Black Diamond Therapeutics Presents Data From its Program Targeting Oncogenic Allosteric Mutations in EGFR for Glioblastoma as Late Breaker at the American Association for Cancer Research (AACR) Annual Meeting

March 29, 2019

CAMBRIDGE, Mass., March 29, 2019

Black Diamond Therapeutics, Inc., a biotechnology company developing next-generation precision medicines for cancer, today announced that data from its first-in-class program targeting a group of epidermal growth factor receptor (EGFR) allosteric mutants that drive glioblastoma multiforme (GBM) will be presented at the American Association for Cancer Research (AACR) Annual Meeting 2019. The AACR Annual Meeting 2019 will be held March 29 to April 3, 2019 at the Georgia World Congress Center, Atlanta, GA.

“Through our MAP platform, we have defined the molecular mechanism by which oncogene activation of a family of extracellular EGFR mutations identified in glioblastoma patients – termed locked-dimer (LoDi)-EGFR oncogenes – renders early generation EGFR inhibitors ineffective,” said David Epstein, Ph.D., President and CEO of Black Diamond. “Glioblastoma multiforme is a highly malignant and aggressive cancer for which there exists limited treatment options and these findings set guidelines for the discovery of selective and potent LoDi-EGFR inhibitors.”

Elizabeth Buck, Ph.D., co-Founder and Executive Vice President of Discovery and Translational Sciences at Black Diamond added, “These data describe our fundamental observation that LoDi- EGFR mutants – the first subset of allosteric oncogenic mutations in the ErbB family to be described by Black Diamond Therapeutics – are not only robust oncogenes, but due to their unique mode of homodimerization exhibit new and distinct pharmacology. Taken together, these results highlight the need for critically understanding the functional consequences of all allosteric mutations in the druggable oncogene landscape to help inform the discovery of therapies that have the greatest chances for treatment success.”

Abstracts are available on the AACR conference website at http://www.aacr.org. Information contained in the abstract was at the time of submission on February 1, 2019.

Title: Epidermal Growth Factor Receptor Oncogenes Expressed in Glioblastoma are Activated as Covalent Dimers and Exhibit Unique Pharmacology. (Abstract #LB-111)
https://www.abstractsonline.com/pp8/#!/6812/presentation/9149

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Session: LBPO.ET01 Late-Breaking Research: Experimental and Molecular Therapeutics 1, Section 40

Session date and time: Monday, April 1, 2019 1:00 PM – 5:00 PM ET

- Extracellular domain EGFR mutations are prevalent in patients with GBM: despite theclinical success seen in targeting EGFR catalytic site mutants, no EGFR-directed drugs havebeen effective in treating glioblastoma patients harboring LoDi-EGFR mutations.
- Black Diamond’s data demonstrate that:

o A group of the most commonly expressed extracellular domain EGFR mutants expressed in glioblastomas is activated by disulfide-bond mediated covalent homodimerization of EGFR, collectively referred to by Black Diamond as LoDi-EGFR oncogenes.

o Strikingly, current generation small molecules binding to the active kinase conformation potently inhibit catalytic site mutants but induce covalent dimerization and further activate LoDi-EGFR receptors: this manifests in paradoxical acceleration of proliferation of LoDi-EGFR driven tumor cells.

o The oncogenic mechanism of locked-dimer EGFR has a profound impact on the activity of small molecules acting at the ATP binding site, providing further evidence for “inside-out” allosteric signaling in EGFR.

o LoDi-EGFR mutant oncogenes are the first subset of allosteric mutant ErbB oncogenes to be described by Black Diamond Therapeutics.

• Collectively, these findings provide a mechanistic understanding for how structural variations affecting receptor regions distal to the active site can confer dramatically different responses to small molecule ATP site inhibitors and provide impetus for optimization of selective EGFR inhibitors tailored against LoDi-EGFR oncogenes in glioblastoma.

Black Diamond’s MAP: a unique platform

Black Diamond’s industry-leading mutation, allostery, and pharmacology (MAP) computational and discovery platform identifies and drugs allosteric mutant disease targets. Oncogenes are activated by kinase domain mutations or by allosteric mutations. While kinase domain mutations have been successfully drugged with selective inhibitors and are standard of care in many malignancies, allosteric mutations represent an undrugged and unexplored space.

As genomic profiling and sequencing of cancer patients is becoming standard clinical practice, Black Diamond’s MAP platform pinpoints new druggable families of mutations from the thousands of lesions identified across individual oncogenes derived from cancer patients, thus leading to the creation of high-impact precision medicines. The prevalence of the allosteric mutations in ErbB ranges from two to 15 percent of patients diagnosed with a given tumor type.

Black Diamond’s MAP platform has generated a pipeline of five programs, including three that have progressed compounds through lead optimization or into IND-enabling studies. The fourth and fifth programs are in lead identification. Black Diamond’s first three disclosed programs are targeting groups of EGFR and HER2 allosteric mutants.

About Black Diamond

Black Diamond Therapeutics is a next-wave cancer precision medicine company. Black Diamond pioneered the development of selective medicines for patients with genetically defined cancers driven by oncogenes activated by allosteric mutations. Using its mutation, allostery, and pharmacology (MAP) computational and discovery platform, Black Diamond is uncovering new ways to functionally assess the mutational landscape of individual oncogenes – to discover and validate new targets and develop novel approaches to creating highly selective

therapeutics. Black Diamond was founded by David M. Epstein, Ph.D., Elizabeth Buck, Ph.D., and Versant Ventures, and is the first new company to emerge from Versant's Ridgeline Discovery Engine in Basel, Switzerland. For more information please visit www.bdtherapeutics.com.

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