



BBOT Announces Publication in Science Highlighting Preclinical Data that Supports the Potential for RAS:PI3K α Breaker BBO-10203 to Provide Therapeutic Benefit across Multiple Tumor Types

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Data show that BBO-10203 covalently and specifically binds to the RAS-binding domain of PI3K α , breaking its interaction with H-, N-, and KRAS and preventing them from activating PI3K α

In preclinical models, BBO-10203 treatment led to significant tumor growth inhibition across multiple tumor types, and demonstrated enhanced efficacy when combined with other anti-tumor agents, without inducing hyperglycemia

BBO-10203 is currently being evaluated in a Phase 1 study in patients with HR+/HER2- or HER2+ BRCA, KRAS mutant colorectal cancer (CRC), and KRAS mutant non-small cell lung cancer (NSCLC)

SOUTH SAN FRANCISCO, Calif. June 12, 2025 (BUSINESS WIRE) —TheRas, Inc. d/b/a BBOT (the “Company”), a clinical-stage biopharmaceutical company focused on RAS-pathway malignancies, today announced the publication of preclinical data supporting the potential for BBO-10203 to provide therapeutic benefit across multiple tumor types. The publication, titled “*BBO-10203 inhibits tumor growth without inducing hyperglycemia by blocking RAS-PI3K α interaction*” was published in the peer-reviewed journal [Science](#).

These data describe the discovery and preclinical evaluation of BBO-10203, a first-in-class, orally available inhibitor that selectively blocks the interaction between RAS proteins and PI3K α without impairing insulin signaling. By covalently binding to a unique cysteine in the RAS-binding domain of PI3K α , BBO-10203 effectively disrupts oncogenic RAS-driven activation of the PI3K α pathway across a range of tumor types, including those with mutations in *KRAS*, *PIK3CA*, and *HER2* amplification, without inducing hyperglycemia. The compound showed broad antitumor activity *in vitro* and *in vivo* and demonstrated enhanced efficacy when combined with targeted therapies such as CDK4/6 inhibitors, ER antagonists, HER2 inhibitors, and KRAS^{G12C} inhibitors. These findings support the potential of BBO-10203 as a well-tolerated, mechanistically distinct therapeutic for PI3K α - and RAS-driven cancers.

“Because the contribution of the second most mutated signaling pathway in human cancers remains underappreciated, we searched for an entirely novel molecular mechanism that is not encumbered by known metabolic liabilities to inhibit PI3K α signaling,” said Pedro Beltran, PhD, Chief Scientific Officer of BBOT. “By blocking the crosstalk between RAS and PI3K α in tumors, without interfering with physiological insulin signaling, we believe BBO-10203 represents a fundamentally differentiated approach with both biological and therapeutic promise.”

“This work stemmed from our goal to elucidate the structural basis of RAS:PI3K α binding and therapeutically target this interaction,” said Dharendra Simanshu, PhD, lead author and Principal Scientist at Frederick National Laboratory for Cancer Research (FNLCR). “Our findings show that targeting RAS-effector interactions is both structurally tractable and has potential across a range of cancers. BBO-10203 exemplifies a paradigm shift – rather than inhibiting RAS directly, it intercepts oncogenic signaling through effectors like PI3K α , enabling tumor suppression while preserving essential physiological functions.”

BBO-10203 is currently being evaluated in our Phase 1 BREAKER-101 study ([NCT06625775](#)) in patients with locally advanced or metastatic HER2+ breast cancer, HR+/HER2- breast cancer, KRAS mutant advanced CRC, and KRAS mutant advanced NSCLC. The discovery of BBO-10203 was the result of a collaboration between the RAS Initiative at Frederick National Laboratory, Lawrence Livermore National Laboratory, and BBOT.

“This work is an excellent example of chemistry bringing clarity to biology,” said Frank McCormick, PhD, FRS, Chairman of the BBOT Board, Advisor to the National Cancer Institute’s RAS Initiative at Frederick National Laboratory for Cancer Research, and Professor of Tumor Biology and Cancer Research at UCSF. “The role of the RAS:PI3K α interaction in cancer biology has long been suspected but challenging to pin down precisely. Now we understand which cancers depend on this interaction, some quite unexpected. With BBO-10203 now in the clinic, there’s real hope that these discoveries will translate into meaningful benefit for many cancer patients.”

About BBOT

BBOT is a clinical-stage biopharmaceutical company advancing a next-generation pipeline of novel small molecule therapeutics targeting RAS and PI3K α malignancies. Initially formed as a subsidiary of BridgeBio Pharma, Inc. (Nasdaq: BBIO), BBOT has the goal of improving outcomes for patients with cancers driven by the two most prevalent oncogenes in human tumors. For more information, visit [bbotx.com](#).

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