Black Diamond Therapeutics Presents Preclinical Data on BDTX-1535 and BDTX-4933 at the 34th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics

October 26, 2022

- *BDTX-1535 is an irreversible MasterKey inhibitor of multiple EGFR alterations that utilize similar activated oncogenic EGFR conformations to drive tumor cell growth in GBM and NSCLC*
- *BDTX-1535 demonstrated potent systemic and CNS anti-tumor activity and survival benefit in multiple PDX models of GBM and NSCLC tumors driven by a family of EGFR alterations, including resistance mutations and EGFR amplification*
- *BDTX-4933 is a MasterKey inhibitor of oncogenic isoforms of the RAF family, which demonstrated on-target cell growth inhibition in vitro and tumor growth regression in in vivo tumor models driven by oncogenic Class I, II and III BRAF alterations and NRAS mutations*

CAMBRIDGE, Mass. and NEW YORK, Oct. 26, 2022 (GLOBE NEWSWIRE) -- Black Diamond Therapeutics, Inc. (Nasdaq: BDTX), a precision oncology medicine company pioneering the discovery and development of MasterKey therapies, today announced the presentation of three posters reporting new preclinical data on BDTX-1535 and BDTX-4933 at the 34th European Organisation for Research and Treatment of Cancer—National Cancer Institute—American Association for Cancer Research (EORTC-NCI-AACR) Symposium on Molecular Targets and Cancer Therapeutics being held in Barcelona, Spain. The poster presentations highlight new preclinical data demonstrating robust anti-tumor activity of both programs in a broad range of preclinical models of oncogene driven cancers.

“Despite the recent advancements in next generation sequencing to allow for tailored oncology therapeutics, less than 15% of metastatic cancer patients are eligible for approved precision oncology medicines. We believe our ability to characterize potentially oncogenic mutations, de-orphan them, and group our targets into druggable oncogene families provides a promising and next-generation approach to precision oncology drug development,” said Elizabeth Buck, Ph.D., Chief Scientific Officer of Black Diamond Therapeutics. “These preclinical results demonstrate key features of our epidermal growth factor receptor (EGFR) MasterKey inhibitor BDTX-1535, including its ability to irreversibly inhibit a family of EGFR driver mutations expressed in both lung and brain cancers while sparing wild type (WT) EGFR, its brain penetrance profile, and its ability to promote tumor regression across a full range of EGFR-driven tumor models representing both cancer types. Similarly, we are pleased that our potent RAF MasterKey inhibitor BDTX-4933 demonstrates tumor regression and central nervous system (CNS) penetrance in preclinical models of cancers driven by BRAF Class I, II and III mutations and NRAS mutations in addition to demonstrating durable intracranial anti-tumor activity. These results further add to our robust understanding of cancer genetics, onco-protein function, and drug discovery, and support the continued development of our MasterKey therapies using the MAP Drug Discovery Engine.”

Preclinical Data Demonstrate BDTX-1535’s Unique Pharmacology, CNS Penetration, and Broad Anti-Tumor Activity
Black Diamond presented two posters highlighting preclinical data showcasing BDTX-1535’s preclinical exposure and anti-tumor activity across patient derived xenograft (PDX) and allograft models of both non-small cell lung cancer (NSCLC) and glioblastoma multiforme (GBM). BDTX-1535 is a CNS penetrant 4th generation irreversible (covalent) EGFR MasterKey inhibitor targeting the family of classical, intrinsic and acquired resistance mutations (e.g., C797S, L718Q, G724S, and S768I) expressed in NSCLC, and amplification and extracellular domain alterations (e.g., EGFRvIII and A289X) expressed in GBM, while sparing WT EGFR. BDTX-1535 was designed using Black Diamond’s proprietary MAP Drug Discovery Engine and targets the common, activated conformations used by oncogenic EGFR to drive tumor cell growth in GBM and NSCLC.

In a poster titled, “Anti-Tumor Activity of BDTX-1535, an Irreversible CNS Penetrant Inhibitor of Multiple EGFR Extracellular Domain Alterations, in Preclinical Glioblastoma Models,” Black Diamond demonstrated that multiple EGFR extracellular domain alterations, which can form active covalent homodimers and result in paradoxical EGFR activation by reversible inhibitors, are blocked by the irreversible CNS penetrant inhibitor BDTX-1535. Black Diamond outlined features of BDTX-1535 that are believed to be essential for an effective EGFR blockade in GBM, including highly potent targeting of the family of oncogenic EGFR alterations in GBM while sparing inhibition of WT EGFR, high CNS penetrance, and an avoidance of paradoxical activation through irreversible inhibition of oncogenic EGFR. Additional highlights include:

- The family of EGFR alterations expressed in GBM forms constitutively active homodimers, which exhibit paradoxical activation by a range of reversible ATP competitive inhibitors, but which are demonstrated to be effectively inhibited *in vitro* and *in vivo* by the irreversible EGFR MasterKey inhibitor, BDTX-1535.
- BDTX-1535 is shown to be highly CNS penetrant and demonstrates robust anti-tumor activity as evidenced by growth regression and survival benefit across PDX and intracranial models expressing EGFR alterations and amplification.
- Real world data based on tumor DNA sequencing provides direct evidence that oncogenic alterations in EGFR, commonly expressed in GBM, are retained throughout current standard of care treatment.

In a poster titled, “BDTX-1535 is a Fourth Generation MasterKey Inhibitor of a Broad Spectrum of Intrinsic and Acquired Resistance Mutations of EGFR Expressed in NSCLC,” Black Diamond outlined the significant unmet clinical need in NSCLC patients with acquired and intrinsic resistance EGFR mutations against 3rd generation EGFR tyrosine kinase inhibitors (TKIs) which is potentially addressed by BDTX-1535 targeting activated conformations of EGFR caused by these alterations. Black Diamond highlighted that BDTX-1535 is designed using Black Diamond’s proprietary MAP Drug Discovery Engine to target common activated EGFR conformations in NSCLC which result from multiple classical, intrinsic, and acquired

oncogenic alterations including C797S, L718Q, G724S, and S768I mutations. Additional highlights include:

- BDTX-1535 potently inhibits multiple classical, intrinsic and acquired EGFR alterations observed in NSCLC patients that are resistant or inadequately addressed by 3rd generation EGFR TKIs (e.g., osimertinib).
- BDTX-1535 demonstrated potent anti-tumor activity and tumor growth regression in multiple mouse models expressing oncogenic EGFR alterations including coexisting EGFR mutations such as EGFR Exon19del + C797S that render osimertinib ineffective.

Black Diamond is currently evaluating BDTX-1535 in a Phase 1 study in GBM patients with EGFR alterations and NSCLC patients with EGFR resistance mutations, including de novo (intrinsic) resistance and acquired resistance to 3rd generation EGFR TKIs. The Company expects to provide a clinical update on BDTX-1535 in 2023.

Preclinical Data Demonstrate BDTX-4933's Ability to Achieve On-Target Inhibition of Oncogenic BRAF Class I/II/III Mutations
Black Diamond presented a poster highlighting Black Diamond's approach to characterizing, de-orphaning potentially oncogenic BRAF and MAPK pathway alterations, and grouping them into druggable oncogene families. BDTX-4933 was designed using Black Diamond's proprietary MAP Drug Discovery Engine to target the common activated conformations of oncogenic RAF which result from a broad family of oncogenic Class I/II/III BRAF mutations and RAS pathway alterations.

In a poster titled, "Preclinical efficacy of BDTX-4933, a brain penetrant MasterKey inhibitor targeting oncogenic BRAF Class I/II/III mutations," Black Diamond highlighted that based on preclinical studies, BDTX-4933 is shown to be a CNS penetrant BRAF inhibitor active against tumors that are driven by a Class I/II/III BRAF mutation, as well as by other oncogenic RAS pathway alterations that promote constitutive RAF dimer activation, including NRAS alterations. Additional highlights include:

- BDTX-4933 is an active-site inhibitor that binds to both monomeric and dimeric forms of a mutant BRAF, achieving on-target inhibition of cell proliferation driven by a large family of oncogenic BRAF and MAPK pathway alterations including NRAS mutations.
- BDTX-4933 demonstrated potent, on-target inhibition of the RAF-MEK-ERK signaling pathway and anti-tumor activity in multiple preclinical tumor models, including intracranial tumor models.
- In mouse xenograft and allograft studies, BDTX-4933 showed regression of tumors carrying BRAF Class I, II and III mutations.
- BDTX-4933 retained potent activity against BRAF V600E PDX cell lines that are resistant to dabrafenib and trametinib combination.

Black Diamond expects to submit an Investigational New Drug (IND) application for BDTX-4933 with the U.S. Food and Drug Administration (FDA) in the first half of 2023.

"These preclinical results demonstrate our compelling approach to precision cancer medicines through our MAP Drug Discovery Engine and MasterKey therapies. We are pleased to share that both MasterKey therapies, BDTX-1535 and BDTX-4933, discovered through our MAP Drug Discovery Engine, have shown anti-tumor activity across a range of tumor models. Our MAP Drug Discovery Engine provides Black Diamond with a scalable approach to validate the oncogenicity of previously uncharacterized mutations. These preclinical results further support this approach as both BDTX-1535 and BDTX-4933 demonstrated the key attributes of next generation small molecule inhibitors with the ability to target families of mutations while sparing wild type," said David M. Epstein, Ph.D., President and Chief Executive Officer of Black Diamond Therapeutics. "We believe the productivity of our drug discovery engine enables us to provide differentiated approaches to cancer treatment with a strong focus on targeting broad families of mutations that previously have not been addressed by approved therapies. The data shared at EORTC-NCI-AACR further support the clinical advancement of both BDTX-1535 and BDTX-4933 and we look forward to sharing updates on our progress for these programs in 2023."

The posters from the EORTC-NCI-AACR Symposium are available on the "Scientific Presentations and Publications" section of the Black Diamond Therapeutics website.

About Black Diamond Therapeutics, Inc.

Black Diamond Therapeutics is a precision oncology medicine company pioneering the development of novel MasterKey therapies. Black Diamond is addressing the significant unmet need for novel precision oncology therapies for patients with genetically defined cancers who have limited treatment options. Black Diamond is built upon a deep understanding of cancer genetics, onco-protein function, and drug discovery. The Company's proprietary Mutation-Allostery-Pharmacology, or MAP drug discovery engine is designed to allow Black Diamond to analyze population-level genetic sequencing tumor data to predict and validate oncogenic mutations that promote cancer across tumor types as MasterKey mutations. Black Diamond discovers and develops selective MasterKey therapies against these families of oncogenic mutations. Black Diamond was founded by David M. Epstein, Ph.D., and Elizabeth Buck, Ph.D. For more information, please visit www.blackdiamondtherapeutics.com.

Forward-Looking Statements

Statements contained in this press release regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding: the continued development and advancement of BDTX-1535 and BDTX-4933, including the ongoing Phase 1 clinical trial and the expected timing for data updates for BDTX-1535, and the timing for initiating Investigational New Drug, or IND-enabling studies for BDTX-4933 and the timing for filing an IND application for BDTX-4933, the timing and potential achievement of upcoming clinical and preclinical milestones for each program, the continued development of the FGFR program, including plans for nominating a development candidate, in addition to plans to disclose an additional development candidate against a new target, and the continued development of the MAP drug discovery engine. Any forward-looking statements in this statement are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could

cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. Risks that contribute to the uncertain nature of the forward-looking statements include those risks and uncertainties set forth in its Annual Report on Form 10-K for the year ended December 31, 2021, filed with the United States Securities and Exchange Commission and in its subsequent filings filed with the United States Securities and Exchange Commission. All forward-looking statements contained in this press release speak only as of the date on which they were made. The Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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