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BI 1482694

BACKGROUNDER

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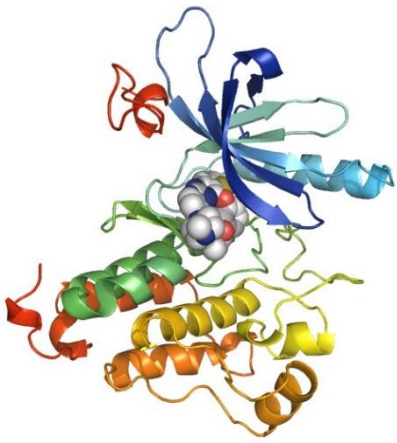
1. ABOUT BI 1482694

BI 1482694* (HM61713**) is an investigational novel, 3rd-generation, oral, irreversible EGFR (epidermal growth factor receptor) mutant-specific TKI developed for the treatment of lung cancer patients whose tumours have EGFR mutations, including the resistance mutation, T790M. This specific mutation is common in tumours progressing on initial 1st- or 2nd-generation EGFR tyrosine kinase inhibitor (TKI) treatment.



3D model of EGFR (T790M) complexed with BI 1482694

2. DISEASE AREA & MECHANISM OF ACTION

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for around 85% of all cases.[1] The most common histological sub-types of NSCLC are adenocarcinoma (40-50% of NSCLC), squamous cell carcinoma (25-40% of NSCLC) and large cell carcinoma (3-5% of NSCLC).[1] Upon diagnosis of NSCLC, in addition to the stage of the cancer, various factors can have an impact on the treatment options available to each individual, including the individual's general health or genetic mutations acquired by cancer cells.[2] EGFR mutations for instance, are found in 10-15% of Caucasian and 40% of Asian patients with adenocarcinoma of the lung.[3]

In EGFR mutation-positive NSCLC, EGFR TKIs have been developed to target tumour cells bearing these mutations. Such targeted therapies are designed to more precisely identify and attack cancer cells, blocking their growth, division and ability to spread, and spare healthy cells. The goal of such treatments is to improve efficacy and reduce side effects for patients, compared to chemotherapy.[4]

Resistance to treatment will eventually develop in most patients with EGFR mutation-positive NSCLC who are receiving a 1st- or 2nd-generation EGFR TKI. The most common resistance mechanism is the T790M mutation, which occurs in approximately 50% of

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NSCLC patients who have received previous EGFR TKI therapy.[5,6] Currently, there are few treatment options for these patients, and burdensome chemotherapy regimens are the main option. For this reason, T790M-positive NSCLC represents an area of great unmet need.

BI 1482694 is a 3rd-generation, irreversible EGFR mutant-specific TKI with a novel mode of action, enabling it to:

- Target only EGFR mutant cells, including sensitising EGFR mutations such as del19 and L858R
- Target cells carrying the T790M resistance mutation
- Spare the cells without EGFR mutations (known as “wild type” EGFR)

3. DEVELOPMENT STATUS

Regulatory status

Boehringer Ingelheim aims to achieve first market authorisation for BI 1482694 in patients with T790M-positive NSCLC in 2017.

- In December 2015, the US Food and Drug Agency (FDA) granted BI 1482694 Breakthrough Therapy designation, a process intended to expedite the development and review of promising drugs for serious or life-threatening conditions.
- In October 2015, a New Drug Application for BI 1482694 (HM61713) was filed with the Korean Ministry of Food and Drug Safety.

ELUXA 1

ELUXA 1 is an ongoing pivotal Phase II global clinical trial. It is designed to further investigate the efficacy and safety of BI 1482694 in patients with NSCLC who acquired T790M-mediated resistance after first-line EGFR TKIs. The ELUXA 1 trial is part of a broad ELUXA pivotal trial programme which includes Phase III studies planned to be initiated in 2016.

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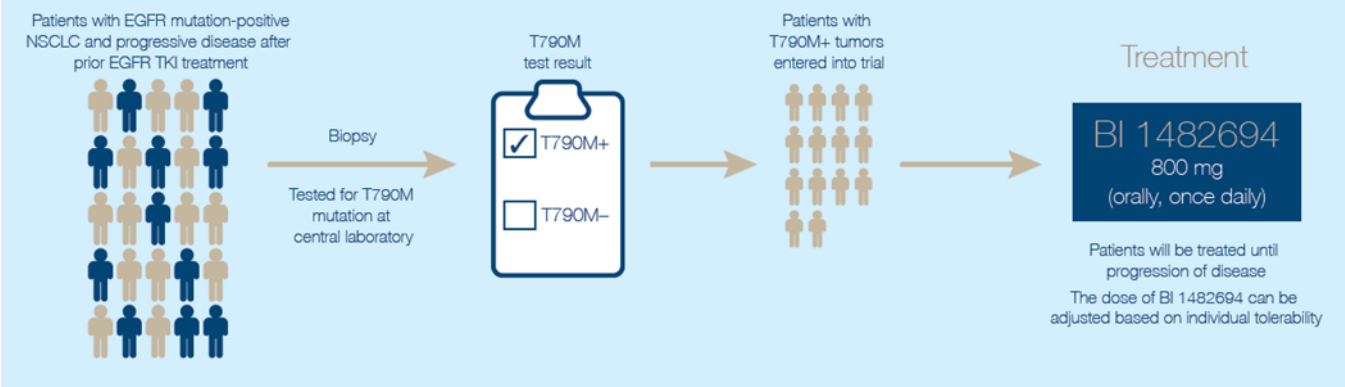
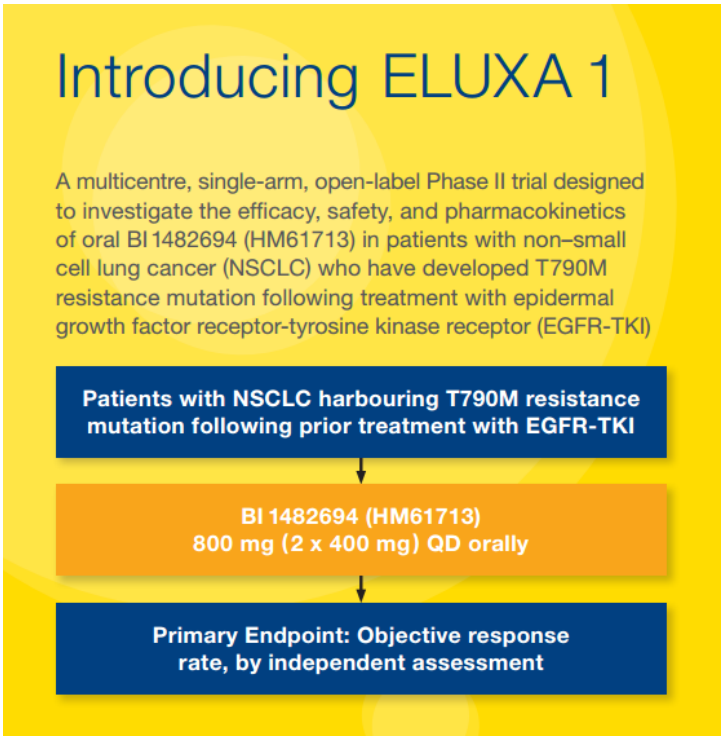
Patients enrolled in the ELUXA 1 study have a confirmed diagnosis of EGFR T790M mutation-positive NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status 0-1 and a life expectancy of at least 3 months. Objective response (OR) rate is the primary endpoint of the study, with secondary endpoints including progression-free survival (PFS) and overall survival (OS).[7]



ELUXA 1 / HM-EMSI-202 Study Design

ELUXA 1 is being conducted in 10 countries (Australia, Canada, Germany, Italy, Malaysia, Republic of Korea, Spain, Taiwan, The Philippines, and the USA). Coordinating investigators are Prof. K. Park and Prof. P. Jänne.



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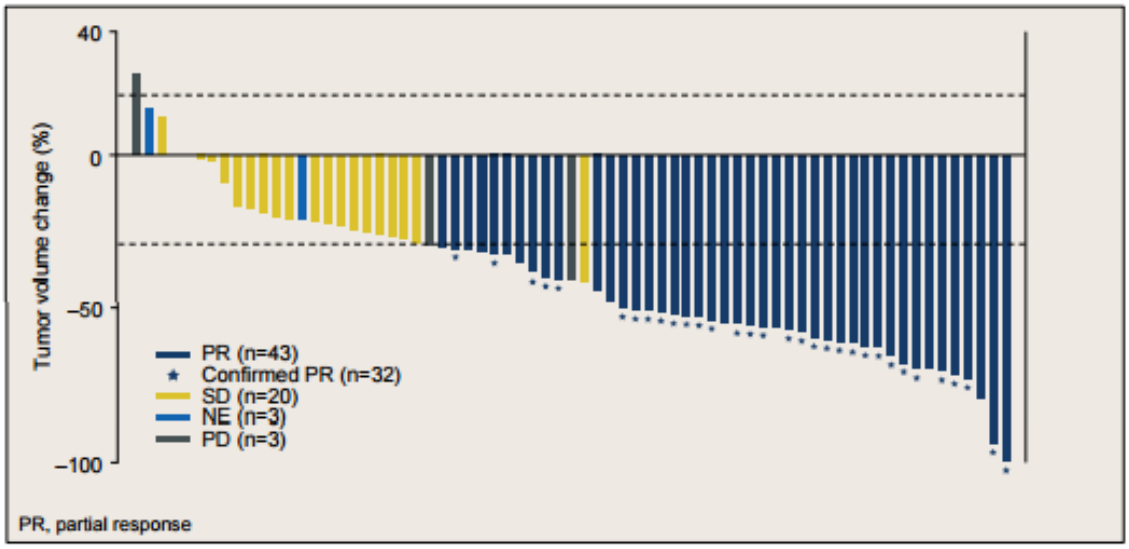
4. DATA OVERVIEW

BI 1482694 has demonstrated anti-tumour activity, combined with a favourable safety profile at the recommended Phase II dose of 800mg once daily in a Phase I/II clinical trial (HM-EMSI-101) in Korean patients with advanced pre-treated EGFR mutation-positive NSCLC, whose tumours acquired T790M-mediated resistance after first-line EGFR TKI therapy. The primary endpoint in this open-label, multi-centre study was OR, and secondary endpoints included duration of response, PFS and safety.

- At the recommended Phase II dose, 800 mg qd ORs by independent assessment were observed in 62% patients, including 32 patients (46%) whose tumour response had been confirmed by the time of data cut-off
- Disease control rate was 91% by independent assessment

The most common treatment-related adverse events (AEs) included (total/grade 3) diarrhoea (55%/0%), nausea (37%/0%), rash (38%/5%) and pruritus (skin itching: 36%/1%) – the majority of AEs were mild-to-moderate.[8]



Individual tumour change in target lesions (independent assessment)

**BI 1482694 is an investigational, novel, oral, 3rd-generation, EGFR mutant-specific tyrosine kinase inhibitor (TKI) developed to target tumours with EGFR mutations including the resistance mutation T790M.*
***Boehringer Ingelheim has an exclusive license and collaboration agreement with Hanmi Pharmaceutical Co. Ltd for the development and global commercialisation rights (except South Korea, China and Hong Kong) of BI 1482694 (HM61713).*

[1] American Cancer Society. Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/ [Last accessed: December 2015]
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[3] Quest Diagnostics – Lung Cancer Mutation Panel; http://www.questdiagnostics.com/testcenter/testguide.action?dc=TS_LungCancerMutation_Panel [Last accessed September 2015]
[4] Targeted Cancer Therapies. National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted. [Last accessed: December 2015]
[5] Oxnard GR., *et al.* Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR mutant lung cancer: Distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res*. 2011 March 15; 17(6): 1616–1622.
[6] Inukai M., *et al*. Presence of epidermal growth factor receptor gene T790M mutation as a minor clone in non-small cell lung cancer. *Cancer Res*. 2006 Aug 15;66(16):7854-8.
[7] Clinicaltrials.gov Identifier: NCT02485652 https://clinicaltrials.gov/ct2/show/NCT02485652?term=BI1482694&rank=1. [Last accessed December 2015]
[8] Lee J-S., *et al*. Clinical activity and safety of the EGFR mutant-specific inhibitor, BI1482694, in patients (pts) with T790M-positive NSCLC. Abstract #425PD. Presented Saturday 19 December ESMO Asia 2015 Congress.