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MEDIA UPDATE

Novartis announces early clinical data for unique KRAS^{G12C} inhibitor at American Association for Cancer Research annual meeting

- *JDQ443, an investigational selective, covalent, and orally bioavailable KRAS^{G12C} inhibitor, shows 57% confirmed ORR at recommended dose of 200 mg twice daily in Phase Ib study in patients with advanced non-small cell lung cancer (NSCLC)*
- *Ongoing investigation of JDQ443 in single agent and multiple combination strategies designed to enhance efficacy of G12C targeted therapy and improve outcomes of patients with KRAS G12C-driven cancers. Phase III study anticipated to begin mid 2022*
- *Innovation in targeted protein degradation also highlighted with debut for protein degrader DKY709, an investigational molecular glue*

Basel, April 11, 2022 — Novartis today announced promising clinical data for JDQ443, an investigational selective, covalent, and orally bioavailable KRAS^{G12C} inhibitor at the annual meeting of American Association for Cancer Research (AACR). Comprehensive information on the discovery of JDQ443 is also included in a poster being presented on Wednesday 13th April with further details published in the journal *Cancer Discovery*[1].

Preliminary data (Phase Ib) from the KontRASt-01 study (NCT04699188) showed that JDQ443, discovered at Novartis, demonstrated anti-tumor activity, high systemic exposure at its recommended dose, and a favorable safety profile based on initial clinical data in patients with *KRAS G12C*-mutated solid tumors[2]. The data were submitted as a late-breaking abstract and will be presented today in an oral session.

KRAS mutations are the most frequent oncogenic drivers in NSCLC, the most common type of lung cancer[3]. The most common form of *KRAS* mutation is *G12C*[4]. JDQ443 inhibits this mutated form of *KRAS* in a structurally distinct way, trapping *KRAS G12C* in a GDP-bound, inactive state while avoiding direct interaction with H95, a recognized route for resistance[5,6]. In preclinical models, JDQ443 potently inhibited *KRAS G12C* cellular signalling and proliferation in a mutant-selective manner and demonstrated dose-dependent antitumor activity[7].

“After decades without a breakthrough, we as an industry are entering a transformative era in targeted treatment for *KRAS-mutated* cancers,” said Jeff Legos, Executive Vice President, Global Head of Oncology & Hematology Development at Novartis. “But challenges remain, in particular drug resistance. We believe that JDQ443 may have the potential for overcoming such challenges. Today’s preliminary data are an encouraging signal that we are on the right path as we continue to investigate single-agent and multiple combination strategies designed

to enhance efficacy of G12C targeted therapy and improve outcomes of patients with *KRAS G12C*-driven cancers."

Also at AACR, Novartis debuted its targeted protein degradation platform with presentations on DKY709, a potential first-in-class "molecular glue" protein degrader that is designed to target the zinc finger transcription factor Helios (IKZF2)[8]. Transcription factors, similar to *KRAS G12C*, are historically "undruggable" targets. Clinical data were drawn from a study (NCT03891953) of advanced solid tumors in which DKY709 is being investigated as a monotherapy and in combination with the anti–PD-1 antibody spartalizumab. The discovery and structure of DKY709 were also presented on April 9th at AACR[9].

About JDQ443 and the KontRASt-01 Study[2]
KontRASt-01 (NCT04699188) is a phase Ib/II open-label, multi-center, dose escalation study of JDQ443, in patients with advanced solid tumors harboring the *KRAS G12C* mutation, including NSCLC and colorectal cancer. The study began in February 2021 and is currently recruiting. The escalation part will further characterize the safety and tolerability profile of JDQ443 as a single agent and JDQ443 in combination with other agents in advanced solid tumor patients. The estimated primary completion date of the study is 2024.

The preliminary data presented at AACR were drawn from the monotherapy dose escalation arm of the KontRASt-01 study. Patients had a median of 3 prior lines of anti-neoplastic therapy. The recommended monotherapy dose of 200 mg taken orally twice daily (BID) will be taken forward for further studies in phase II dose expansion. Efficacy data (cutoff of 05 Jan 2022) from the pooled Phase Ib JDQ443 single agent cohort (n=39) showed:

- 57% (4/7) confirmed overall response rate (ORR) at 200 mg BID in NSCLC
- 45% (9/20) confirmed and unconfirmed ORR across doses in NSCLC
- 35% (7/20) confirmed ORR across doses in NSCLC
- PD/PK modeling predicts sustained, high-level target occupancy at the recommended dose of 200 mg BID

Ongoing enrollment to the KontRASt-01 study continues across a number of arms:

- JDQ443 single agent expansion (Ph II) in *KRAS G12C*-mutated NSCLC
- JDQ443 single agent expansion (Ph II) in *KRAS G12C*-mutated CRC
- JDQ443 + TNO155 (SHP2 inhibitor) dose escalation (Ph Ib) in *KRAS G12C*-mutated solid tumors
- JDQ443 + tislelizumab dose escalation (Ph Ib) in *KRAS G12C*-mutated solid tumors

A Phase III study, KontRASt-02 (NCT05132075) of JDQ443 versus docetaxel in patients with previously treated, locally advanced or metastatic *KRAS G12C*-mutated NSCLC is anticipated to begin enrolling patients by mid-2022.

Novartis in Lung Cancer
The needs in lung cancer are urgent and significant. Each year, more than 2 million people are newly diagnosed globally[10], and lung cancer remains the number one cause of cancer-related death worldwide[11].There are two main types of lung cancer—small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 85% of lung cancer diagnoses[12].

Novartis is making bold investments in advancing the science to research treatments that may make an impact for patients around the world. The company is committed to working with the scientific and medical communities to reimagine the treatment of lung cancer and pursue advances in medicine that could extend the survival of people living with lung cancer.

With one of the most diverse lung cancer development programs in the industry, Novartis is developing therapies that may block cancer growth and activate the body's immune system; working to understand the relationship between chronic inflammation and tumor growth and progression; and exploring the potential for advanced nuclear medicine to fight the disease. Through these programs, Novartis aims to redefine possibilities in lung cancer and pursue a trajectory to make lung cancer history.

Targeted Protein Degradation at Novartis
Targeted protein degradation (TPD) offers first-in-class potential for multiple previously undruggable targets. The approach induces proximity of a target to a ubiquitin ligase, thereby tagging the target for destruction by the cell. Novartis is making an enterprise scale investment in TPD innovation, focusing on the discovery of molecular glues and bifunctional degraders, as well as the development of chemical libraries and the discovery of structural insights.

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