A Phase 1/2 Study Targeting Acquired Resistance Mechanisms in Patients with EGFR Mutant Non-Small Cell Lung Cancer

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Phase 1• To determine the maximum tolerated dose (MTD) and RP2D of BLU 945 as monotherapy and in combination with osimertinib• To determine the safety and tolerability of BLU 945 as monotherapy and in combination with osimertinibPhase 2• To assess...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52248

Source
ToetsingOnline

Brief title
BLU-945-1101

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Non-Small Cell Lung Cancer, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Blueprint Medicines Corporation
Source(s) of monetary or material Support: Blueprint Medicines Corporation

Intervention

Keyword: Aquired resistance, EGFR, non-small cell lung cancer (NSCLC), pathway inhibition

Outcome measures

Primary outcome

Phase 1

Maximum tolerated dose (MTD) is calculated with dose-limiting toxicity rate

Recommended Phase 2 dose (RP2D) of BLU-945 is based on dose-limiting toxicity, pharmacokinetics, pharmacodynamics, and preliminary safety and anticancer activity data.

Overall safety profile of BLU-945, as assessed by the type, frequency, severity, timing, and relationship to study drug of treatment-emergent adverse events (TEAEs), and changes in vital signs, electrocardiograms, and safety laboratory tests

Phase 2

Overall response rate, defined as the proportion of patients who experience a best response of confirmed complete response or partial response according to RECIST 1.1

Secondary outcome

Phase 1

• ORR, defined as the proportion of patients who experience a best response of confirmed CR or PR according to RECIST 1.1

• DOR, defined as the time from first documented response of CR or PR to the date of first documented progressive disease or death due to any cause,

whichever occurs first

• PK parameters of BLU-945: Pharmacokinetic parameters of interest will include, as appropriate, maximum plasma drug concentration (Cmax), time to maximum plasma drug concentration (Tmax), time of last quantifiable plasma drug concentration (Tlast), area under the plasma concentration versus time curve from time 0 to the end of the dosing interval (AUC0-24 for QD and AUC0-12 for BID), trough concentration (Ctrough), apparent volume of distribution (Vz/F), terminal elimination half-life (t*), apparent oral clearance (CL/F), and accumulation ratio®. BLU-945 metabolites may also be measured.

• Profile pharmacodynamic changes in expression levels of the EGFR pathway biomarkers dual specificity phosphatase (DUSP6) and sprouty RTK signaling antagonist 4 (SPRY4).

Phase 2

• DOR, defined as the time from first documented response of CR or PR to the date of first documented progressive disease or death due to any cause, whichever occurs first

• DCR, defined as the proportion of patients who experience a best response of CR, PR, or stable disease (SD) according to RECIST 1.1

• CBR, defined as the proportion of patients who experience a confirmed CR or PR, or SD with a duration of at least 16 weeks according to RECIST 1.1

• PFS, defined as the time from the first dose of BLU-945 until the date of first documented progressive disease or death due to any cause, whichever occurs first

• Overall survival (OS), defined as the time from the first dose of BLU-945 until the date of death due to any cause

• CNS-ORR, defined as the proportion of patients with measurable (target) intracranial metastases at baseline who experience a confirmed intracranial CR or PR according to RECIST 1.1 principles

• CNS-DOR, defined as the time from first documented intracranial CR or PR to the date of first documented intracranial PD

• CNS progression rate, defined as the proportion of patients with CNS progression as a component of first disease progression on study

• Overall safety profile of BLU-945, as assessed by the type, frequency, severity, timing, and relationship to study drug of TEAEs, and changes in vital signs, electrocardiograms, and safety laboratory tests.

• ECG parameters extracted from continuous 12-lead Holter recordings for 25 patients in the expansion phase: The primary QTc parameter will be QTcF. Secondary parameters (other correction methods for QT, heart rate, PR, QRS, and T-wave morphology) will also be evaluated.

• PK parameters of BLU 945 (as described above in Section 3.1).

• Correlations between PK parameters and safety findings of interest, including ECG intervals, will be performed.

Study description

Background summary

In summary, although EGFR TKIs have transformed the treatment paradigm and have improved survival for advanced EGFR-mutant NSCLC, many patients treated with

currently available EGFR TKIs, including osimertinib, will eventually develop metastatic lesions harboring resistance mutations. As there are no approved TKIs for patients with NSCLC harboring T790M/C797S-resistant mutations, these patients have limited treatment options resulting in lethal clinical progression. Antitumor activity of EGFR TKIs in the brain, particularly in the resistant setting, is critical as nearly 50% of patients with metastatic NSCLC will be affected by brain metastases during the course of their disease. The targeted patient population in the second line or subsequent settings is heterogeneous with other EGFR and non-EGFR driver mutations. Thus, the ideal EGFRm/T790M/C797S inhibitor could also be explored in combination with other therapies to achieve broader mutation and target coverage or in combination with chemotherapy. BLU-945, an orally available EGFR TKI that demonstrates significant antitumoral pharmacological activity in preclinical osimertinib-resistant models, has the potential to address this unmet clinical need.

Study objective

Phase 1
• To determine the maximum tolerated dose (MTD) and RP2D of BLU 945 as monotherapy and in combination with osimertinib
• To determine the safety and tolerability of BLU 945 as monotherapy and in combination with osimertinib

Phase 2
• To assess anticancer activity (ORR) of BLU 945 at the RP2D as monotherapy and in combination with osimertinib in patients with NSCLC harboring EGFR mutations

Study design

Phase 1
The first cohort of patients will receive BLU-945 at a starting dose of 25 mg once daily as monotherapy (Part 1A) or in combination with osimertinib (Part 1B). To limit the number of patients treated at potentially subtherapeutic dose levels, the study will initially use a cohort size of 1-3 patients, and the incremental dose increase between cohorts will be up to 100%, to find the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of BLU-945 that will be used in Phase 2.

Phase 2
All patients enrolled into the BLU-945 monotherapy expansion groups will be treated with BLU-945 at the RP2D and schedule selected in Part 1A, and will be enrolled into one of 3 expansion groups based on EGFR mutation profile.
All patients enrolled into the BLU-945 with osimertinib expansion group will be treated with BLU-945 and osimertinib at the RP2D and schedule selected in Part 1B.

Intervention

Oral administration of BLU-945 capsules or tablets as monotherapy or in combination with osimertinib.

Study burden and risks

Results from the repeated-dose GLP-compliant 28-day toxicology study in rats and monkeys, the cardiovascular electrocardiogram (ECG) assessment in the repeated-dose GLP-compliant 28-day toxicology study in the monkey, and other toxicology studies all inform the clinical program of potential risks to humans in the FIH study. As described in Section 2.3.1.2, the main findings from these studies were epithelial changes in the gastrointestinal tract, effects on reproductive tissues, and increased inflammation. In addition, brain hemorrhage was observed in male rats at exposures 86- to 100-fold higher than that projected for the starting dose of 25 mg to be utilized in the current clinical study. Genotoxicity studies suggest no risk for BLU-945 causing damage to deoxyribonucleic acid (DNA) or chromosomes. Nonclinical pharmacology suggest a low potential for QT interval prolongation. Phototoxic effects of BLU-945 are currently unknown.

There are also risks associated with the study procedures:
- Blood drawing could cause some pain and/or bruising. infection, nerve damage, excess bleeding, clotting, or fainting are also possible.
- ECG: the sticky patches could cause some redness or itching.
- Tumor Biopsy could cause pain, bleeding, infection, scarring at the site of the biopsy, accidental injury to a nearby organ (rare) and pneumothorax (when lung biopsy is performed)
- CT scan could cause claustrophobia and a slightly higher risk of developing cancer due to the radiation exposure. The contrast media injected could results in a sensation of warmth, a strange taste, transient nausea. Possible risks of the injection include allergic reactions, pain or swelling at site of injection, damage to organs, rash, severe reaction (uncommon) and life-threatening reaction (rare; e.g. difficulty breathing, decrease in blood pressure).
-MRI could cause claustrophobia and makes loud banging noises. The contrast media injected could results in a sensation of warmth, a strange taste, transient nausea. Possible risks of the injection include allergic reactions, pain or swelling at site of injection, damage to organs, rash, severe reaction (uncommon) and life-threatening reaction (rare; e.g. difficulty breathing, decrease in blood pressure).

other risks:
- Because the phototoxicity risk is unknown, patients should use protective clothing and apply sunscreen when outside to avoid direct sun exposure while receiving BLU-945 and for 1*week thereafter.

Nonclinical pharmacology studies support the potential for clinical benefit, in the form of selective and potent EGFR pathway inhibition as well as antitumor activity, including intracranial activity, in an unmet medical need population of patients with tumors bearing EGFR resistance mutations.

Overall, when taken together, the results from the described nonclinical toxicology and pharmacology studies indicate an acceptable benefit/risk profile to allow the clinical evaluation of BLU-945 as a single agent and in combination with osimertinib.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. >=18 years of age at the time of signing the informed consent.

2. Pathologically confirmed, definitively diagnosed, metastatic NSCLC harboring an activating EGFR mutation.
3. Previously received at least 1 prior EGFR-targeted TKI with activity against the T790M mutation, such as osimertinib.
a. Phase 1 Part 1B and Phase 2 Group 4: Patients must have experienced progressive disease while on osimertinib, were able to tolerate prior osimertinib 80 mg QD dose, and continuing on osimertinib is deemed to be in the patient*s best interests in the opinion of the Investigator. Patients who have discontinued osimertinib may be eligible if no more than 6 weeks elapse between the discontinuation of prior osimertinib and resumption of osimertinib on study.
4. Tumor mutation profile determined locally via a Sponsor-approved testing methodology (NGS is preferred and will be required for Phase 2), using tumor tissue (ideally from a progressing lesion) and/or ctDNA in plasma. For Phase 1, it is preferable that samples used for analysis be obtained during or after disease progression on the last EGFR-targeted TKI received. For Phase 2, pre-treatment tumor sample must be obtained during or after disease progression on the last EGFR-targeted TKI received.
a. Dose Escalation (Phase 1 Part 1A and Part 1B): At each dose level, slots may be reserved for patients with the mutations of interest.
b. BLU-945 Monotherapy Expansion (Phase 2 Group 1, Group 2, and Group 3): Patients must have NSCLC harboring EGFR T790M and C797S mutation (Group 1); EGFR T790M but not C797S (Group 2); or EGFR C797S but not T790M (Group 3).
c. BLU-945 with Osimertinib Expansion (Phase 2 Group 4): Slots may be reserved for patients with mutations of interest, but at least 12 slots will be allocated to patients with NSCLC harboring EGFR T790M and C797S mutation.
5. Pretreatment tumor sample (either an archival sample or a sample obtained by pretreatment biopsy) submitted for central analysis. For Phase 1, it is preferable that pretreatment tumor samples be obtained from a progressing lesion, during or after disease progression on the last EGFR-targeted TKI received. For Phase 2, pre-treatment tumor sample must be obtained during or after disease progression on the last EGFR-targeted TKI received. Patients without appropriate archival tissue available, where biopsy is not considered safe and/or medically feasible, may be discussed with the study medical monitor and may be approved for enrollment on a case-by-case basis.
6. Patients enrolled in Phase 1 Part 1A at doses expected to result in efficacious exposure levels (anticipated to be >=100 mg QD, but may be modified by the Sponsor based on emerging PK and clinical data) must consent to undergo on-treatment biopsy for central submission of tumor sample. Following approval from the Sponsor, on-treatment biopsy may be omitted for patients for whom the investigator does not feel that biopsy would be safe and/or feasible. Collection of these tumor samples may be discontinued for particular dose-escalation cohorts or expansion groups, if the Sponsor determines that adequate data have been obtained.
7. Phase 2 Expansion Groups: Patient has at least 1 measurable target lesion evaluable by RECIST 1.1 as assessed by the investigator.
8. Able to swallow an oral medication.
9. Eastern Cooperative Oncology Group (ECOG) performance status is 0-1.

10. Agrees to use contraception consistent with the protocol and local regulations, as outlined in Section 5.4.2.
11. Patient or legal guardian provides informed consent to participate in the study.

Exclusion criteria

1. Tumor harbors any additional known driver alterations (including but not limited to EGFR exon 20 insertion, or pathologic abnormalities of KRAS, BRAF V600E, NTRK1/2/3, HER2, ALK, ROS1, MET, or RET).
2. NSCLC with mixed cell histology or a tumor with histologic transformation (NSCLC to SCLC, SCLC to NSCLC, or epithelial to mesenchymal transition).
3. Received the following anticancer therapy:
a. EGFR-targeted TKI within 7 days prior to the first dose of study drug. Note: patients in Phase 1 Part 1B and Phase 2 Group 4 do not require a wash-out period for osimertinib.
b. Any immunotherapy or other antibody therapy (including EGFR-targeted antibodies or bi-specific antibodies) within 28 days prior to the first dose of study drug (immune-related toxicities must have resolved to < Grade 2 prior to starting BLU 945).
c. Any other systemic anticancer therapy within 14 days or 5 half-lives prior to the first dose of study drug, whichever is the shortest, but with a minimum of 7 days in all circumstances. BLU 945 may be started within these washout periods if considered by the Investigator to be safe and within the best interest of the patient, with prior Sponsor approval.
d. Radiotherapy to a large field or including a vital organ (including whole brain radiotherapy or stereotactic radiosurgery to brain) within 14 days before the first dose of study drug. Participant received radiotherapy to a focal site of disease that did not include a vital organ (such as a limb) within 7 days before the first dose of study drug.
4. CNS metastases or spinal cord compression that is associated with progressive neurological symptoms or requires increasing doses of corticosteroids to control the CNS disease. If a patient requires corticosteroids for management of CNS disease, the dose must have been stable for the 2 weeks preceding treatment. Asymptomatic CNS and leptomeningeal disease is allowed and, when measurable, should be captured as target lesions.
5. Any of the following abnormalities on the most recent laboratory test prior to the first dose of study drug (ie, Cycle 1 Day 1 [C1D1] or screening):
a. Absolute neutrophil count (ANC) <1.0×109/L.
b. Platelet count <75×109/L.
c. Hemoglobin <=8.0 g/dL (red blood cell transfusion and erythropoietin may be used to reach at least 8.0 g/dL, but must have been administered at least 2 weeks prior to the first dose of study drug).
d. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3× the upper limit of normal (ULN) if no hepatic metastases are present; >5× ULN if

hepatic metastases are present.
e. Total bilirubin >1.5× ULN; >3× ULN in presence of Gilbert*s disease.
f. Estimated (Cockroft-Gault formula, Appendix 1) or measured creatinine clearance <40 mL/min.
g. International normalized ratio (INR) >2.3 or prothrombin time (PT) >6 seconds above control or a patient-specific INR or PT abnormality that the treating investigator considers clinically relevant and/or increases the risk for hemorrhage in that individual patient.
6. Known intracranial hemorrhage and/or bleeding diatheses.
7. Clinically active ongoing interstitial lung disease (ILD) of any etiology, including drug-induced ILD, and radiation pneumonitis within 28 days prior to initiation of study treatment. Patients with prior ILD associated with clinically resolved COVID 19 infection may be enrolled upon discussion with, and approval by, the Medical Monitor.
8. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or that have not resolved to baseline at the time of starting the study. Exceptions include alopecia and fatigue, and, upon discussion with and approval by the Medical Monitor, other toxicities that are not thought to present a risk to patient safety.
9. Mean resting QT interval corrected using Fridericia*s formula (QTcF) >450 msec, a history of prolonged QT syndrome or Torsades de pointes, or a familial history of prolonged QT syndrome.
10. Clinically significant, uncontrolled, cardiovascular disease including congestive heart failure Grade III or IV according to the New York Heart Association classification; myocardial infarction or unstable angina within the previous 6 months, uncontrolled hypertension, or clinically significant, uncontrolled arrhythmias, including bradyarrhythmia that may cause QT prolongation (eg, Type II second degree heart block or third-degree heart block).
11. History of another primary malignancy (other than completely resected carcinomas in situ) that has been diagnosed or required therapy within 2 years prior to initiation of study treatment. However, upon discussion with the Sponsor, the following categories of patients with prior malignancy are eligible to participate:
a. Patients with a previous malignancy that completed all anticancer treatment at least 2 years before and with no evidence of residual disease from the prior malignancy at registration
b. Patients who have another concurrent malignancy (not lung cancer) that is clinically stable and does not require tumor-directed treatment. (Examples include, but are not limited to, completely resected basal cell carcinoma and squamous cell carcinoma of skin, curatively treated prostate cancer, breast cancer and early gastric cancer cured by endoscopic mucosal resection or endoscopic submucosal dissection.
12. Active, uncontrolled infection (viral, bacterial, or fungal) or active tuberculosis, hepatitis B, hepatitis C, AIDS-related illness, or known COVID 19 infection. Controlled infections, including HIV and *cured* hepatitis C (no active fever, no evidence of systemic inflammatory response syndrome) that are

stable on antiviral treatment may be eligible if benefit/risk is justified and permission is granted from the Sponsor.
13. Dose-escalation (Parts 1A and 1B): Received neutrophil or platelet growth factor support within 14 days of the first dose of study drug.
14. Requires treatment with a prohibited medication or herbal remedy (as specified in Section 6.9.1 and Appendix 2) that cannot be discontinued at least 2 weeks before the start of study drug administration. BLU 945 may be started within 14 days or 5 half-lives of these therapies if considered by the Investigator to be safe and within the best interest of the patient, with prior Sponsor approval.
15. Major surgical procedure within 14 days of the first dose of study drug (procedures such as central venous catheter placement, tumor needle biopsy, and feeding tube placement are not considered major surgical procedures).
16. Unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures and study restrictions.
17. Patient is a women who is not postmenopausal or surgically sterile, and is unwilling to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least 30 days after the last dose of study drug OR is a man who is not surgically sterile, and is unwilling to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least 90 days after the last dose of study drug. Refer to Section 5.4.2 for acceptable methods of contraception.
18. Patient is a pregnant female, as documented by a serum beta human chorionic gonadotropin (β hCG) pregnancy test consistent with pregnancy, obtained within 7 days prior to the first dose of study drug. Females with β hCG values that are within the range for pregnancy but are not pregnant (false-positives) may be enrolled with written consent of the Sponsor, after pregnancy has been ruled out. Females of non-childbearing potential (as defined in Section 5.4.2) do not require a serum β hCG test.
19. Patient is breastfeeding.
20. Known hypersensitivity to BLU 945 or any of its ingredients.
21. Any prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the Investigator*s or Sponsor*s opinion, could affect the safety of the patient; alter the absorption, distribution, metabolism, or excretion of the study drug; or impair the assessment of study results.

Study design

Design

Study phase: 2

Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-03-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BLU-945
Generic name:	N/A
Product type:	Medicine
Brand name:	Osimertinib
Generic name:	Tagrisso
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	12-07-2021
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	11-12-2021
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO

Date:	04-01-2022
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	10-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-005822-27-NL
ClinicalTrials.gov	NCT04862780
CCMO	NL77262.031.21