Phase 1/2a study: Safety and efficacy of new inhibitor in patients with advanced solid and CNS tumors

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An early-phase study led by researchers at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine

along with other Cancer Centers, suggests that an experimental therapy may have promising results in treating cancers with BRAF gene alterations—including certain mutations not previously targeted by BRAF inhibitors.

The Phase 1/2a study looking at safety and dosing enrolled 113 patients and targeted a wide range of cancers, including high-grade glioma, low-grade glioma, colorectal cancer, papillary thyroid cancer, melanoma, pancreatic cancer, ovarian cancer, non-small cell lung cancer, anaplastic thyroid cancer, and others.

The BRAF protein is part of a communication pathway that controls vital processes in cells. Several alterations of the BRAF gene can cause mutant forms of the BRAF protein to be made, leading to cancer development. V600 mutations—including V600E, V600K, and V600R—are common in melanoma and certain other cancers. Currently available BRAF inhibitors target V600 mutations but do not target the much less common non-V600 mutations.

"Our study, which included adults and children with advanced, solid tumors that could not be surgically removed, showed promising activity against V600 and non-V600 BRAF mutant tumors, including primary central nervous system (CNS) tumors," said Dr. Macarena de la Fuente, chief of Neuro-Oncology at Sylvester, whose research focuses on developing treatments for primary brain tumors. "The drug is well tolerated, comparing very favorably with other BRAF inhibitor therapies, with mostly low-grade adverse events at all dosing levels."

In addition to its ability to target non-V600 mutations, the investigational drug, FORE8394, appears to thwart cancer cells' ability to escape BRAF inhibition by activating another pathway, the MAPK signaling pathway.

"Combining a BRAF inhibitor and an MEK inhibitor is the most

common approach to treating cancers with BRAF mutations. However, due to its pharmacological features, treatment with this drug does not result in paradoxical activation of the MAPK pathway avoiding the need for combination with an MEK inhibitor," said de la Fuente, first author of the presentation involving a multicenter research team. She said the results support continuation of ongoing studies with the drug in tumors with BRAF "fusion"—a rare mechanism of BRAF activation—and in recurrent primary CNS tumors with BRAF V600E mutations.

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