia was observed in 21.8% of all patients treated. No grade 4 or worse anemia was reported during the trial.

After assessing the adverse events, pharmacokinetic, pharmacodynamic and antitumor activity, the researchers determined the RP2D of RP-3500 to be 160mg once daily for three days, followed by four days off.

Early analysis of antitumor activity shows promising clinical activity across a spectrum of tumor types and genetic alterations, including ATM or
CDK12-mutated castration-resistant prostate cancer, PARP inhibitor-resistant ovarian cancer with BRCA1 or RAD51C mutations, BRCA1-mutated ER+ breast cancer, BRCA1 mutated head and neck squamous cell carcinomas and BRCA2 mutated melanoma.

While the study is ongoing, Yap is encouraged by the initial data and will soon open enrollment to the TRESR Phase II expansion cohorts.

"Our promising early clinical data of this potent and highly selective ATR inhibitor offer a clear direction for further development of RP-3500," Yap said. "We will continue to assess RP-3500 in patients with defined molecular alterations and also in novel rational combinations."

Provided by University of Texas M. D. Anderson Cancer Center


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