BAYER21607 (Bayer)

First in Human Study of BAY2927088 in Participants Who Have Advanced Non-small Cell Lung Cancer (NSCLC) With Mutations in the Genes of Epidermal Growth Factor Receptor (EGFR) and/or Human Epidermal Growth Factor Receptor 2 (HER2).

This is the trial summary as assessed on clinicaltrials.gov on 17/04//2023.

Minor changes in the protocol may occur. You can check this on this direct link: https://clinicaltrials.gov/ct2/show/NCT05099172 .

Trial Design:

ARM	INTERVENTION
Experimental: PART A (EGFR ex20ins mutation and naïve to EGFR ex20ins-targeted therapy e.g., mobocertinib, CLN-081, amivantamab, poziotinib).	PO BAY2927088 20 mg BID
Experimental: PART D (HER2 activating mutations including ex20ins and naïve to treatment with a HER2 ex20ins-targeted therapy e.g., poziotinib, trastuzumab deruxtecan).	PO BAY2927088 20 mg BID

Inclusion criteria:

- Documented histologically or cytologically confirmed locally advanced NSCLC, not suitable for definitive therapy or recurrent or metastatic NSCLC at screening (small cell or mixed histologies are excluded).
- Documented disease progression after treatment with at least one prior systemic therapy for advanced disease. Participants who do not have standard of care access due to any reason, are intolerant to, or are not eligible for standard treatments, may also be eligible.
- Adequate archival tumor tissue (ideally taken after last targeted treatment and not older than 6 months) has to be available, either from primary or metastatic sites. If archival material is not available, a fresh tumor biopsy should be performed if feasible and if the procedure poses no significant risk for the participant.
- Measurable disease by RECIST v1.1 with at least one lesion not chosen for biopsy during the screening period (if a biopsy is taken during screening) that can be accurately measured at baseline with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements. A biopsied lesion should not be used as a target lesion for RECIST 1.1 tumor assessments. Previously irradiated lesions must have shown progression to be considered measurable.
- Documented activating EGFR and/or HER2 mutation assessed by a Clinical Laboratory Improvement Amendments (CLIA)-certified (United States [US] sites) or an equally accredited (outside of the US) local laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Minimum life expectancy of 12 weeks.
- Adequate bone marrow function as assessed by the following laboratory tests to be conducted within 7 days before the first dose of study treatment:
    1. Hemoglobin ≥ 9.0 g/dL. Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within 2 weeks prior to testing.
    2. Platelets ≥ 100 × 10^9 cells/L.

3. Absolute neutrophil count ≥ 1.5 ×10^9 cells/L. Criteria must be met without the use of hematopoietic growth factors (e.g., G-CSF) within 2 weeks prior to testing.

- Adequate kidney function as assessed by following laboratory test to be conducted within 7 days before the first dose of study treatment:

  a. Estimated glomerular filtration rate (eGFR) > 60 mL/min per 1.73 m^2 according to the Modification of Diet in renal Disease Study Group (MDRD) formula.

- Adequate liver function as assessed by following laboratory tests to be conducted within 7 days before the first dose of study treatment:

  1. Total bilirubin ≤ 1.5 × ULN (or ≤ 3 X ULN for participants with documented Gilbert-Meulengracht Syndrome, or for participants with hyperbilirubinemia considered due to liver metastasis).
  2. Aspartate transaminase and alanine transaminase ≤ 2.5 × ULN (or ≤ 5 × ULN if due to liver involvement by tumor).

Exclusion criteria:

- Treatment with an EGFR tyrosine kinase inhibitor (TKI) ≤ 8 days or 5x the terminal phase, elimination half-lives, whichever is shorter, prior to the first dose of study drug.
- Treatment with a systemic anti-cancer treatment (excluding EGFR TKIs as described above) ≤ 14 days prior to the first dose of study drug.
- Radiation therapy, stereotactic radiosurgery (SRS) and palliative radiation ≤ 14 days prior to the first dose of study drug.
- Treatment with immunotherapy ≤ 28 days prior to the first dose of study drug.
- Have any unresolved toxicity of Grade ≥ 2 from previous anti-cancer treatment, except for alopecia and skin pigmentation. Participants with chronic, but stable Grade 2 toxicities may be allowed to enroll after agreement between the Investigator and Sponsor.
- Any history of primary brain or leptomeningeal disease (symptomatic or asymptomatic), presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local treatment (such as radiotherapy or surgery).
- History of spinal cord compression or brain metastases with the following exceptions:
- Participants with treated brain metastases that are asymptomatic at screening and who are off or receiving low-dose of corticosteroids (≤10 mg prednisone or equivalent) for at least 7 days prior to first dose of BAY 2927088 are eligible to enroll in Dose Escalation and Backfill.
- Participants with treated brain metastases that are asymptomatic at screening are eligible in Dose Expansion if all of the following criteria are met:
- there is no evidence of progression (new or enlarging brain metastases) for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period.
- Participants must be off or receiving low-dose of corticosteroids (≤10 mg prednisone or equivalent) for 7 days prior to first dose of BAY2927088.
- Participants with history of spinal cord compression >3 months from definitive therapy and stable by imaging (MRI or CT) during the screening period and clinically asymptomatic.
- History of congestive heart failure (CHF) Class >II according to the New York Heart Association (NYHA) Functional Classification or serious cardiac arrhythmias requiring treatment (e.g. ventricular arrhythmias, atrial fibrillation) or any clinically important abnormalities in rhythm, conduction or morphology or resting ECG (e.g., complete left

bundle branch block, third degree heart block, second degree heart block, PR interval >250 msec)

- Participants with:
- Known human immunodeficiency virus (HIV), except as noted below: Participants with history of HIV infection are eligible at the Investigator's discretion provided that: • CD4+ T-cell (CD4+) counts are ≥ 350 cells/uL • The participant has been on established antiretroviral therapy (ART) for at least 4 weeks prior to the start of study drug and has an HIV viral load less than 400 copies/mL prior to start of the study treatment • The ART being used does not contain strong inducers or inhibitors of CYP3A4, and is not anticipated to cause overlapping toxicities with study drug • The participant has not had an opportunistic infection within the past 12 months
- Active Hepatitis B infection (positive for Hepatitis B surface antigen [HbsAg]) and Hepatitis B virus [HBV] DNA).
- Active Hepatitis C infection (positive anti-HCV Antibody and quantitative HCV RNA results greater than the lower limits of detection of the assay).
- NOTE: Participants with history of chronic HBV or HCV infection are eligible at the Investigator's discretion provided that the disease is stable and sufficiently controlled under treatment.
- Use of strong CYP3A4 inhibitors and inducers from 14 days prior to first administration of study drug. Strong CYP3A4 inhibitors and inducers are prohibited during the study and until Safety FU (follow up) visit.